SiNAPSA

SLOVENSKO DRUŠTVO ZA NEVROZNANOST
SLOVENIAN NEUROSCIENCE ASSOCIATION

SNC'23

SiNAPSA NEUROSCIENCE CONFERENCE '23

28-30 September 2023
LJUBLJANA, SLOVENIA

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SiNAPSA Neuroscience Conference ‘23
Ljubljana, 28–30 September 2023

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in partnership with Faculty of Medicine, University of Ljubljana

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www.sinapsa.org/SNC23
Ljubljana, Slovenia
28–30 September 2023

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SiNAPSA Neuroscience Conference '23 Programme

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SiNAPSA Neuroscience Conference ’23 Programme

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10.15-10.25 **Assessing cognitive sequelae of COVID-19 using telepsychological testing**
Ana Kuder

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10.25-10.35 **Inferring coupling functions of brain regions from synthetic EEG data by using graph neural networks**
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Experience with the oral drug Evrysdi in adult patients with SMA in Slovenia
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Myasthenia gravis – A look forward

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Filippo Rocca

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Mateja Baruca Grad

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Optimising management of ATTRv amyloidosis in clinical practice – from patisiran to vutrisiran
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Jerneja Nimac

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Sara Cappelli

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Educational Workshop on Pain Programme

www.sinapsa.org/SNC23/workshop/programme
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Apkar Vania Apkarian

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Ljubljana Clinical Neurophysiology Symposium 2023 – Regional ALS Meeting Programme

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Efgartigimod: The significance of a new treatment option for generalized myasthenia gravis
Filippo Rocca

Challenges, limitations, and new opportunities for patients with generalized myasthenia gravis
Mateja Baruca Grad

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The evolving treatment landscape in ATTRv Amyloidosis

Diagnostic challenges and importance of early intervention in ATTRv amyloidosis
Janez Zidar

Optimising management of ATTRv amyloidosis in clinical practice – from patisiran to vutrisiran
Elena Zamba-Papanicolaou

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Žiga Špiclin

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Abstracts

SNC'23 Plenary and Special Lectures

www.sinapsa.org/SNC23
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Thursday, September 28th, 13:00

Molecular neuroimaging, brain connectivity, neurodegenerative conditions: a challenging interplay

Daniela Perani

Istituto Scientifico H.S. Raffaele, INB-CNR, Università di Milano, Italy

Positron emission tomography (PET) allows in vivo measurements of multiple parameters of regional cerebral physiology, such as glucose metabolism, and molecular biology, such as multiple neurotransmitter/neuroreceptor systems of the human brain.

FDG-PET data analyses are mostly based on univariate approaches, however, in the last decade the increasing interest in multivariate methods has paved the way to the assessment of unexplored cerebral features, from resting state brain networks to the whole-brain connectome assessment. These potentialities are becoming more and more important as the field of research that includes system and molecular levels of investigation.

The combination of PET molecular neuroimaging techniques with multivariate connectivity methods represents one of the most powerful, yet still emerging, approach to achieve novel insights into the pathophysiology of neurodegenerative diseases. In particular, the analytical tools for connectivity assessment of derangement due to neurodegeneration can characterize the abnormal neural circuitry that underlies brain pathology. Neurodegenerative disorders are characterized by spread of pathology along discrete neural pathways and the identification and validation of disease-specific brain connectivity changes is expected to broaden the application of connectivity approaches to large and diverse patient populations.

In this lecture the most common methods for FDG-PET molecular connectivity assessment will be reviewed together with examples from the related literature. For example, in amyloidopathy, tauopathy and synucleopathy diseases specific derangement of whole brain connectivity and resting state networks has been reported, also revealing compensatory or maladaptive effects. According to these results, brain dysfunctions and cognitive impairment in neurodegenerative conditions, depend on altered interactions between distributed brain regions operating in large-scale networks.

Together with [18F]FDG–PET metabolic connectivity studies, the application of connectivity approaches has now been extended to other PET targets, including neurotransmission systems. So far, molecular connectivity approaches have demonstrated novel network-level alterations in a range of neurodegenerative diseases. Possible future perspectives in the field, with reference to newly available PET tracers, will expand the application of molecular connectivity to new, exciting, unforeseen possibilities.

A crucial issue concerns validation, reproducibility, and resolution of the multiple statistical and mathematical approaches and data results. A possibility can be represented by an integrative approach whereby MRI-based, electrophysiological techniques, and PET molecular imaging together contribute to the brain connectome study.

These applied studies will increase the understanding of biological and clinical aspects of neurological and psychiatric diseases, hopefully providing information for early diagnosis programs, and for pharmacological and rehabilitative treatments.

Saturday, September 30th, 11:15

Deregulation of immunity in injured brain: exploring novel regulatory mechanisms and targets

Jasna Križ

Department of Psychiatry and Neuroscience & CERVO Brain Research Centre, Faculty of Medicine, Université Laval, Québec, QC, Canada

Inflammation is a key component of the innate immune response. Primarily designed to remove noxious agents and limit their detrimental effects, once prolonged and/or inappropriately scaled innate immune response may be detrimental to the host and lead to disease. There is increasing evidence that a deregulation of innate immunity may represent one of the key elements in the pathobiology of acute and chronic neurodegeneration. Microglia are the principal immune cells of the brain. Under physiological conditions microglial cells are essential for the maintenance of brain tissue homeostasis. It is becoming increasingly clear that in the context of disease and/or injury, microglial cells have pivotal role in initiation and regulation of inflammatory responses in the brain. The current consensus is that once activated, microglia can acquire a wide repertoire of immune profiles ranging from the classical pro-inflammatory to alternative, anti-inflammatory polarization phenotypes. Yet, the molecular mechanisms involved in the control of microglia polarization profiles remain elusive. We recently described a novel ribosome-based check-point mechanism involved in translation control of innate immune genes and microglia activation. The mechanism is based on a selective translational repression of ribosome-bound immune mRNAs orchestrated by RNA binding protein SRSF3. Our initial evidence suggests that targeting SRSF3 mRNA translation may open new avenues for therapeutic reprogramming of immune response in acute and chronic CNS pathologies.

Saturday, September 30th, 18:30

Astroglia in ageing and neurodegeneration

Alexej Verkhratsky

Faculty of Biology, Medicine and Health, The University of Manchester, United Kingdom

Challenging inflammageing of the brain: glial paralysis, rather than reactivity defines brain ageing and opens the gate for neurodegeneration

Ageing is associated with morphological and functional remodelling of astrocytes with a prevalence of morphological atrophy and loss of function, not of the widely popularised 'inflammation'. In particular ageing is associated with (i) decrease in astroglial synaptic coverage; (ii) deficits in glutamate and potassium clearance; (iii) reduced astroglial synthesis of synaptogenic factors such as cholesterol; (iv) decrease in

aquaporin 4 channels in astroglial endfeet with subsequent decline in the glymphatic clearance; (v) decrease in astroglial metabolic support through the lactate shuttle; (vi) decreased adult neurogenesis resulting from diminished proliferative capacity of radial stem astrocytes; (vii) decline in the astroglial-vascular coupling and deficient blood-brain barrier and (viii) decrease in astroglial ability to mount reactive astrogliosis. Decrease in reactive capabilities of astroglia as well as degeneration off dystrophy of microglia are permissive for age-dependent neurodegenerative diseases. Neuroglial morphology and function can be influenced and improved by lifestyle interventions such as intellectual engagement, social interactions physical exercise, caloric restriction, and healthy diet. These modifications of lifestyle are paramount for cognitive longevity.

Friday, September 29th, 18:30

Predicting chronic pain

Apkar Vania Apkarian

Feinberg School of Medicine, Chicago, IL, USA

Classically, chronic pain has been conceptualized as the persistent nociceptive barrage invading the central nervous system. Yet even its definition suggests this notion is not tenable. I will begin my lecture by revisiting fundamental definitions of nociception, pain, and chronic pain. I will then present human and rodent studies that complimentarily identify critical brain circuitry that seems causally engaged in the transition from acute to chronic pain. Multiple mesolimbic circuits are now recognized, each suggesting distinct mechanistic concepts and providing venues for novel treatment options for chronic pain. If time allows I will also cover the topic of identifying pain from brain activity – reading the mind in pain, and discuss recent concepts of perceptual states existing everywhere in the brain.

Friday, September 29th, 11:10

Biomarker development in ALS: from muscle to brain to blood

Martin Turner

Nuffield Department of Clinical Neurosciences, Oxford, United Kingdom

The ability to objectively measure disease activity in amyotrophic lateral sclerosis (ALS) has been one of the greatest barriers to therapeutic development. A focus on biomarker research for more than 20 years has coincided with the acceptance of a fundamental brain pathology associated with ALS, which has clinical, histopathological and genetic overlap with frontotemporal dementia (FTD). The focus on downstream markers of muscle denervation and has widened to include consideration of cortical hyperexcitability as a hallmark through transcranial magnetic stimulation and the application of advanced neuroimaging tools to study cortical function as well as structure. These have been increasingly applied to asymptomatic carriers of ALS-causing monogenetic variants, unveiling the clinical syndrome as the common endpoint of a long pathological process with many different starting points and possibly neurodevelopmental underpinnings. Most recently, blood neurofilament level has matured as the leading prognostic marker in ALS, whose lowering in response to drugs has great potential to be used as an early confidence-building marker of likely human clinical benefit.

Thursday, September 28th, 18:15

ICGEB Lecture: NOS1AP and RGNEF as novel RNA-binding protein modifiers of TDP-43 pathology in Amyotrophic Lateral Sclerosis

Yasmine Abbassi, Sara Cappelli, Cristiana Stuani, Luca Zangrando, Francesca Paron, Emanuele Buratti

International Centre for Genetic Engineering and Biotechnology (ICGEB), Trieste, Italy

Pathological aggregation of TDP-43 is principally associated with Amyotrophic Lateral Sclerosis (ALS) but is also present in approximately 50% of all Frontotemporal dementia patients and is a co-pathology in ~40% of Alzheimer's disease cases and in Chronic traumatic encephalopathy (CTE). These observations suggest that TDP-43 pathological aggregation can occur in different brain areas/tissues and in many different pathological conditions, which can be differentially affected depending on the relative abundance and expression of other RNA binding proteins that are present in the local context.

To address this issue, several years ago we performed transcriptome analysis of SH-SY5Y cells silenced for DAZAP1, hnRNP Q, hnRNP D, hnRNP K and hnRNP U that were shown to affect TDP-43 pathology in fly and human cell models of disease. After cross-comparing transcriptomic profiles of cells depleted by each of these factors, we identified seven commonly regulated transcripts: CHPF2, IGF2, IRAK2, RNF112, UBE2E3, C1orf226 and NOS1AP. Out of this list, NOS1AP (also known as CAPON) has recently emerged as an important player in brain physiology and pathophysiology for the formation of neuronal processes and probably in the onset of schizophrenia. Most importantly, we observed a clear correlation between the reduction of NOS1AP and the inclusion of two previously characterized cryptic exons in different brain regions of patients with TDP-43 pathology. Then, using primary mouse neuronal cultures we demonstrated that decrease of TDP-43 induced a drop in NOS1AP expression and this correlated with a significant decrease in several essential component of the synaptic network: PSD93, PSD95, SynGAP, and Synapsin-3. Finally, we observed that upregulation of NOS1AP in TDP-43 depleted SH-SY5Y cells can successfully rescue of many of these genes in the absence of TDP-43. In addition, downregulation of NOS1AP is also capable to rescue on its own the degenerative phenotype induced by TDP-43 overexpression in fly eyes. More recently, we have started analyzing Rho guanine nucleotide exchange factor (RGNEF). RGNEF is a guanine nucleotide exchange factor (GEF) mainly involved in regulating the activity of Rho-family GTPases. In neurodegenerative diseases, RGNEF is known to act as a destabilising factor of neurofilaments (NEFL) RNA in motor neurons of ALS patients and it could potentially contribute to their sequestration in nuclear cytoplasmic inclusions. Most importantly, RGNEF inclusions in the spinal motor neurons of ALS patients have been shown to colocalise with inclusions of TDP-43. To further characterise their relationship, we have compared the transcriptomic profiles of neuronal cells depleted of TDP-43 and RGNEF and show that these two fac-

tors predominantly act in an antagonistic manner when regulating the expression of axon guidance genes. From a mechanistic point of view, our experiments show that the effect of these genes on the processivity of long introns can explain their mode of action. Taken together, our results show that loss-of-function of factors co-aggregating with TDP-43 can potentially affect the expression of commonly regulated neuronal genes in a very significant manner. This finding further highlights that neurodegenerative processes at the RNA level are the result of combinatorial interactions between different RNA binding factors that can be co-aggregating in neuronal cells.

Taken together, our identification of NOS1AP and RGNEF as TDP-43 modifiers link these genes with modulating the neurological dysfunctions associated with ALS, allowing a better understanding of the variability of patients affected by this disease, and making them a suitable candidate for the development of novel therapeutic strategies in the context of this pathology.

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Ljubljana, Slovenia
28–30 September 2023

Thursday, September 28th, 13:45

Tracking brain connections in neurodegenerative brain disorders

Matej Perovnik, Maja Trošt

Department of Neurology, University Medical Centre Ljubljana, Slovenia

Neurodegenerative brain disorders are chronic proteinopathies that cause a major burden for the affected individual, caregiver, and the society. Their prevalence is growing with the ageing population. Various neuroimaging approaches are used in clinic and research settings to improve early diagnostic and differential diagnostic accuracy and help us better understand underlying pathophysiological processes of neurodegenerative brain disorders. Molecular brain imaging using positron emission tomography (PET) and various radiopharmaceuticals that show brain activity (glucose metabolism), blood flow, accumulation of abnormal proteins and neurotransmitter systems is a well-established research and clinical tool. Analytical advancements in recent years have brought forth the field of molecular connectivity that enables insight into molecular networks of healthy and diseased individuals. These advances are transforming the landscape of neurodegenerative research by providing additional information on the development and progression of the disease process. Furthermore, as the changes in the brain activity and accumulation of abnormal proteins begin early in the disease process, we can follow these changes already in early or even pre-symptomatic disease stages.

Keywords: neuroimaging, neurodegenerative brain disorders, network analysis

1. The concept of molecular connectivity

Igor Yakushev
Technical University of Munich, Germany

Do you apply molecular imaging to study brain connectivity? My talk will encourage you to consider doing this. Why? The current knowledge on how brain connectivity and networks underpin brain function (and dysfunction) disproportionately stems from the hemodynamic signal of functional MRI (fMRI). In fact, this method has been dominating the field of brain connectivity for decades, generating valuable knowledge about functional brain organization. As compared to fMRI, molecular imaging captures a broad range of biological processes such as neural function, neurotransmission, and proteinopathies. Thanks to its robustness, molecular imaging has been successfully utilized in the diagnosis of neurodegenerative brain disorders. In this talk I will introduce the concept of molecular connectivity, application of molecular imaging to estimate brain connectivity. Herewith, I will explain the notion of ergodicity and compare glucose PET with fMRI as markers of neural function. Approaches to estimate molecular connectivity will be explained by Dr. Arianna Sala in the subsequent talk. In the end, I will discuss outstanding questions and provide a vision of a future of molecular connectivity by the Molecular Connectivity Working Group, a recently established initiative of neuroimaging experts. Overall, we encourage the neuroscientific community to take an integrative approach whereby MRI-based, electrophysiological techniques, and molecular imaging contribute to our understanding of the brain connectome.

2. Methods in molecular connectivity: getting at the single-subject level

Arianna Sala
University of Liége, Belgium

My talk will provide a practical overview of the different approaches and methods to estimate molecular connectivity, with a particular focus on derivation of single-subject measures, i.e. with potential for application as clinical biomarkers. Advantages and disadvantages of each approach and method will be critically discussed.

First, I will provide an overview of the main approaches available to derive molecular connectivity, based on the inter-subject vs. the intra-subject estimation of molecular connectivity.

Second, I will cover the main families of methods for the estimation of molecular connectivity, including: (1) seed correlation or interregional correlation analysis (IRCA), (2) principal and independent component analysis (PCA and ICA) and (3) regional correlations.

Finally, I will explain which combinations of approaches and methods allow to achieve either the single-subject estimation of molecular connectivity or the derivation of connectivity-based single-subject indices that may likewise serve as potential clinical biomarkers.

Practical examples of application in the field of neurology will be provided throughout the talk.

3. Dynamic reconfiguration of metabolic brain connectivity during progression from MCI to Alzheimer's disease dementia

Silvia Caminiti
San Raffaele, Milano, Italy

Introduction: longitudinal design to investigate FDG-PET brain connectivity reconfigurations along the progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD) dementia.

Methods: Patients classified according to ATN pipeline in MCI (AD-MCI, N=31), mild dementia (mild-AD, N=31) and AD-dementia (AD-D, N=20). A group of age/sex-matched healthy controls (HC) was longitudinally evaluated for comparison. Between-nodes pairwise correlation analysis was applied to obtain adjacent matrices. The extent of connectivity alterations was quantified by means of nodal summary indices. The obtained indices also served as input for k-means cluster-analysis (KM1 and KM2).

Results: The AD-MCI showed less connectivity alterations than mild-AD and AD-D, specifically characterized by relatively higher numbers of gained than lost connections. KM1 identified two clusters: "altered cluster" and "spared cluster". In AD-MCI, altered cluster involved connections of subcortical/limbic regions, occipito-parietal cortices/cerebellum. At mild-AD and AD-D stages, the altered cluster involved a large portion of connections within occipito-parietal cortices/cerebellum. KM2 identified four clusters: Cluster1 included nodes with low-levels of lost/gained connections in frontal cortex, insula, and basal ganglia across the whole-disease course; Cluster2 grouped nodes with high levels of gained connections in occipito-temporo-parietal regions; Cluster3 grouped nodes with high-levels of lost connections in subcortical/limbic regions; in Cluster4 only the precuneus showed the highest levels of lost/gained connections, constant along the whole-disease.

Conclusion: The initial prevalent hyperconnectivity might represent an early response to neurodegeneration. As disease progresses, connectivity alteration was limited to the cortical-associative regions and cerebellum. Moreover, our results shed light on the critical role of precuneus in the dynamic connectivity reconfigurations of AD.

4. Metabolic brain networks in neurodegenerative parkinsonisms

Tomaž Rus
Department of Neurology, University Medical Centre Ljubljana, Slovenia

In the era of emerging disease-modifying therapies for neurodegenerative disorders, the importance of accurate and timely diagnosis of neurodegenerative disorders – dementias, and parkinsonisms – is steadily increasing. While there has been a shift from syndromic to biology-based diagnoses in the case of Alzheimer's disease, the diagnosis of neurodegenerative parkinsonian disorders still predominantly relies on clinical criteria. However, in recent years, a range of biomarkers has become available to help distinguish among these conditions. In addition to emerging cerebrospinal fluid and blood-based biomarkers, such as alpha-synuclein, biomarkers based on brain connectivity are increasingly accessible and ready for utilization in both research and clinical applications.

Aberrant brain circuitry can be explored using various imaging techniques, with FDG PET and functional MRI (fMRI) being the most readily accessible. Advanced analytical methods like the scaled subprofile model based on principal component analysis (SSM-PCA), independent component analysis (ICA), and graph theory approaches enable us to investigate connectivity within resting-state metabolic activity maps (captured through FDG PET) or regional blood oxygenation signals (captured via fMRI). While the fMRI-based approach is emerging as a cost-effective alternative, distinct disease-specific metabolic patterns based on FDG PET have been identified and validated across multiple centers in several neurodegenerative parkinsonian syndromes and are already being used in clinical settings.

The Parkinson's disease (PD) related pattern (PDRP) was first identified in the 1990s and has since been validated in diverse cohorts of PD patients at various disease stages worldwide. This pattern is characterized by relative hypermetabolism in the putamen, pallidum, thalamus, pons, and cerebellum, alongside hypometabolism in the premotor and posterior parietal regions. The expression of this PD-specific network correlates with the core signs of the disease, bradykinesia and rigidity, underscoring the pattern's biological significance. However, it's worth noting that the expression of PDRP does not align with parkinsonian tremor, as a distinct network, known as the PD tremor pattern, is associated with tremor and is primarily represented in the cerebello-thalamo-cortical regions.

In addition to the PDRP and PD tremor patterns, researchers have identified a separate metabolic network associated with cognitive decline in PD, so called PD cognitive pattern (PDCP). PDCP is characterized by functional changes within the ventral default mode network and other neocortical regions. PDCP becomes evident in PD patients with a noticeable delay after PDRP. This difference between the expressions of PDRP and PDCP is a distinctive feature of PD and aligns with the progression of neuropathological changes from the Braak 3 to Braak 4/5 stage.

While the characteristic relationship between PDRP and PDCP can offer valuable insights for differential diagnosis, other disease-specific metabolic networks have been identified for atypical parkinsonism, including the multiple system atrophy-related pattern (MSARP), progressive supranuclear palsy-related pattern (PSPRP), corticobasal degeneration-related pattern (CBDRP), and other networks associated with rare movement disorders. Based on the expression of these networks, machine learning-based algorithms have been developed to accurately differentiate among different syndromes, particularly in the early clinical stages when clinical differentiation is challenging. A recent real-world study has demonstrated that these algorithms can enhance the diagnosis of PD and atypical parkinsonisms by 15-20% in the early stages of the disease.

Beyond their role in differential diagnosis, metabolic brain networks also play an important role in assessing treatment responses in clinical trials. Several research groups have shown that positive clinical responses to symptomatic therapies, such as levodopa, deep brain stimulation, or therapeutic thalamotomy, are associated with a reduction in PDRP. Furthermore, these metabolic brain network-based approaches facilitate the examination of treatment impacts on network reconfiguration, which involves the development of new functional connections. This capability was showcased in two studies: one focused on STN AAV2-GAD gene therapy, and the other on an oral supplement targeting mitochondrial respiratory function. Both treatments, considered disease-modifying, were associated with distinct treatment-induced network alterations.

The metabolic brain network approach for studying brain changes in neurodegenerative parkinsonisms is a robust and reliable technique, valuable both in research and clinical practice. In conjunction with other emerging biomarkers, it is guiding us toward a deeper comprehension of the disease mechanisms, enabling more accurate diagnoses, and facilitating advanced treatment options for parkinsonian syndromes.

5. Metabolic brain networks in neurodegenerative dementias

Matej Perovnik
Department of Neurology, University Medical Centre Ljubljana, Slovenia

Metabolic brain imaging with Fluorodeoxyglucose positron emission tomography (FDG PET) and a special form of network analysis, so called scaled subprofile model/principal component analysis (SSM/PCA) is used to detect specific disease-related brain networks. These networks represent topographic patterns of neural activity in which interconnected brain regions form discrete networks. They are identified by using scans of diseased and healthy individuals and have been characterized for different neurodegenerative dementia disorders. After a successful identification and validation of such network pattern, we can then calculate the expression levels/subject scores, which quantify the extent to which a given network is represented in an individual's scan. This forward application of the SSM/PCA procedure enables the clinicians to obtain valuable, quantifiable information from an individual's FDG PET image that can be then used alongside a more traditional visual report. Using SSM/PCA and FDG PET scans from patients with dementia due to Alzheimer's disease and healthy controls an Alzheimer's disease related pattern (ADRP) has been identified in different sites across the world. The pattern's topography has been well validated, and it consistently involves the hypometabolic changes in the precuneus and temporoparietal cortices with relative hypermetabolic changes in the cerebellum, pons and primary sensorimotor cortex. Furthermore, it has been shown that ADRP subject scores can be used to separate patients with dementia or mild cognitive impairment (MCI) due to Alzheimer's disease from patients with dementia or MCI due to other causes. The subject scores also correlate with the degree of cognitive impairment.

Finally, in a recent longitudinal study we also showed that the subject scores increased monotonically in patient's with worsening cognition and that they can be used to predict conversion from normal cognition to MCI and from MCI to dementia.

Similarly, to ADRP a metabolic brain network characteristic for dementia with Lewy bodies (DLBRP), frontotemporal dementia (FTDRP), and most recently Creutzfeld-Jakob's disease (CJDRP) have been identified. In all three diseases the subject scores showed to bear excellent diagnostic value and a differential diagnostic machine learning algorithm utilizing the expression of ADRP, FTDRP and DLBRP was shown to be able to accurately distinguish between patients with AD, FTD, DLB and healthy controls.

Thursday, September 28th, 13:45

Neuroimmune disorders

Ivana Munitić

Department of Biotechnology, University of Rijeka, Croatia

This symposium will cover several hot topics in the neuroimmune crosstalk: immune disbalance in neurodegenerative diseases, multiple sclerosis, viral meningoencephalitis, inflammageing, immunosurveillance in health and disease, immune biomarkers, and/or immunotherapeutic approaches in neurological diseases.

Neuroimmunology is an increasingly prominent field since genetic and epigenetic analyses have implicated innate and adaptive immune pathways as either initiators or accelerators of a broad spectrum of neurological pathologies (autoimmune diseases of the CNS, neurodegenerative diseases, stroke and others). Some of them are also linked to exaggerated or failed responses to infection, as recently exemplified in the pandemic of SARS-Cov2. Importantly, experimental immunotherapeutic approaches for neurological disorders are on the rise because of the greater plasticity and accessibility of the immune than the nervous system.

Keywords: immunity, inflammation, neurodegeneration, inflammageing

1. Suppressing NLRP3 inflammasome

Iva Hafner-Bratkovič
Department of Synthetic Biology and Immunology, National Institute of Chemistry, Ljubljana, Slovenia
EN-FIST Centre of Excellence, Ljubljana, Slovenia

Multiprotein complexes inflammasomes are central components of the early inflammatory response to invading pathogens, however, particularly NLRP3 inflammasome has been shown to support inflammation in various sterile conditions, such as neurodegenerative diseases, where amyloids activate NLRP3. Upon sensing disrupted tissue homeostasis, NLRP3 through oligomerization leads to the recruitment of adapter ASC and assembly of inflammasomes, followed by the activation of inflammatory caspase-1. Caspase-1 afterward proteolytically activates proinflammatory cytokines IL-1b and IL-18. Gasdermin D is another substrate of inflammatory caspases. In a dormant state, gasdermin D molecules are present in autoinhibited form, while cleavage and recognition of negatively charged phospholipids enable the N-terminal domain of Gasdermin D to form pores in the membranes and facilitate pyroptotic cell death.

We investigate the regulation of the initial steps of NLRP3 inflammasome assembly and downstream responses that are common to all inflammasomes. We are exploring different ways to inhibit NLRP3 inflammasome activation, using small molecules and designed peptides. We demonstrated that the peptide corresponding to H2-H3 segment of ASC pyrin domain selectively inhibited NLRP3 inflammasome by binding to NLRP3 pyrin domain in the micromolar range. The peptide had no effect on AIM2 and NLRC4 inflammasomes as well as NF-κB pathway. The peptide effectively dampened neutrophil infiltration in the silica-induced peritonitis and when equipped with Antennapedia or Angiopep-2 motifs crossed the blood-brain barrier in a mouse model. Our study demonstrates that peptides represent an important tool for targeting multiprotein inflammatory complexes and can serve as the basis for the development of novel anti-inflammatory strategies for neurodegeneration.

2. Fluid biomarkers of neurodegeneration in neuroinflammatory diseases

Uroš Rot
Department of Neurology, University Medical Centre Ljubljana, Slovenia

Cerebrospinal fluid (CSF) and blood biomarkers of neurodegeneration could become useful in assessment of acute neuronal damage and prediction of long-term outcomes in many central nervous system inflammatory diseases. Frequently studied biomarkes include amyloid beta measurements reflecting amyloid metabolism in the brain, neurofilament light chain (NFL, axonal injury), tau (neuronal injury), phosphorylated tau (neurofibrillary pathology), glial fibrillary acidic protein (GFAP, astrogliosis) and YKL-40 (microglial activation). In multiple sclerosis (MS) high CSF NFL associates with acute axonal injury and is in correlation with relapses and early MRI activity. It decreases after immune treatment. NFL can also be measured in blood and its determination has already entered clinical routine. CSF YKL-40 is on the other hand more often associated with silent progression which is especially important in primary progressive MS. GFAP can also be determined in blood and is a promising biomarker of the immune treatment response in neuromyelitis optica spectrum disorder. In fulminant infections such as tick-borne meningoencephalitis high CSF NFL levels are found. CSF NFL concentrations are somewhat lower in infections with more protracted clinical course such us neuroborreliosis. Both of the diseases are associated with altered amyloid metabolism as reflected by low CSF amyloid beta concentrations. Neuroinflammation may also affect tau phosphorylation. Neuropathological studies report accumulation of abnormally phosphorylated tau in primary and secondary progressive MS, suggesting possible contribution of tau pathology to disease progression. Fluid biomarkers can provide insights into underlying pathogenetic processes and are therefore valuable in the diagnosis and prognosis of many degenerative but also inflammatory central nervous system diseases.

3. Immune imbalance during ageing

Ivana Munitić, Nikolina Mohović
Department of Biotechnology, Rijeka, Croatia

Immune functions are dramatically affected by ageing, a major trigger for adult-onset neurodegenerative diseases like amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). In the adaptive immune system, the most prominent changes comprise a decreased numbers and lower diversity of naive T and B cells, with an increase in effector and memory populations. In the innate immune system, ageing is linked to functional defects in phagocytosis, which lead to a lower capacity to cope with various exogenous and endogenous stressors, ultimately leading to higher inflammatory responses and low-grade chronic inflammation (termed inflammageing). Numerous studies have found mutations in the genes directly regulating immune functions in ALS and FTD, including those in C9ORF72, TBK1, OPTN and CYLD. In this talk I will discuss the lessons that we learned by analysing the effect of ageing on neuroimmune functions in a mouse model of OPTN insufficiency.

4. Stress-induced lipid droplet accumulation in astrocytes

Anemari Horvat[1,2], Tina Smolič[1], Petra Tavčar[1], Urška Černe[1], Larisa Tratnjek[3], Mateja Erdani Kreft[3], Maja Matis[4,5], Toni Petan[6], Robert Zorec[1,2], Nina Vardjan[1,2]

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3 Institute of Cell Biology, Faculty of Medicine, University of Ljubljana, Slovenia
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5 Cells in Motion Interfaculty Centre, University of Münster, Germany
6 Department of Molecular and Biomedical Sciences, Jožef Stefan Institute, Ljubljana, Slovenia

Lipid droplets (LDs) are cellular organelles involved in lipid turnover and stress response and provide substrates for energy metabolism and protection against lipotoxicity. In brain pathologies LD content increases. This occurs mainly in neuroglial cells. The characteristics of LDs and the mechanisms driving the accumulation of LDs in astrocytes, a subtype of neuroglial cells with key homeostatic functions, are poorly understood. We studied the (sub)cellular localization and LD content using fluorescent and electron microscopy in isolated and brain tissue rat astrocytes, and in Drosophila melanogaster brain, under various stress stimuli associated with brain pathologies. In resting astrocytes, LDs were found to be ~450 nm in diameter and located close to mitochondria and the endoplasmic reticulum. Following attenuation of de novo LD biogenesis by inhibiting DGAT1 and DGAT2 enzymes, the astrocyte number decreased by ~40%, indicating the importance of LD turnover for cell survival and/or proliferation. Exposure to metabolic and hypoxic stress significantly increased LD content in astrocytes, indicating LD accumulation. Increased LD accumulation was also observed in astrocytes exposed to a brain stress response system neuromodulator noradrenaline, upon β- and α2-adrenergic receptor activation that affects cAMP signaling. Finally, the accumulation of LDs was observed also in Drosophila brain upon exposure of flies to 24 h-hypoxic and nutrient stress. Thus noradrenergic activation and metabolic and hypoxic stress, which are associated with many brain pathologies, trigger LD accumulation in astrocytes. This response may serve to support energy metabolism and/or provide neuroprotection against lipotoxicity, increasing the viability of stressed astrocytes and neighboring cells.

5. Genetic polymorphisms in oxidative stress and inflammatory pathways as potential biomarkers in Alzheimer's disease and dementia

David Vogrinc[1], Milica Gregorič Kramberger[2,3,4], Andreja Emeršič[2], Saša Čučnik[2,5,6], Katja Goričar[1], Vita Dolžan[1]

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3 Faculty of Medicine, University of Ljubljana, Slovenia
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5 Department of Rheumatology, University Medical Centre Ljubljana, Slovenia
6 Faculty of Pharmacy, University of Ljubljana, Slovenia

Background: Oxidative stress and neuroinflammation are important processes involved in Alzheimer's disease (AD) and mild cognitive impairment (MCI). Numerous risk factors, including genetic background, can affect the complex interplay between those mechanisms in the aging brain and can also affect typical AD hallmarks: amyloid plaques and neurofibrillary tangles. Our aim was to evaluate the association of polymorphisms in oxidative stress- and inflammation-related genes with cerebrospinal fluid (CSF) biomarker levels and cognitive test results.
Methods: The study included 54 AD patients, 14 MCI patients with pathological CSF biomarker levels, 20 MCI patients with normal CSF biomarker levels and 62 controls. Isolated DNA from blood was genotyped for polymorphisms in SOD2, CAT, GPX1, IL1B, MIR146A, IL6, TNF, CARD8, NLRP3, GSTP1, NOS1, KEAP1 and NFE2L2 using competitive allele-specific PCR. Association of polymorphisms with CSF biomarker levels and cognitive tests was evaluated using nonparametric tests.

Results: Carriers of two polymorphic IL1B rs16944 alleles had higher CSF Aβ1–42 levels ($p = 0.025$), while carriers of at least one polymorphic NFE2L2 rs35652124 allele had lower CSF Aβ1–42 levels ($p = 0.040$). Association with IL1B rs16944 remained significant in the AD group ($p = 0.029$). Additionally, MIR146A rs2910164 was associated with Aβ42/40 ratio ($p = 0.043$) in AD. Significant associations with cognitive test scores were observed for CAT rs1001179 ($p = 0.022$), GSTP1 rs1138272 ($p = 0.005$), KEAP1 rs1048290 and rs9676881 (both $p = 0.019$), as well as NFE2L2 rs35652124 ($p = 0.030$). In the AD group, IL1B rs1071676 ($p = 0.004$), KEAP1 rs1048290 and rs9676881 (both $p = 0.035$) remained associated with cognitive scores.

Conclusions: Polymorphisms in antioxidative and inflammation genes might be associated with CSF biomarkers and cognitive test scores and could serve as additional biomarkers contributing to early diagnosis of dementia.

6. Microbiome in Parkinson's disease

Eliša Papić, Valentino Rački, Vladimira Vuletić
Clinic for Neurology, Clinical Hospital Center Rijeka, Croatia

Parkinson's disease (PD) is a neurodegenerative disease with a multifactorial etiopathogenesis. The main pathophysiological mechanism involves the loss of dopaminergic neurons due to α-synuclein accumulation. Increasing evidence has identified microbiota as a potential factor in the earliest, prodromal phases of the disease. Thus far, research has shown a significant difference between microbiota composition in PD patients as opposed to healthy controls. Furthermore, the relative abundance of certain microbiota has been correlated with motor and non-motor symptom severity, with varied findings between different bacterial taxa. Besides microbiome composition, metabolic side-products of microbiota with potential effects on Parkinson's disease have also been identified, with short-chain fatty acids (SCFA) being the most prominent ones. Various therapeutic approaches targeting gut microbiota have also been explored, such as antibiotics, prebiotics, probiotics, specific diets as well as fecal microbiota transplantation (FMT) and enema. At the Clinic for Neurology of the Clinical Hospital Center Rijeka, we are currently conducting a longitudinal study with de-novo patients and are looking to add to the current knowledge of both symptom/abundance correlation and the effects of therapy on the composition and metabolic function of microbiota.

Further research into the field could offer a better and more individualized approach to Parkinson's disease treatment.

Thursday, September 28th, 16:15

Mobile Brain/Body Imaging (MoBI) – understanding brain oscillations and movement in natural and extreme environments

Uroš Marušič[1], Klaus Gramann[2]

1 Science and Research Centre Koper, Slovenia
2 Technische Universität Berlin, Germany

Mobile Brain/Body Imaging (MoBI) is a neuroimaging technique that allows researchers to investigate brain activity while a person is engaged in natural movements and behaviors, such as walking or reaching movements. Unlike traditional neuroimaging methods such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), MoBI allows neural activity to be recorded outside the laboratory setting. MoBI uses portable EEG systems in combination with motion capture devices and other wearable sensors to record brain activity, muscle movements, and other physiological signals to better understand the complex interactions between the brain and body during real-world activities and to gain insights into how the brain controls movement and how movement affects brain function. MoBI has the potential to revolutionize our understanding of the brain-body relationship and has applications in areas such as rehabilitation, sports science, and human-computer interaction.

In this symposium, we will introduce the expanding research field of MoBI, which includes the scientific background of MoBI and current applications in studies assessing the behavioral and neural bases of spatial navigation in real and virtual spaces (Speaker #1); an overview of the behavioral and neurophysiological bases of embodiment and motor control in the field of telerobotics (Speaker #2); Clinical aspect of MoBI for early signs of Parkinson's disease (Speaker #3); High-density EEG source imaging for mapping brain sources in extreme environments while subjecting the human body to increased gravity in a short-arm human centrifuge (Speaker #4).

Keywords: Mobile EEG, embodied cognition, advanced brain mapping

1. Linking human behavior with brain responses using Mobile **Brain/Body Imaging**

Klaus Gramann
Technische Universität Berlin, Germany

Decades of human brain imaging studies have used methods that are either to heavy to follow participants movements (e.g., MRI) or that required participants to sit still to avoid movement-related artifacts that might impact the feeble signal of interest (e.g., M/EEG). As a consequence to the restrictions of the imaging modality, embodied cognitive processes and their underlying neural correlates have not been investigated and the impressive capacities of the human brain to support flexible cognition during interaction with dynamic environments remains elusive.

Recent technological advancements have provided brain imaging modalities that are small and lightweight and allow for recording of human brain activity in actively moving participants. In combination with virtual reality (VR), such systems enable controlled experiments beyond standard laboratory protocols offering new opportunities in cognitive neuroscience research introducing hitherto unknown possibilities for mapping out human brain function in ecological valid scenarios. While a combination of virtual reality, motion capture, and brain imaging can assess the most important aspects of embodied cognitive processes, it further provides unprecedented opportunities for systematically manipulating the constituent factors of sensory-motor integration underlying natural cognitive processes with protocols that would not be possible without VR.

I report results from MoBI experiments that reveal striking differences in brain dynamics underlying active behavior as compared to stationary protocols. The results give new insights into human brain activity during active behaviors and a critical perspective on problems arising from the combination of new technologies.

2. Neurophysiological bases of embodiment during physical manoeuvring of a virtual robot in VR

Federica Nenna
University of Padua, Italy

Virtual Reality (VR) is increasingly being used to teleoperate or simulate robotic systems. Human-robot interfaces leveraging intuitive body motion and gestures, such as body-machine interfaces, likely trigger embodiment mechanisms, increasing the teleoperation's transparency, leading to higher telepresence and oftentimes even altered body ownership. In such cases, users might forget about the mediator (i.e., the interface itself) and act more naturally. All these mechanisms were proposed to improve human-robot teleoperation performance and particularly motor control, despite scarce empirical findings currently supporting this hypothesis in the telerobotics sector.

In our last research, we covered these aspects within a VR-based industrial scenario, where our participants maneuvered a faithful reproduction of the robotic arm e-Series UR10e via their own physical movements. Given the abstraction and the psychological nature of the variables of interest, we relied upon a multimodal setup for measuring explicit and implicit metrics related to embodiment, presence, workload, and motor control. Specifically, in addition to a battery of self-report questionnaires, we tracked the users' motor performance in combination with a Mobile Brain/Body Imaging (MoBI) approach to additionally measure brain dynamics (i.e., EEG) without constraints throughout the task execution. This allowed linking users' perceptions, performance, and related brain activity, offering a broad overview of behavioral and neurophysiological bases of embodiment and motor control in the telerobotics sector.

3. Detecting early signs of Parkinson's disease using Mobile **Brain/Body Imaging**

Manca Peskar
Science and Research Centre Koper, Slovenia

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting approximately 3% of people aged 65 and over 10% of people above 80 years. Typically, the first symptoms manifest in the motor domain which remains the most severely affected domain throughout the disease. To compensate for the lack of automaticity in balance and/or movement control, PD patients typically employ attentional strategies. However, this process is also impeded because the disease manifests in non-motor symptoms too. Already in the early disease stages, approximately one-third of patients reported cognitive impairment. These cognitive changes are difficult to diagnose in PD because the patients retain their mental acuity and continue their daily living activities.

In pursuit of gaining a better understanding of the cortical underpinnings supporting natural behaviors in early PD patients, the aim of our study was to manipulate the motor load across balancing and overground walking tasks, both with and without the addition of a secondary cognitive task. Using the Mobile Brain/Body Imaging (MoBI) approach we were able to simultaneously record behavior and neurophysiology associated with both motor and cognitive tasks. We present one of the first MoBI protocols investigating cognitive-motor dual tasking in a fully mobile setting. For the balancing task, we report the preliminary results comparing 10 healthy and 12 PD patients on postural sway and event-related potentials, while for the walking task, we present a preliminary gait cycle-related spectral modulation analysis approach.

4. Brain mapping during increased gravity gradients

Uroš Marušič
Science and Research Centre Koper, Slovenia

The human brain's remarkable ability to adapt and reorganize its function and structure, known as neuroplasticity, plays a critical role in acquiring skills and adapting to a changing environment. In light of future space missions to the Moon, Mars, and beyond, the impact of changing gravity conditions on neuroplasticity is becoming a pressing concern. The human centrifuge, originally developed for high-g training in aviators and astronauts, has gained new attention for its potential as a medical device. High-g training on the centrifuge protects against acceleration-induced loss of consciousness (g- LOC), a condition in which excessive g-forces displace blood from the brain and lead to unconsciousness. Incidents of g- LOC have tragically resulted in fatal accidents in high-performance aircraft capable of sustaining high g conditions for extended periods of time. In addition to its role in high-g training, the centrifuge has also shown promise as a tool for personalized gravity therapy (GT). GT has shown potential in the treatment and rehabilitation of individuals with neuromuscular disorders, balance disorders, stroke and sports injuries. The precise tailoring of GT to individual needs opens new avenues for therapeutic interventions that take advantage of the body's response to gravity gradients. In my talk, I will present the feasibility of measuring electroencephalography (EEG) in the presence of elevated g-values, as well as preliminary data on possible differences in sensorimotor processing in healthy adults.

Thursday, September 28th, 16:15

Neurodegeneration and protein aggregation; are aggregates protective or harmful; what comes first protein aggregation or oxidative stress?

Eva Žerovnik

Department of Biochemistry and Molecular and Structural Biology, **Jožef Stefan Institute, Ljubljana, Slovenia**

We will show evidence for various amyloid forming proteins causing neurodegenerative disease, how their aggregates affect cells' and neurons' fate. Can we trace smaller oligomeric species perforating membranes? What comes first protein aggregation or oxidative stress or we have a vicious circle? We will argue that in aging and neurodegeneration, first, by UV radiation or H2O2 exposure proteins get oxidized then they produce toxic still soluble aggregates and increase mitochondrial ROS release, thus, other proteins aggregate even more. Examples of the protein aggregates causing various neurodegenerative pathologies will be described, such as SOD-1 aggregation, alpha- synuclein, amyloid-beta, amylin (islet amyloid polypeptide - IIAP), cystatin C and stefin B. We will give hints for other diseases of the CNS, which may be linked to protein aggregation, such as progressive myoclonus epilepsies and major mental illnesses.

Keywords: protein aggregation, amyloid formation, neurodegeneration, aging, major mental diseases

1. Introduction to the topic of protein aggregation

Eva Žerovnik
Department of Biochemistry and Molecular and Structural Biology, Jožef Stefan Institute, Ljubljana, Slovenia

2. Additional features of the mechanism of amyloid formation by **human stefin B as revealed by infrared spectroscopy**

Eva Žerovnik[1], Urban Novak[2], Ajda Taler-Verčič[3], Barbara Zupančič[2], Magda Tušek-Žnidarič[4], Jože Grdadolnik[2]

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Modulation of the model for the mechanism of amyloid fibril formation by human stefin B was obtained by using FTIR/1/. The model differs slightly from the previously proposed one/2/ and is most in line with the proposal obtained by heteronuclear NMR/3/. Native state is made by four β-strands which form one β-sheet and one α-helix. The core of amyloid fibrils is formed from β-strands 3 and 4, which form a cross-β-structure. Around the fibril core α-helixes are placed. However, somewhat decrease population of the α-helical structures were observed, which can be ascribed to partial unfolding of the ends of α-helices. Intermediates with partially unfolded secondary elements were detected for the first time.

Keywords: mechanism of amyloid aggregation, human cystatin B, infrared spectroscopy, secondary structures

3. Structural aspects of oligomerization processes of the Abeta peptides under interaction with nanoparticles utilized by NMR spectroscopy

Thomas Okoth[1,2], Lesia Kolomiiets[1], Karolina Rucińska[3], Joanna Maksim[3], Maciej Kozak[3,4], Igor Zhukov[1]

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S100B proteins, a specific type of calcium-binding protein, are essential for regulating various processes associated with Alzheimer's disease (AD). Among these processes, the S100B protein plays a critical role in the modulation of the amyloid precursor protein (APP) processing, the regulation of Abeta peptides (Aβ), and Tau phosphorylation. The interaction between S100B and Aβ amyloid suggests that S100B acts as a regulatory factor, controlling the levels of Aβ oligomers in the human brain. In our study, we utilized NMR spectroscopy to explore the structural changes that occur during the interaction between human S100B in its calcium-loaded form and Aβ(1-40) peptide. Analysis of chemical shift perturbations makes it possible to identify a structural motif consisting of α-helices formed intersubunit interface, interacting with the Aβ(1-40) peptide. Our finding corroborates with previous reports about complex S100B with Aβ(1-42), exhibiting the changes in the dynamics of the S100B backbone in the absence and presence of Aβ(1-40). Specifically, the complex S100B with Aβ(1-40) characterized a reduction of molecular dynamic processes within the μs – ns time-frame compared to the S100B protein. At the same time, the intensity of the dynamic motions increased for the residues located in the 'hinge' loop between two Ca-binding EF-hand motifs. The presence of CuO nanoparticles leads to dramatic changes in the 3D structure and dynamic processes for the S100B protein but not for the Aβ amyloid in S100B-Aβ(1-40) complex. Acknowledgments The research was supported by a grant 2021/41/B/ST4/03807 from National Science Commitee (Poland).

Keywords: S100B, Abeta amyloid, metal nanoparticles, NMR spectroscopy

4. Modulation of the stability of cystatin C by intra- and extramolecular factors

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1 Department of Biomedicinal Chemistry, Faculty of Chemistry, University of Gdańsk, Poland
2 Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland

Human cystatin C (hCC) is associated with physiological and pathological processes in human organism. It functions mainly as an inhibitor of cysteine proteases, but also exhibits neurodegenerative and neuroprotective properties. The wild-type protein modulates the amyloid-β peptide oligomerization and toxicity, protecting at the same time neuron cells. The L68Q variant of hCC, on the other hand, is associated with severe state called hereditary cerebral amyloid angiopathy (HCAA), a disease resulting from the protein oligomerization, causing brain artery damage. Oligomerization of hCC is a result of domain swapping. The protein conformational stability and unfolding necessary for the process to occur is partially controlled by the sequence of the L1 loop and hydrophobic interaction network, centered around leucine at position 68 located in the hydrophobic core of the protein. In certain conditions, the L1 loop can induce intermolecular self-association of two hCC molecules through a "steric zipper" motif. hCC oligomerization occurs spontaneously as a result of the above mentioned L68Q mutation or can be induced by external factors including temperature, pH changes or denaturation agents. Redox-active metal ions and biological membranes also play a vital role in the process. Understanding the impact of intra- and intermolecular factors on hCC's conformational stability and propensity for oligomerization can provide insights into the mechanisms underlying amyloidogenic protein folding. It may aid in preventing pathological processes resulting from its misfolding and become a starting point for a design of an effective treatment against HCAA.

Keywords: cystatin C, protein aggregation, amyloid formation, neurodegeneration

5. FUS phosphorylation in FTLD

Helena Motaln[1], Urša Čerček[1], Anand Goswami[2], Boris Rogelj[1,3]

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Nuclear to cytoplasmic mislocalization and aggregation of RNA-binding proteins (RBPs), including Fused in sarcoma (FUS), are the main neuropathological features of amyotrophic lateral sclerosis (ALS) and frontotemporal lobular degeneration (FTLD). In ALS-FUS these aggregates arise from disease-associated mutations in FUS, whereas in FTLD-FUS the cytoplasmic inclusions do not contain mutant FUS, suggesting different molecular mechanisms of FUS pathogenesis. We have shown that phosphorylation of the C-terminal Tyr526 of FUS results in increased cytoplasmic retention of FUS due to impaired binding to Transportin 1. Here we developed a novel antibody against the C-terminally phosphorylated Tyr526 FUS (FUSp-Y526) that is specifically capable of recognizing phosphorylated cytoplasmic FUS, which is poorly recognized by commercially available FUS antibodies. Using this FUSp-Y526 antibody, we demonstrated a FUS phosphorylation-specific effect on the cytoplasmic distribution of soluble and insoluble FUSp-Y526 in various cells. We found that FUSp-Y526 expression pattern corelates with active pSrc/pAbl kinases in specific brain regions of mice, indicating preferential involvement of cAbl in the cytoplasmic mislocalization of FUSp-Y526 in cortical neurons. Finally, altered cytoplasmic distribution of FUSp-Y526 was observed in cortical neurons of post-mortem frontal cortex tissue from FTLD patients compared with controls. Given the overlapping patterns of cAbl activity and FUSp-Y526 distribution in cortical neurons, and cAbl induced sequestration of FUSp-Y526 into G3BP1 positive granules in stressed cells, we propose that cAbl kinase is actively involved in mediating cytoplasmic mislocalization and promoting toxic aggregation of wild-type FUS in the brains of FTLD patients, as a novel putative underlying mechanism of FTLD-FUS pathophysiology.

6. Alzheimer's disease and canine cognitive dysfunction – two faces of the same disease?

Gregor Majdič
Veterinary Faculty, University of Ljubljana, Slovenia

Advances in Alzheimer's research are among other reasons limited by the lack of good animal models, as neurodegenerative diseases do not occur spontaneously in laboratory rodents. Although there are some models of genetically engineered mice that develop certain pathological processes in the brain, such as the loading of amyloid plaques, the relevance of such models is questionable, as disease is not occurring spontaneously. However, neurodegenerative diseases occur in some domestic animals. Cognitive impairment of dogs - canine cognitive dysfunction is disease of older dogs that is similar in many ways to Alzheimer's dementia in humans. Dogs have problems with memory, spatial orientation, problems with recognizing the owners, changes in day-night rhythm, changes in character etc. Pathophysiologically, similar changes occur in the brain as in human patients with Alzheimer's dementia, with brain cells dying and amyloid plaques being deposited in the brain. There are fewer reports of neurofibrillary tangles in brain cells, and some studies suggest that neurofibrillary tangles do not occur in dogs with cognitive impairment, while other studies show that these tangles also exist in the brain cells of canine patients, but to a lesser extent than in human patients. Because the disease has been poorly studied, it is also possible that the neurofibrillary tangles appear similar to humans, but we do not have the right tools to detect them in the brain tissue.

Disease in dogs is important from two points of view - since it is a fairly common disease in dogs, it is estimated that the prevalence of the disease is more than 60% in dogs over the age of 12, the disease is of interest for the development of new drugs and treatment methods for use in veterinary medicine, as quality of life of dogs and their owners is severely compromised of dogs have this disease. On the other hand, dogs with this disease also represent an important model for better understanding of Alzheimer's disease and for the development of new drugs, but this model has only begun to be recognized in recent years. Dogs are undoubtedly an extremely interesting model for understanding dementia in humans, not only because the pathophysiological changes in humans and dogs are similar, but also because dogs share with us their living environment, our daily habits (too little movement and associated obesity often occurs simultaneously with owners and their dogs) and are exposed to similar environmental factors. These are certainly completely different from the environment to which laboratory rodents are exposed in controlled breeding facilities, so studying dogs with cognitive impairment could offer us many answers to the unknowns in the development of Alzheimer's dementia.

Friday, September 29th, 14:00

Neuroendocrine plasticity of the brain: from biology to therapy

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2 Faculty of Pharmacy, University of Ljubljana, Slovenia

The brain is a composite neuro-endocrine organ, influenced by intricate neuronal and peripheral hormonal signaling conveying information from internal and external environments. In turn, complex neuropeptide networks enable efficient adaptation to an ever-changing environment and affect many bodily functions, such as metabolic status/ energy consumption, fertility, and stress responses. Dysregulation in any of the systems due to genetic or epigenetic changes can lead to neurodevelopmental, reproductive, and cognitive disorders, or obesity, and can have wide-ranging effects on behavior, mood, and overall health, leading to different diseases, including Prader-Willi Syndrome and Alzheimer disease. This symposium will address, from an interdisciplinary and comparative point of view, the neuroendocrine plasticity of the brain. The topics to be presented by confirmed speakers range from basic molecular biology and genetics to translational research at preclinical and clinical levels, applicable in human and veterinary medicine.

Keywords: brain endocrine functions, neuroplasticity, stress, cognitive dysfunction, precocious/delayed puberty

1. Prader-Willi Syndrome-associated MAGEL2 in the regulation of stress and endocrine function of the hypothalamus

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The hypothalamus regulates fundamental aspects of physiological homeostasis and behavior, including stress response, reproduction, growth, sleep, and feeding, several of which are affected in patients with Prader–Willi (PWS) and Schaaf-Yang syndrome (SYS). PWS is caused by the loss of expression of a maternally imprinted region of chromosome 15 encompassing five noncoding RNAs and six protein-coding genes; MAGEL2 is one of the coding genes that is also mutated in SYS patients. Management of PWS and SYS is mostly symptomatic and finding cures is one of the unmet medical needs. Research over several decades into the molecular and cellular roles of PWS genes has uncovered that several impinge on the neuroendocrine system. Notably, studies using mouse models with Magel2 loss have implicated the requirement of this protein for regulated secretion in the hypothalamus. On a cellular level, MAGEL2 regulates retromer-dependent endosomal protein trafficking and recycling of membrane proteins. However, the specific reasons why MAGEL2 is crucial for the secretory process in the hypothalamus, and which other molecular pathways are regulated by MAGEL2 under different conditions, in particular stress, remain poorly understood. To gain an unbiased understanding of Magel2's role in the hypothalamus, wild-type, and Magel2m+/pΔ mice were subjected to 24-hour fasting and analyzed on a single-cell level by single-nuclei RNA sequencing. The insights gained from our studies will be presented, which may provide novel perspectives on the pathogenesis of Prader-Willi syndrome, potentially leading to the discovery of innovative therapeutic interventions for affected patients.

Acknowledgments/Funding: This work was supported by the Foundation for Prader–Willi Syndrome Research Grant 22-0321 and 23-0447 (to K.F.T. and Z.K.), Texas Tech University start-up (to K.F.T.), and Cancer Prevention and Research Institute of Texas Scholar Award RR200059 (to K.F.T.).

Keywords: retromer, protein recycling, hormone, neuropeptide secretion, single-cell RNAseq, neurodevelopmental disease, rare disease

2. Noradrenergic regulation of astrocytes allows metabolic and morphological plasticity of astrocytes and therapeutic opportunity

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Neurons from the noradrenergic nucleus locus coeruleus (LC) play a key neuromodulator role in the brain. They project axons to the most brain areas and release noradrenaline from their numerous axonal varicosities triggering global excitation by volume transmission. Noradrenaline preferentially activates astrocytes, homeostatic neuroglial cells, enriched with adrenergic receptors. Noradrenergic activation triggers in astrocytes Ca^{2+} and cAMP elevations and augments aerobic glycolysis with production of lactate, an important energy fuel that supports neuronal function, including learning and memory formation. In most neurodegenerative diseases and aging one of the first areas undergoing degeneration is the LC, suggesting that this may be the cause of age-related brain hypometabolism and disease progression. By measuring lipid and glucose metabolism in astrocytes using fluorescent sensors and microscopy, we have recently demonstrated that adrenergic receptor expression and signaling as well as lipid and glucose metabolism and lactate release are dysregulated in stressed astrocytes that form intracellular protein (TDP-43) inclusions. These may suggest that astroglial capacity to homeostatically support neurons is impaired, contributing to disease progression. The morphology of astrocytes determines the structural association between astrocytes and the synapse, consequently modulating synaptic function. We will also discuss how noradrenergic excitability in astrocytes regulates morphology. In vivo and in vitro imaging of astrocytes revealed that adrenaline reduces hypotonicity and trauma-induced cellular edema in astrocytes. Adrenaline, via modifying cAMP-signaling, reduces hypotonicity-induced cytosolic Ca^{2+} excitability, which may prevent astrocyte swelling. These findings reveal astrocytes as new targets for the treatment of neurodegeneration and cellular edema in the central nervous system.

3. Selective butyrylcholinesterase inhibitor for alleviating symptoms of canine cognitive dysfunction

Urban Košak[1], Damijan Knez[1], Anže Meden[1], Simon Žakelj[1], Jurij Trontelj[1], Jure Stojan[2], Maja Zakošek Pipan[3], Kinga Sałat[4], Florian Nachon[5], Xavier Brazzolotto[5], Gregor Majdič[3], Stanislav Gobec[1]

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4 Faculty of Pharmacy, Jagiellonian University, Krakow, Poland
5 Institut de Recherche Biomédicale des Armées, Brétigny sur Orge, France

Canine cognitive dysfunction (CCD) is an incurable neurodegenerative disease which effects 60% of older dogs and its most prominent sign is cholinergic hypofunction. (1) As long as this disease cannot be prevented or cured, symptomatic treatment is critical. The only FDA approved drug for treating symptoms CCD is selegiline. This monoamine B inhibitor has adverse effects which make tolerability a significant limitation. (2) However, this problem can be overcome by inhibiting a different enzyme, butyrylcholinesterase (BChE).

We used virtual screening to discover our hit compound, a novel piperidine-based nanomolar selective BChE inhibitor. (3) Using ligand-based and structure-based drug design for hit-to-lead optimization, we produced and evaluated a huge number of various derivatives. (4) Our most promising compound is the sulfonamide derivative which improved memory, cognitive functions and learning abilities of dogs suffering from CCD with no adverse effects. All owners of treated dogs reported a drastic improvement in the quality of life and dog-owner interaction. (5) Our selective BChE inhibitor is a new drug for treating CCD and is a drug candidate for treating other forms of dementia, like Alzheimer's disease in humans.

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4. Endocrinology of precocious/delayed puberty

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Pubertal timing is regulated by a balance between inhibitory and excitatory signals acting upstream of gonadotropin releasing factor (GnRH), a key hypothalamic hormone that orchestrates puberty and reproduction. Yet, what triggers puberty remains unanswered.

Monozygotic twin studies suggest that genetic factors majorly determinate pubertal timing; furthermore, around 400 genes are associated with age at menarche by genome-wide association studies. Precocious and delayed puberty also commonly appear as familial traits. Nevertheless, monogenic causes are identified in a minority of pedigrees.

Major secular trends toward earlier pubertal timing occurred along with improved nutrition in recent centuries, and in recent decades the age at the onset of puberty is further decreasing. Some factors that could be responsible, are childhood obesity, exposure to hormone disrupting chemicals and epigenetic changes. Adoption as a specific stressor, significantly increases the risk for precocious puberty.

Stress, weight loss, or excessive exercise can cause reversible hypogonadism (in females termed hypothalamic amenorrhea (HA)), which can delay or arrest puberty. Similar effect have various endocrine disorders and chronic illness. The commonest cause of delayed puberty is constitutional delay in growth and puberty (CDGP), which is a self-limited condition.

At the other end congenital hypogonadism (CH) presents with incomplete or absent puberty, needing therapy. Above 50 genes implicated in GnRH neuron development, action or homeostasis are causative in about 50% of CH patients. Genetic heterogeneity, various inheritance patterns, oligogenicity, and incomplete penetrance, make genetic counseling difficult. Some genetic overlap is observed also with HA, CDGP and patients with hypopituitarism. Interestingly, 10-20% of CH patients achieve remission of hypogonadism, the common denominator being normal blood sex hormone level achieved by therapy.
While the current knowledge of puberty regulation is incomplete, it is evident that multiple developmental and neuroendocrine pathways are involved, likely to facilitate adaptation to diverse environmental pressures on reproductive capacity.

Keywords: puberty, gonadotropin releasing hormone, sex hormones, genetics

5. Neuroplastin in normal brain physiology and disease

Katarina Ilić[1], Rodrigo-Herrera Molina[2], Kristina Mlinac Jerković[3], Goran Sedmak[3], Nataša Jovanov Milošević[3], Goran Šimić[3], Borna Puljko[3], Mario Stojanović[3], Ivana Rosenzweig[4], Svjetlana Kalanj Bognar[3]

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Transmembrane glycoprotein neuroplastin (Np) is a member of the immunoglobulin superfamily of cell adhesion molecules. In animal cells, two Np isoforms are produced by alternative splicing of the same gene: Np55 isoform is expressed in many different tissues while Np65 is brain-specific and abundant in synaptic membranes. Studying neuroplastin-deficient mice revealed variety of important physiological actions of neuroplastin, such as involvement of brain-specific Np65 in synaptic plasticity and associative memory formation. Interestingly, some of the phenotypic characteristics of neuroplastin-deficient mice include reduced life span, corticosterone elevation in blood, disregulation of the hypothalamic-pituitary axis and male infertility, indicating potential roles of Np65 in neuroendocrine homeostasis maintenance. Recent evidence suggests that effects of neuroplastins are associated with cellular calcium transport and homeostasis through the established structural interaction of Np with plasma membrane calcium ATPases. Also, it has been demonstrated that the specific lipid microenvironment influences greatly on the intramembrane position, distribution, and functions of neuroplastin in brain tissue. In this lecture, we will review the present knowledge about neuroplastins in animal tissues and elaborate in more details the involvement of Np65 in human brain (patho)physiology. We suggest that neuroplastin acts as a housekeeper of neuroplasticity and may be considered as one of the important cognition-related molecules in humans. Several potential routes for future investigations will be discussed, which might add to broader understanding of neuroplastin actions in animal tissues.

Keywords: neuroplasticity, neuroendocrine homeostasis, neurodevelopment, neurodegeneration

6. Impact of oxidation on SOD-1 aggregation and interaction with lipid membranes

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Amyotrophic lateral sclerosis (ALS) is an age-related neurodegenerative disease characterized by the progressive loss of motor neurons that control voluntary movement. Genetic studies revealed the involvement of superoxide dismutase 1 enzyme (SOD1) in the pathophysiology of the disease. Both wild-type and mutant forms of SOD1 can gain toxic function, which is reflected in their aggregation and cytotoxicity in ALS patients. However, it remains unclear how aging contributes to this toxic gain-of-function in SOD1. Since oxidative damage to proteins accumulates with age, in this study we investigated how oxidation contributes to SOD1 toxicity. Thus, we analyzed the impact of oxidation on SOD1 aggregation properties and cellular behaviour, with the focus on its interactions with the lipid membranes.

Keywords: ALS, SOD1, oxidation, protein carbonylation, aging

Friday, September 29th, 16:30

Brain health: public interest, assessment tools, effects of modifying lifestyle factors

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High prevalence and steadily increasing burden of neuropsychiatric disorders worldwide demand new and effective prevention strategies. Successful prevention hinges on early identification of individuals at high risk for development of a disorder, and on effective and accessible prevention measures. For many brain disorders, no disease modifying treatment is available, yet, so value of any predictive tools could be questioned. In some disorders, even those with a huge public health and economy impact, like dementia, scientific evidence points to the role of modifiable risk factors. These factors are promising targets for prevention strategies. We propose a symposium to tackle public awareness of brain health and the role of modifiable factors in brain health, public interest in brain health testing, recently developed tools for assessment of risk for certain brain disorders (dementia and stroke), and the recent progress in determining the effects of lifestyle modification on incidence and course of dementia.

Keywords: primary prevention, neuropsychiatric disorders

1. Public awareness and active care for brain health in Slovenia

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4 Public Opinion and Mass Communication Research Centre, Faculty of Social Sciencies, University of Ljubljana, Slovenia

The aim of our work has been to gain insight into Slovenian public interest and active engagement in care for brain health. We carried out online surveys in 2017 and 2022 with different samples of the adult population in Slovenia. The surveys revealed that the majority of the Slovenian public correctly recognised brain health as optimal brain functioning, and not a mere absence of an illness. In both surveys, a vast majority of respondents (> 84%) considered brain health to be important or very important for quality of life. Interestingly, large segments (39% in 2017 and 73% in 2022) considered their knowledge on maintaining brain health as sufficient relative to their needs. A majority of respondents denied having been diagnosed with a neurological or psychiatric disorder. More than half stated, however, that they have a close friend or a family member with such a diagnosis. Most respondents successfully identified science-based lifestyle choices that favor brain health, but struggled to adhere to the same choices in daily life. Women and older respondents were more actively engaged in maintaining brain health. Personal diagnosis or diagnoses of brain disorders among family members and friends were not associated with higher frequency of healthy practices. Key listed obstacles to engagement in healthy activities were lack of time (> 22%), motivation (> 19 %) and information (> 17%). Information was obtained primarily from television (> 38%), followed by newspapers and magazines, the internet, and conversations with people (friends and experts) in different proportions. Importantly, 38% of respondents struggled with the veracity of information sources. The highest-rated desired sources of information on brain and brain health were: direct communication by experts and formal education. Our findings can inform new strategies to improve public awareness and engagement, and design policies for improving active care for brain health in Slovenia.

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2. Public interest in brain health testing - Insights from the Global Brain Health Survey

Rebecca B. Carver[1], Nanna Alida Grit Fredheim[2], Athanasia Monika Mowinckel[3], Klaus P. Ebmeier[4], Barbara Bodorkos Friedman[3], Tor Atle Rosnes[5], Christian A. Drevon[6,7], Sana Suri[4,8], William F. C. Baaré[9], Eniko Zsoldos[4,8], Cristina Solé-Padullés[10], David Bartrés-Faz[10,11], Sandra Düzel[12], Kathrine Skak Madsen[9,13], Anders M. Fjell[3], Ulman Lindenberger[14,15], Kristine B. Walhovd[3], Isabelle Budin-Ljøsne[16]

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9 Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Amager and Hvidovre, Copenhagen, Denmark
10 Department of Medicine, Faculty of Medicine and Health Sciences & Institute of Neurosciences, University of Barcelona, Spain

11 Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
12 Center for Lifespan Psychology, Max Planck Institute for Human Development, Berlin, Germany
13 Radiography, Department of Technology, University College Copenhagen, Denmark
14 Center for Lifespan Psychology, Max Planck Institute for Human Development, Berlin, Germany
15 Max Planck UCL Centre for Computational Psychiatry and Ageing Research, Berlin, Germany
16 Department of Food Safety, Norwegian Institute of Public Health, Oslo, Norway

This study investigated people's interest in learning about personal brain health, understood as mental wellbeing and cognitive health in the absence of brain disorders. Through a cross-sectional multilanguage survey, respondents were asked to estimate their willingness and reasons to—or not to—undertake a hypothetical brain health test to learn about personal risk of developing a brain disease. The survey was open to the public between June 2019 and August 2020, and formed part of the Global Brain Health Survey, hosted by the Lifebrain project. In total, 27,590 people aged 18 years or older responded to the online survey. Respondents were largely recruited via European brain councils and research organizations, and were predominantly women (71%), middle-aged or older (>40 years; 83%), and highly educated (69%). Responses were analyzed to explore the relationship between demographic variables and responses. The study finds an overall high interest in brain health testing. Over 91% of respondents would definitely or probably take a brain health test and 86% would do so even if it gave information about a disease that cannot be treated or prevented. The main reason for taking a test was the ability to respond if one was found to be at risk of brain disease, such as changing lifestyle, seeking counseling or starting treatment. Higher interest in brain health testing was found in men, respondents with lower education levels and those with poor self-reported cognitive health.

3. Multi-dimensional McCance Brain Care Score - an accessible tool to maintain and improve brain health

Sanjula Dhillon Singh
McCance Center and Harvard Medical School, Boston, MA, USA

Dr. Sanjula Singh will introduce the McCance Center for Brain Health's mission and unveil the McCance Brain Care Score™, a novel, patient-informed tool that simplifies science-backed lifestyle choices to lower their risk of dementia, stroke, and late-life depression. Developed in collaboration with patients throughout the Harvard system, the McCance Brain Care Score™ empowers both patients and providers to proactively manage and enhance brain health.

Furthering the conversation around brain care, Dr. Singh will also touch on the REACH-ICH study, which represents an innovative initiative, focusing on the social determinants of health (SDOH) that influence participation in a state-of-the-art blood pressure program in intracerebral hemorrhage (ICH survivors from underrepresented communities throughout the US. The REACH-ICH study aims to assess if particular modifiable SDOH are associated with (i) vascular cognitive impairment and dementia and recurrent stroke (ii) increased blood pressure, and (iii) patient engagement in a blood pressure program, after a primary ICH – in order to test interventions targeting those specific SDOH.

The integration of the McCance Brain Care Score™ and the findings from the REACH-ICH study are expected to reshape perceptions of brain care and contribute significantly to reducing the incidence of stroke, dementia and late-life depression for populations across the globe.

4. Validation of the LIBRA Index in assessing modifiable risk factors and helping identify people who could benefit from primary prevention interventions

Stephanie J. B. Vos
Maastricht University, Maastricht, The Netherlands

Alzheimer's disease can already be identified at early disease stages using biomarkers in cerebrospinal fluid or on brain PET scans. These biomarkers can predict cognitive decline. In midlife and later life also lifestyle and vascular problems play a role in brain health. For instance, it is known that physical activity, smoking and diabetes can influence brain health and cognition. However, it remains unclear how lifestyle and vascular problems are related to Alzheimer's disease and how these processes influence each other. Dr. Stephanie Vos will address in her presentation the association of Alzheimer's disease with lifestyle and vascular problems. More specifically, she will show findings on the relation of individual lifestyle factors and an overall lifestyle for brain health (LIBRA) index with Alzheimer's disease biomarkers and cognitive decline. In addition, she will highlight findings regarding the association of diabetes with Alzheimer's disease biomarkers and cognitive decline.

Keywords: dementia, biomarkers, diabetes, vascular health

5. Can a city prevent dementia?

Jeremy D. Isaacs
St George's University Hospitals NHS Foundation Trust, St George's University of London
NHS England London Dementia Clinical Network, London, United Kingdom

Individual risk of developing dementia is falling in the global North. However, due to demographic ageing, the overall number of people living with dementia is predicted to increase significantly; by 42% in London between 2019 and 2030. We are not powerless in the face of this change. The Lancet Commission identified 12 modifiable risk factors which if optimally addressed could prevent or delay up to 40% of dementia cases. In London we have started to formulate a comprehensive dementia prevention plan based on these 12 risk factors. The first step was a scoping exercise to identify existing health programmes that are addressing these factors even if dementia is not explicitly mentioned. The next step will require co-ordination between multiple agencies and system leadership. Air quality is a current area of contention because of the introduction of a road pricing system targeting the most polluting vehicles. However, air quality in London has improved significantly in response to such policies and it is likely that this has already prevented or delayed dementia in thousands of people. I will contrast these population-level interventions with individualised solutions such as the FINGER study and "brain health clinics" and propose that the latter approaches are less likely to be effective or scalable or produce equitable health outcomes.

Saturday, September 30th, 14:00

Novel approaches in treatment of depression with transcranial magnetic stimulation

Jurij Bon[1,2], Grega Repovš[3]

1 University Psychiatric Clinic Ljubljana, Slovenia
2 Department of Psychiatry, Faculty of Medicine, University of Ljubljana, Slovenia
3 Department of Psychology, Faculty of Arts, University of Ljubljana, Slovenia

Symposium will present novel approaches in the treatment of depression with transcranial magnetic stimulation of the brain. We will show how the field is moving towards individualized treatment plans in patients, where stimulation targets are selected based on their specific resting state brain network activity. The general usability of resting state brain network activity for clinical applications will be discussed and local work presented that aims to generate usable and robust treatment protocols. We will also discuss recent improvements in accelerated theta burst stimulation and individually localized deep TMS stimulation.

Keywords: TMS, neuronavigation, depression

1. Advances in the use of resting state data for clinical application

Grega Repovš
Department of Psychology, Faculty of Arts, University of Ljubljana, Slovenia

The ease of acquisition and the wealth of information embedded in resting-state functional connectivity have driven its use in recent decades, bringing it to the forefront of neuroimaging research. As it requires no cognitive engagement on the part of the subject, it has had a particularly profound impact on both basic and applied clinical research. This introductory talk will provide a brief introduction to the use of resting-state data, methods of data analysis, and examples of empirical findings. It will outline its potential, when combined with Research Domain Criteria approach to psychopathlogy, for targeted therapy development and validation, and personalised treatment. Finally, it will highlight some of the challenges and possible future developments in the use of resting-state data for basic research and clinical applications.

2. Development of treatment protocols and methodological procedures for resting state networks based neuronavigation

Nina Purg, Andraž Matkovič
Department of Psychology, Faculty of Arts, University of Ljubljana, Slovenia

Transcranial magnetic stimulation (TMS) has emerged as a promising therapeutic approach for psychiatric disorders, but achieving optimal outcomes necessitates precise targeting of specific brain regions. The general assumption is that the optimal TMS target varies from person to person due to individual differences in the structure and function of the brain. We provide an overview of the most prominent methods employed to determine personalized target locations for TMS treatment in psychiatric disorders. Techniques such as neuronavigation based on structural and functional neuroimaging approaches will be discussed. Additionally, advancements in the understanding of the role of resting-state networks in psychiatric disorders are explored as potential avenues for enhancing target localization. The integration of these methods offers the potential to tailor TMS treatment to individual patients, ultimately improving the efficacy and therapeutic impact of TMS in the realm of psychiatric disorders.

3. Accelerated and neuronavigated TMS therapy of depression

Jurij Bon
University Psychiatric Clinic Ljubljana, Slovenia
Department of Psychiatry, Faculty of Medicine, University of Ljubljana, Slovenia

The Slovenian national guidelines for the treatment of depression have recently been updated. Treatment of drug-resistant depression now includes non-invasive methods of brain stimulation. Newer forms of depression treatment are difficult to introduce as publicly funded health services in Slovenia, in part because it is difficult to objectively measure the success of depression treatment. On the other hand, Slovenian health authorities are aware of the importance of introducing new treatments given the high social burden of depression. Recent TMS treatment protocols for depression, such as the neuronavigated and accelerated theta burst protocol, show the possibility of a significant breakthrough in the clinical effectiveness of non-invasive brain stimulation. I will present current developments in this field and our own clinical experience with TMS treatment of depression at University Psychiatric Clinic Ljubljana.

4. Electroencephalograhy for early prediction of TMS treatment success

Aleš Oblak
University Psychiatric Clinic Ljubljana, Slovenia

TMS has proven to be an efficient clinical intervention for treatment-resistant depression. However, depending on the study, only 50-75% patients respond to TMS treatment. TMS treatment protocols are time consuming, lasting in the order of a couple of weeks, and can thus represent an additional burden for the patients if unsuccessful. It is therefore imperative to discern early biomarkers that could predict treatment outcome. We discuss some behavioral and EEG biomarkers that may serve as potential candidates. We focus particularly on the role of anhedonia, dysphoria, cognition, and rumination as potential modifiers of treatment outcomes. Finally, we focus on alpha and theta EEG bands, which have been previously shown to be predictive of TMS outcome. We discuss theta cordance, an approximation of cerebral perfusion as a golden-standard biomarker.

Saturday, September 30th, 16:30

Biology of schizoaffective contiuum

Milica Velimirović Bogosavljević

School of Medicine, University of Belgrade, Serbia

Schizoaffective contiuum is a group of mental health condition that includes mental disorders ranging from schizophrenia to mood disorders such as bipolar disorder or even depression. It is characterized by wide range of signs and symptoms that makes the targeted diagnostics often challenging. Mental disorders pertaining to the schizoaffective contiuum disorders usually become evident in adolescence or young adulthood with variety of difficulties including psychotic and/or affetctive symptoms, cognitive impairment or even metabolic changes. People with these disorders can have higher risk of substance abuse problems and suicide than the general population.

The exact pathophysiology responsible for overlap of symptoms or specific differences among the disorders pertaining to schizoaffective contiuum is currently unknown. The potential causes may be laying in genetics, abnormalities of neurotransmitters (dopamine, norepinephrine, and serotonin), and disorders of white matter in multiple areas of the brain, reduced hippocampal volumes and distinct deformations in the medial and lateral thalamic regions. Moreover, due to overlap of symptoms between the disorders the analysis of neurobiological underpinnings of the disorders is of additional importance. However, the exact causes of disorders of schizoaffective continuum are still a matter of study.

Since the treatment of these disorders is of great importance for their course, staging and quality of life of the patients it is necessary to focus on novel diagbistic and treatment strategies in order provide timely and adequate treatment, prevent neurodegeneration and foster neuroprotection.

Keywords: schizoaffective, dementia, bipolar, schizophrenia, mental health

1. Redox dysregulation in schizoaffective disorders continuum

Tihomir Stojković, Milica Velimirović, Tatjana Nikolić, Nataša Petronijević
Institute of Clinical and Medical Biochemistry, School of Medicine, University of Belgrade, Serbia

The neurobiological exploration of schizoaffective disorder mainly relies on data from the studies of schizophrenia and psychotic mood disorders (bipolar disorder and depression), due to similar clinical features and presumed similar etiology and pathological mechanisms of these diseases. Converging evidence indicates that redox dysregulation plays an important role in the development of psychosis. Redox dysregulation is the alteration of the physiological balance in the production and elimination of reactive oxygen (ROS) and nitrogen (RNS) species that impair the cellular redox state and can even lead to oxidative damage of macromolecules, including lipids, proteins and nucleic acids. The brain is particularly susceptible to oxidative damage due to its high demand for oxygen and relatively low levels of antioxidative defenses. Redox dysregulation can be caused by a variety of genetic and environmental factors. Results from clinical research and animal model studies, including the phencyclidine (PCP) model of glutamatergic NMDA receptor hypofunction, have shown reduced levels of the antioxidant glutathione in certain brain regions, including medial prefrontal cortex, striatum and thalamus. There is evidence that this is associated with the reduction of GABAergic interneurons, white matter abnormalities and microglial activations, all of which are implicated in the pathogenesis of schizophrenia spectrum disorders. In addition, abnormal function of the NADPH oxidase family of enzymes that normally produces ROS may contribute to the disease. These and other redox-related molecular species should be further investigated to elucidate their role as potential biological markers to improve the diagnosis of schizoaffective and other schizophrenia spectrum disorders but also as new therapeutic targets for future treatment strategies.

Keywords: schizophrenia spectrum disorders, psychosis, redox state, glutathione, NADPH oxidase

2. Underlying inflammation in Schizoaffective disorders continuum

Milica Velimirović[1], Maja Pantović Stefanović[2], Bojana Dunjić Kostić[2], Tihomir Stojković[1], Tatjana Nikolić[1], Milica Živković[1], Nataša Petronijević[1]

1 Institute of Clinical and Medical Biochemistry, School of Medicine, University of Belgrade, Serbia
2 Clinic for Psychiatry, Clinical Centre of Serbia, Belgrade, Serbia

There is an increasing interest in the role of inflammation in the pathophysiology of various mental health disorders. Inflammation involves the activation of the immune system in response to various stressors, infections, or other factors. In some cases, excessive or chronic inflammation may contribute to changes in brain function and structure, potentially contributing to the development or progression of mental disorders. Pro-inflammatory cytokines, such as C reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and others are often altered during inflammatory responses. These cytokines can cross the blood-brain barrier and affect brain function through activation of the hypothalamic-pituitary-adrenal (HPA) axis, induction of oxidative stress, interference with neurotransmitter systems, affecting mood, cognition, damaging neurons, impairing neural circuits and provoking psychosis. Findings suggest that mentioned cytokines could potentially serve as early indicators of psychiatric disorders offering insights into the risk of developing a broad spectrum of symptoms, ranging from affective temperaments to full blown disorders. Also these molecules could serve as indicators of immune system involvement in both affective and psychotic disorders reflecting the progression and offer insights into potential immune-related mechanisms underlying these disorders. Further, they may be potential indicators of association between inflammation, disease activity and symptom severity. Additionally, specific cytokine patterns may be associated with different, clinical subtypes (endophenotypes) of major disorders of schizoaffective continuum. These markers could offer insights into the immunomodulatory aspects of medication and could potentially inform treatment strategies. However, the exact nature of inflammation and psychiatric disorders relationship is complex and still not fully understood, nonetheless it did draw the attention on developing novel treatment strategies.

Keywords: schizoaffective disorders continuum, inflammation, cytokines, CNS

3. Bipolar spectrum disorders - neurobiology and treatment

Maja Pantović Stefanović[1,2], Marta Gostiljac[1], Emilija Erić[1], Bojana Dunjić Kostić[1,2], Milica Velimirović[2,3]

1 Clinic for Psychiatry, University Clinical Center of Serbia, Belgrade, Serbia
2 School of Medicine, University of Belgrade, Serbia
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A continuum-based approach to psychopathology of mood disorders, embedded into a prospective long-term follow-up is a new paradigm of multidimensional patient assessment throughout their clinical journey. Novel diagnostic guidelines and contemporary view of affective disorders allows more focus on dimensional approach and staging of bipolar disorders. Bipolar disorders are now perceived to exist on a continuum of wide range of symptoms varying in their duration, severity, and pattern of appearance, often resulting in the delay of treatment and poor prognosis. Their biological underpinning is complex, involving multiple systems and external factors shaping the clinical presentation, course of illness and response to treatment. Moreover, the interplay of inherent and environmental factors can be responsible for the specific relationship of these disorders with other diseases, but primarily for their longitudinal development. The assessment of biological markers involved in both neurodegenerative, but also neuroprotective processes is of vital importance in evaluating the course of the disorders and particularly treatment response. Early detection of the disease and timely and continuous treatment can significantly help to strengthen neuroprotection and lead to a better course of bipolar disorders.

Keywords: bipolar disorders, treatment, biomarkers, continuum, stagin

4. The price of becoming human: schizophrenia in the light of evolutionary neuroscience

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School of Medicine, University of Belgrade, Serbia

Schizophrenia is a debilitating and chronic psychiatric disorder. The etiology of schizophrenia is still poorly understood. Moreover, schizophrenia presents an intriguing evolutionary paradox – even though it is heritable and decreases fecundity, it is still maintained in the population at a disproportionally high rate. Several different theories aim to explain this paradox. For instance, some authors suggest that schizophrenia is the "price" mankind pays for human-specific faculties (such as language). According to others, certain schizophrenia risk variants may have benefits patients or their relatives (e.g., creativity). Recent advances in comparative genomics (especially comparisons of the human genome and the genomes of related species, such as chimpanzees and extinct hominids), neuroimaging, and neuropsychology have finally put long standing evolutionary theories of schizophrenia to the test and here I present some of the most outstanding findings. The exploration of evolutionary background of schizophrenia is important not only to better understand the etiology of the disorder, but to also uncover the fundamental processes of becoming human.

Keywords: psychosis, natural selection, cognition, adaptation

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CEL.01 Friday, September 29th, 13:00 [Cellular Neuroscience A]

FUS phosphorylation in FTLD

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Nuclear to cytoplasmic mislocalization and aggregation of RNA-binding proteins (RBPs), including Fused in sarcoma (FUS), are the main neuropathological features of amyotrophic lateral sclerosis (ALS) and frontotemporal lobular degeneration (FTLD). In ALS-FUS these aggregates arise from disease-associated mutations in FUS, whereas in FTLD-FUS the cytoplasmic inclusions do not contain mutant FUS, suggesting different molecular mechanisms of FUS pathogenesis. We have shown that phosphorylation of the C-terminal Tyr526 of FUS results in increased cytoplasmic retention of FUS due to impaired binding to Transportin 1. Here we developed a novel antibody against the C-terminally phosphorylated Tyr526 FUS (FUSp-Y526) that is specifically capable of recognizing phosphorylated cytoplasmic FUS, which is poorly recognized by commercially available FUS antibodies. Using this FUSp-Y526 antibody, we demonstrated a FUS phosphorylation-specific effect on the cytoplasmic distribution of soluble and insoluble FUSp-Y526 in various cells. We found that FUSp-Y526 expression pattern corelates with active pSrc/pAbl kinases in specific brain regions of mice, indicating preferential involvement of cAbl in the cytoplasmic mislocalization of FUSp-Y526 in cortical neurons. Finally, altered cytoplasmic distribution of FUSp-Y526 was observed in cortical neurons of post-mortem frontal cortex tissue from FTLD patients compared with controls. Given the overlapping patterns of cAbl activity and FUSp-Y526 distribution in cortical neurons, and cAbl induced sequestration of FUSp-Y526 into G3BP1 positive granules in stressed cells, we propose that cAbl kinase is actively involved in mediating cytoplasmic mislocalization and promoting toxic aggregation of wild-type FUS in the brains of FTLD patients, as a novel putative underlying mechanism of FTLD-FUS pathophysiology.

Keywords: FUS, phosphorylation, dementia

CEL.03 Friday, September 29th, 13:00 [Cellular Neuroscience A]

Expression patterns of secretory pathway kinase FAM20C and its regulator FAM20A vary with differentiation stage in cultured skeletal muscle cells

Katja Fink, Katarina Miš, Marjeta Milostnik, Sergej Pirkmajer

Laboratory for Molecular Neurobiology, Institute of Pathophysiology, Faculty of Medicine, University of Ljubljana, Slovenia

Skeletal muscle cells share more common ground with motor neurons than just the neuromuscular junction. They are, like neurons, electrically excitable and secretory cells. While motor neurons signal to muscle via acetylcholine and agrin, muscle secretes neurotrophic factors and myokines that signal back to motor neurons as well as the brain. Myokines, such as interleukin-6 (IL-6), whose secretion is driven by skeletal muscle contractions are thought to provide an important link between regular physical activity and its beneficial effects on the nervous system. The majority of extracellular proteins, including IL-6, which plays an important role in myogenesis, muscle regeneration, inflammation and metabolism, are thought to be phosphorylated by FAM20C kinase. However, its function in skeletal muscle and neurons has not been characterized.

Using primary human skeletal muscle cells, we investigated the expression of FAM20C and FAM20A, a pseudokinase and an allosteric activator of FAM20C, during proliferation of myoblasts and their differentiation into multinucleated myotubes. FAM20A showed increased expression in differentiated myotubes, while FAM20C expression declined during differentiation. Gene silencing of FAM20A expression moderately increased the expression of IL-6, its receptors (IL-6Rα and gp130), and the phosphorylation of its downstream effector STAT3, while gene silencing of FAM20C had no effect.
These findings suggest that FAM20C and FAM20A expression depends on the differentiation stage of skeletal muscle cells, potentially affecting IL-6 signalling and the extracellular phosphoproteome during myogenesis. Elucidation of the interplay between FAM20C and IL-6 may provide valuable insights into the complex communication between skeletal muscle and the nervous system.

Keywords: FAM20C, skeletal muscle cell, IL-6, physical activity, gene expression

CEL.05 Friday, September 29th, 13:00 [Cellular Neuroscience A]

Innervation of cultured human myotubes by α-motor neurons has divergent and time-dependent effects on the mRNA expression of Na^+,K^+-ATPase and myokines

Vid Jan[1], Katarina Miš[1], Natasa Nikolic[2], Klemen Dolinar[1], Metka Petrič[1], Andraž Bone[1], G. Hege Thoresen[2,3], Arild C. Rustan[2], Tomaž Marš[1], Alexander V. Chibalin[4,5], Sergej Pirkmajer[1]

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Na^+,K^+-ATPase (NKA), a heterodimeric (α/β) ion pump and P-type ATPase, maintains transmembrane ion gradients and is essential for skeletal muscle excitability and contractility. Under in vivo conditions, denervation reduces the abundance of NKA in skeletal muscle, while subsequent reinnervation increases it. Cultured human myotubes,

a widely used experimental model to study human skeletal muscle in vitro, typically do not contract spontaneously unless innervated by α-motor neurons. Using the co-culture of primary human myotubes and embryonic rat spinal cord explants, we determined whether innervation by α-motor neurons modulated mRNA levels of NKA subunits (α and β). In addition, we determined the effect of innervation on mRNA levels of muscle-derived cytokines (myokines), whose expression in vivo is also regulated by contractions. Innervated myotubes, which started to contract 7-10 days after establishment of co-culture, had higher mRNA levels of myokines, such as IL-6, IL-7, IL-8, and IL-15, after 10-11 days of co-culture. In contrast, the mRNA levels of NKA subunits and myokines, such as musclin, cathepsin B, meteorin-like protein, or SPARC, remained similar between the innervated and non-innervated cultures. In 21-day-old co-cultures the mRNA levels of NKA subunits and myokines did not differ from those in non-innervated cultures. The NKA mRNA levels were not affected by neuromuscular blocking agents α-bungarotoxin or tubocurarine. Taken together, this study shows that in vitro innervation of human myotubes exerts divergent, time-dependent effects on the expression of NKA subunits and myokines. Importantly, NKA expression in cultured myotubes seems to be independent of innervation, which suggests that the expression pattern of NKA subunits is determined by an intrinsic myogenic program.

Keywords: innervation, myotubes, Na^+,K^+-ATPase

CEL.07 Friday, September 29th, 13:00 [Cellular Neuroscience A]

Remote post-conditioning reduced inflammation markers and infarct size after focal ischemia associated with hyper-inflammatory reaction (simulation of COVID-19)

Jana Končeková, Miroslav Gottlieb, Klaudia Kotorová, Petra Bonová

Institute of Neurobiology, Biomedical Research Center, Slovak Academy of Sciences, Košice, Slovak Republic

Statistical prognoses for stroke are changing worldwide after SARS-CoV-2 pandemic. Infection-induced release of pro-inflammatory cytokines and abnormal levels of coagulation factors are cause of thrombus formation. The only one treatment in a clinic (tPA) has many limitations in these patients. The increased demand for developing novel non-pharmacological therapies to elevate the tolerance to ischemia has been paying attention. Remote ischemic conditioning (RIPC) meets these conditions because of the ability to stimulate the endogenous protective mechanisms ensuring resistance to stroke.

COVID-19 was simulated by lipopolysaccharide (LPS) intratracheal administration. We induced focal ischemia after one day of LPS administration (development of hyper-inflammatory reaction). RIPC was applied after one hour of reperfusion in the form of hind limb ischemia. Efficiency of RIPC was evaluated by infarct size determination using TTC staining. Moreover, we investigated effect of this therapy on sedimentation rate and hematocrit.

Our results confirmed neuroprotective potential of RIPC even in rats with hyper-inflammatory reaction. We observed reduced infarct size about 50% in RIPC treated animals, compared to non-treated. Moreover, RIPC affect the inflammatory markers associated with LPS administration and ischemia induction. We observed lower hematocrit level about 30% after 3 hours of reperfusion in non-treated rats and two-fold increase in sedimentation rate. Animals with RIPC induction have hematocrit level in normal range, as well as sedimentation rate. On the base of our results, we assumed that RIPC should influence inflammation, what predispose this approach as treatment and possible prevention of COVID-19 positive patients.

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Keywords: Remote conditioning, Stroke, COVID-19, inflammation

CEL.09 Friday, September 29th, 13:00 [Cellular Neuroscience A]

The role of tenascin-C on the structural plasticity of perineuronal nets and synaptic expression in the hippocampus

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2 Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA, USA
3 Institut für Anatomie und Klinische Morphologie, Universität Witten/Herdecke, Witten, Germany

Neuronal plasticity is a fundamental property of a nervous system that allows its change in response to the stimulus by reorganizing structure, functions, and connections. Among the main regulators of neuronal plasticity are perineuronal nets (PNNs), condensed forms of extracellular matrix (ECM) that enwraps mostly parvalbumin (PV+) expressing inhibitory interneurons. Next, a member of a family of ECM glycoproteins, protein tenascin-C (TnC) was demonstrated to modulate synaptic plasticity in the hippocampus. This study aims to show if TnC deficiency affects the number, intensity, and ultrastructure of PNNs around PV+ and PV- cells and the expression of inhibitory and excitatory synaptic markers in the hippocampus. To enhance neuronal plasticity, TnC-deficient (TnC -/-) and wild-type mice were reared in an enriched environment (EE), and control standard environment (SE) for 8 weeks and 4 weeks. Results have shown that TnC deficiency caused regional-specific changes in PNNs expression and ultrastructure, as well as the expression of synaptic markers.

Keywords: neuronal plasticity, perineuronal nets, tenascin-C

CEL.11 Friday, September 29th, 13:00 [Cellular Neuroscience A]

Effects of elevated extracellular K^+ on astrocyte metabolism and morphology

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Neurons are highly specialized cells in the brain that transmit information by electrical impulses (action potentials), which requires a lot of energy. Astrocytes, homeostatic neuroglial cells, can sense the increased neuronal activity and energy demand via released neurotransmitters (e.g., glutamate, noradrenaline, ATP). They begin to degrade glucose to lactate, which is considered to be delivered to neurons as energy fuel. This is crucial for learning and memory formation. Increased neuronal activity is accompanied with an extracellular rise in K^+, which is released from neurons. Here, we investigated in rat cortical astrocytes (in vitro) and in astrocytes in Drosophila brains (ex vivo) by using fluorescent sensors (Fluo-4 AM dye and GcaMP (Ca^{2+}), Epac1-camps (cAMP), FLII12Pglu-700μδ6 (D-glucose), Laconic (L-lactate)) and real-time confocal microscopy how rise in extracellular K^+ concentration ($[K^+]$out) affects intracellular glucose and lactate levels and Ca^{2+} and cAMP signals. The latter have previously been linked to the regulation of astrocytic lactate production. Elevated $[K^+]$out (physiological (15 mM) and pathological (50 mM) $[K^+]$out (epilepsy, migraine, brain injury)) increased intracellular Ca^{2+}, cAMP, D-glucose and L-lactate levels in cortical astrocytes. This indicates that K^+ is an important regulator of astrocytic metabolism during increased neuronal activity and may contribute to astroglial metabolic support of neurons by L-lactate. Because astrocytes swell in response to increased $[K^+]$out, we also measured morphological changes in astrocytes. Elevated $[K^+]$out resulted not only in astrocytic volume increase (15%), but also in processes length increase (40%), which may affect the diffusion of molecules, including metabolites, in the extracellular space and neurotransmission.

CEL.02 Saturday, September 30th, 13:00 [Cellular Neuroscience B]

Impaired octopamine-mediated calcium signaling and glucose metabolism in Drosophila aging brain

Urška Černe[1], Anemari Horvat[1,2], Nika Kozoderc[1], Anne-Kristin Dahse[3], Robert Zorec[1,2], Nicole Scholz[3], Nina Vardjan[1,2]

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Age-related decline in brain glucose utilization may be due to malfunction of the noradrenergic system, which controls the brain metabolism. This may contribute to the age-related cognitive decline. Noradrenaline release from the noradrenergic neurons triggers in astrocytes, neuroglial cell, intracellular Ca^{2+} and cAMP signals, facilitating glucose uptake, glycogen degradation and aerobic glycolysis with the end-product lactate. During increased brain activity, lactate is shuttled from astrocytes to neurons to serve as a fuel. Whether noradrenergic regulation of brain cell metabolism is impaired in aged brains and contributes to cognitive decline is poorly understood.

We expressed fluorescent sensors for Ca^{2+}, cAMP, glucose and lactate in brain cells in young and aged Drosophila brains to measure changes of intracellular second messengers and metabolites upon octopamine stimulation (an invertebrate analogue of noradrenaline). Octopamine triggered Ca^{2+} signals in neurons and glial cells in young, but not aged brains. Octopamine triggered intracellular cAMP signal and lactate increases only in neurons, indicating that cAMP-mediated aerobic glycolysis occurs primarily in neurons. The latter were not affected by aging. Octopamine increased cytosolic glucose levels (glucose uptake) only in astrocytes, which was absent in aged brains. When exposed to elevated glucose or lactate levels, both neurons and glial cells were able to uptake nutrients, although in neurons the glucose uptake was reduced in aged brains.

Our results suggest impaired octopaminergic Ca^{2+} signaling in brain cells and glucose uptake in astrocytes and reduced glucose delivery to neurons in aged Drosophila brains, which may contribute to the age-related cognitive deficits.

Keywords: glial cells, neurons, Drosophila, cell signaling, metabolism

CEL.04 Saturday, September 30th, 13:00 [Cellular Neuroscience B]

Astroglial P2X7R and Cx-43 expression pattern in the vicinity of autoreactive immune cells in EAE model

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Multiple sclerosis (MS) is a neuroinflammatory disorder of the central nervous system (CNS) characterized by immune cell infiltration, glial cell activation, demyelination, and neuronal loss. Astrocytic interaction with CNS-infiltrated immune cells (CNS-IICs) is an important contributor to the pathology of MS. In our previous study on experimental autoimmune encephalomyelitis (EAE) model of MS, we showed that CNS-IICs induce hemichannel-dependent ATP release and subsequent P2X7 receptor P2X7R-mediated cytosolic Ca^{2+} increase in astrocytes in an in vitro experimental setup. The aim of this study was to further investigate the coupling of astrocytic connexin-43 (Cx-43) and P2X7R in EAE. Thus, we combined Western blot and immunohistochemistry to examine the P2X7R and Cx-43 protein expression in EAE and their expression pattern on astrocytes in the vicinity of CNS-IICs. We found that P2X7R protein expression is decreased in the spinal cords of both EAE males and females, while the expression of Cx-43 remains undisturbed. Furthermore, colocalization analysis of immunolabeled P2X7R and Cx-43 demonstrated decreased co-occurrence of these two proteins in EAE. However, distribution analysis showed that P2X7R signal intensity and its colocalization with astrocytic Cx-43 is increased at the border surface of CD4+ CNS-IIC. By defining determinants of direct astrocyte-immune cell interaction in the pathology of EAE, our findings move forward our understanding of the CNS-immune system communication in MS.

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Keywords: astrocyte, immune cell, P2X7 receptor, connexin-43

CEL.06 Saturday, September 30th, 13:00 [Cellular Neuroscience B]

Neurotoxicity of cumyl-PINACA synthetic cannabinoid: involvement of multiple cannabinoid receptors

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Synthetic cannabinoids, as potent recreational drugs, interfere with the endocannabinoid system in the brain and can cause severe mental and behavioral consequences. Cumyl-PINACA or SGT-24 is a synthetic agonist designed to bind cannabinoid receptor 1 (CB1) with very high affinity, but the molecular mechanisms underlying its central toxic effects are poorly understood.

Here, we elucidated the response of rat cortical neurons and astrocytes to SGT-24 at nanomolar concentrations (0.1 - 1000 nM). The effect of SGT-24 was dose- and time-dependent and cell-specific. In neurons, 10 nM SGT-24 caused immediate dysregulation of mitochondrial membrane potential (ΔΨm), ATP depletion and activation of caspases, resulting in early apoptotic cell death with reduction and shortening of dendrites, cell shrinkage and chromatin condensation. The reduction in neuronal viability and the initiation of apoptotic processes were prevented by selective antagonists of the CB1 and cannabinoid-like receptors peroxisome proliferator-activator receptor gama (PPAR-γ) and transient receptor potential cation channel subfamily V member 1 (TrpV1). In astrocytes, SGT-24 was effective at 10-fold higher concentrations (100 nM) and induced a progressive dysregulation of ΔΨm and ATP depletion by activation of caspases and leakage of lactate dehydrogenase, leading to early apoptosis and subsequent necroptosis. CB1 and PPAR-γ antagonists protected astrocyte viability and prevented death of these cells.

SGT-24 is neurotoxic on acute exposure of neural brain cells and acts on both cannabinoid and non-cannabinoid receptors. A better understanding of the complexity of the action of synthetic cannabinoids would contribute to the development of multi-target treatment of intoxication.

Keywords: cumyl-PINACA, astrocytes, neurons, neurotoxicity, receptors

CEL.08 Saturday, September 30th, 13:00 [Cellular Neuroscience B]

The role of glial potassium channel in Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease caused by the death of motor neurons in the spinal cord and the brain. Glial cells surrounding motor neurons are strongly implicated in the ALS onset and progression. They play an important role in the maintenance of K^+ homeostasis through inwardly rectifying potassium channel Kir4.1. By using SOD1G93A rat model of ALS, we here demonstrate a reduced expression of oligodendrocyte Kir4.1 channel in the spinal cord and more specifically in the myelin fraction isolated from ALS spinal cord. Moreover, we show that the alteration in the Kir4.1 expression was associated with impaired membrane properties and a lower Kir current density in the SOD1G93A oligodendrocytes in culture. Although the overall expression of Kir4.1 was reduced in ALS spinal cord, we could observe isolated regions, Kir4.1+ clusters, displaying pronounced Kir4.1 immunoreactivity in SOD1G93A ventral horns. Interestingly, Kir4.1+ clusters were enriched in the presence of Iba1+ microglial cells. Our data show that Kir4.1+/Iba1+ clusters are formed at the sites of prominent aggregation of mutant SOD1 (mSOD1) suggesting the presence of degenerating motor neurons within Kir4.1+/Iba1+ clusters. Collectively, our findings on Kir4.1 provide the evidence of a compromised K^+ homeostasis in ALS and point out biomarker properties of this potassium channel.

Keywords: oligodendrocytes, microglia, Kir4.1, ALS

CEL.10 Saturday, September 30th, 13:00 [Cellular Neuroscience B]

Transcriptomic screen of MASC-derived neurons from Niemann Pick C patients, reveals a feedback loop mechanism between TDP-43 and two novel TDP-43 potential second modifiers: ITPR1, and EPDR1

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Niemann-Pick disease is an autosomal recessive disorder due to NCP1

(95%) and NPC2 (5%) gene mutations. It is characterized by cholesterol abnormal accumulation with visceral and neurological symptoms, especially cerebellar ataxia. The visceral signs can be explained by a defect in LDL-lysosomal pathway, while the molecular mechanisms causing neurodegeneration in NPC are unknown. In 2016, TDP-43 potential involvement was tested to explain the NPC neurological symptom. TDP-43 is a well-known RNA binding protein that plays an important role in many neurodegenerative disorders, like Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. Also in different NPC disease models, TDP-43 was described to be shuttled from the nucleus to the cytosol, and to be hyperphosphorylated. The aim of this work is to characterize TDP-43 disfunctions in NPC disease by studying potential second modifiers derived from a transcriptomic analysis of MASC-derived neurons from NPC patients. By this analysis, two potential modifiers have been described to modulate TDP-43 phenotype, such as ITPR1 and EPDR1. These two genes establish a feedback loop by which TDP-43 loss of function will lead to their downregulation, and when this misregulation occurs, it impairs TDP-43 pathological phenotype, especially related to its subcellular localization and phosphorylation. In this work, we studied in parallel the mechanism by which TDP-43 loss is driving to ITPR1 and EPDR1 downregulation, focusing on the presence of long introns in both genes. In addition, we evaluated how ITPR1 and EPDR1 downregulation was affecting TDP-43 pathological phenotype, involving the Calcium metabolism.

Keywords: TDP-43, NPC, ITPR1, EPDR1

CLIN.01 Friday, September 29th, 13:00 [Clinical Neuroscience A]

Nucleus accumbens valence processing during offset analgesia

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Pain is not a static function of a noxious stimulus. Instead, it is a time-evolving experience with a complex history dependence. This is especially apparent in offset analgesia, a pain psychophysical phenomenon characterized by disproportionately large decreases in pain following a small decrease in the intensity of a noxious stimulus. Efforts to understand the circuits governing offset analgesia have ruled out the roles of opioidergic (e.g., descending inhibition) and NMDAergic (e.g., diffuse noxious inhibitory control) circuits. This work examines the novel hypothesis that offset analgesia arises from mesolimbic dopamine circuits. We combined psychophysics, modeling, and functional magnetic resonance imaging (fMRI) to study how dopamine circuit dynamics (nucleus accumbens, NAc) relate to offset analgesia.

We collected fMRI brain scans on 14 participants while applying offset analgesia stimulus trains to their volar forearms. We then fit a circuit-based model, which we call the "mesolimbic valence competition model", to the participants' pain ratings. Our model consists of two latent competing states—reward and aversion, each representing the firing of a distinct subpopulation of dopamine neurons. By assuming that aversion is necessary for pain, our model captures offset analgesia's salient dynamics: Decreasing nociception activates rewarding dopamine neurons, which silence aversive neurons to promote analgesia. We then used the latent reward and aversion time series in a voxelwise general linear model of NAc activity. Our preliminary results provide a concrete mechanistic hypothesis and complementary neuroimaging evidence of how positive and negative valence-related NAc activity may interact to produce complex pain dynamics.

CLIN.02 Saturday, September 30th, 13:00 [Clinical Neuroscience B]

Challenging the search for neuromarkers of mental disorders

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Over the past two decades, researchers have been actively investigating ways to objectively diagnose mental health conditions using biomarkers based on neural activity (for here on: neuromarkers). Despite some occasionally report high predictive accuracy, neuromarkers have yet to demonstrate their clinical usefulness. While the lack of success can be attributed to various methodological challenges (including low statistical power and selective reporting, which have resulted in a lack of reproducibility in this field of research), this study focuses on the theoretical issues with neuromarkers.

The present study challenges the prevailing notion of biological reductionism, which underlies the conviction that objective neuromarkers are both feasible and desirable. One of the challenges to this notion is multiple realizability, proposing that mental states can be realized through various different physical states. Further, the study explores emergence, according to which mental states arise from the interactions of the individual parts, rather than the parts themselves. Additionally, we explore the influence of general and immediate environmental factors on the identification of these neuromarkers.

To illustrate the implications of these notions, we simulated data and trained classifiers to shed light on how these concerns impact the accuracy of neuromarkers. An important part of the research was the operationalization of the issues and conceptualization of the models. This process demonstrates a method for translating and comparing theoretical models in neuromarker research. The findings emphasize the importance of critically evaluating the plausibility of neuromarkers and identifying the factors that limit their predictive power.

Keywords: diagnostics, biomarkers, multiple realizability, emergence, theory modelling, mental health

COG.01 Friday, September 29th, 13:00 [Cognitive Neuroscience A]

Assessing cognitive sequelae of COVID-19 using telepsychological testing

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From the start of the COVID-19 pandemic, evidence about prolonged symptoms of COVID-19 has been accumulating, with some individuals experiencing several symptoms for weeks or months after the acute infection has passed. Cognitive sequelae after COVID-19 are a common complaint. Current findings about the impairment of individual domains in cognitive abilities are somewhat contradictory. Thus we studied the differences in perceived and evaluated cognitive abilities in the COVID-19 recovered group, compared to a group, that has not had the disease. We used telepsychological testing for the evaluation of cognitive abilities. We included 35 participants who have recovered from COVID-19 at least three months before testing and 19 controls. Lower abilities in semantic fluency, executive functions and attention, speed of information processing and visual working memory were observed in a group of participants, who have recovered from COVID-19. We did not demonstrate a relationship between perceived and evaluated cognitive abilities. In this study, we find that some psychological tests can be adapted and used in the context of telepsychological testing. The findings represent an important starting point for further research into the cognitive sequelae of COVID-19. We conclude that in the future, it will be necessary to monitor the cognitive functioning of people, who have recovered from COVID-19 over a longer period of time.

Keywords: COVID-19, SARS-CoV-2, cognitive sequelae, telepsychology

COG.03 Friday, September 29th, 13:00 [Cognitive Neuroscience A]

Cortical changes during the learning of sequences of simultaneous finger presses

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The cortical alterations underpinning the acquisition of motor skills remain debated. In this longitudinal study in younger adults, we acquired performance and neuroimaging (7T MRI) measures weekly over the course of 6 weeks to investigate neural changes associated with learning sequences of simultaneous finger presses executed with the non-dominant hand. Both the intervention group (n = 33) and the control group (n = 30) showed general performance improvements, but performance improved more and became more consistent for sequences that were intensively trained by the intervention group, relative to those that were not. Brain activity for trained sequences decreased compared with untrained sequences in the bilateral parietal and premotor cortices. No trainingrelated changes in the primary sensorimotor areas were detected. The similarity of activation patterns between trained and untrained sequences decreased in secondary, but not primary, sensorimotor areas, while the similarity of the activation patterns between different trained sequences did not show reliable changes. Neither the variability of activation patterns across trials, nor the estimates of brain structure displayed practice-related changes that reached statistical significance. Overall, the main correlate of learning configural sequences was a reduction in brain activity in secondary motor areas.

Keywords: skill acquisition, motor learning, cortical changes, plasticity, activation patterns

COG.02 Saturday, September 30th, 13:00 [Cognitive Neuroscience B]

Brain-derived neurotrophic factor and cognitive decline in patients diagnosed with mild cognitive impairment and Alzheimer's disease

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Brain derived neurotrophic factor (BDNF) is important in development and function of neurons and recently, there is increasing evidence that alterations in its expression might contribute to development of Alzheimer's disease (AD). AD is progressive neurodegenerative disorder and a leading cause of dementia in elderly people. Mild cognitive impairment (MCI) is transitional sate between the normal cognitive changes of aging and more severe cognitive decline associated with AD or other types of dementia. It has been shown that people with MCI are at higher risk of developing dementia compared to those without MCI. Various studies reported that changes in BDNF concentrations affect cognition and memory in different cognitive disorders, including AD and MCI. The aim of this study was to investigate relationships between

plasma BDNF levels and cognitive decline in AD and MCI patients. The study included 295 patients with AD and 209 subjects with MCI and their cognitive performances were evaluated using a Mini-Mental State Examination (MMSE) and Clock Drawing test (CDT). To determine the concentration of BDNF in plasma, enzyme-linked immunosorbent assay (ELISA) was used. Our results showed significantly increased plasma BDNF concentration in AD patients compared to MCI subjects. Furthermore, there is a significant negative correlation between cognitive functions and BDNF plasma concentration, indicating that patients with more pronounced cognitive decline have higher BDNF levels. To summarize, further investigations are required to fully understand the potential use of BDNF as a novel diagnostic biomarker in clinical practice and enhance the treatment of patients with AD and MCI.

Keywords: BDNF, Alzheimer's disease, Mild Cognitive Impairment, cognitive decline

COG.04 Saturday, September 30th, 13:00 [Cognitive Neuroscience B]

Survival and self-expression values in Slovenia and North Macedonia: exploring moderators in the relationship between cognitive reserve and cognitive performance

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Cognitive reserve is a mechanism that enables maintenance of adequate cognitive abilities despite the presence of age or pathology induced brain changes. Knowing that cognitive reserve reflects the activities of everyday life (e.g., education and work engagement), which altogether aggregate with age, it is important to consider the cultural value systems that contribute to shaping and prioritizing said activities. The present study examines a subset of cultural values, within two countries, Slovenia and North Macedonia. Survival values place emphasis on economic/physical security and low outgroup trust (typically found in developing countries, like North Macedonia), while self-expression values prioritize environmental protection, equality, well-being, and quality of life (characteristic of developed countries, like Slovenia). Taking the above into consideration, we aim to explore whether prioritization of certain values moderates the relationship between cognitive reserve and cognitive performance in healthy older adults from Slovenia and North Macedonia. We hypothesize that the positive predictive value of cognitive reserve on cognitive performance will be stronger when self-expression values are higher (and survival values are lower). Similarly, referring to results from an open-source database where Slovenia has steadily high self-expression values (opposite is true for North Macedonia), we hypothesize that the positive predictive value of cognitive reserve on cognitive performance will be stronger in the Slovenian sample, compared to the North Macedonian sample.

Keywords: cognitive reserve, cross-cultural comparisons, cognitive performance, ageing, cultural values

COM.02 Saturday, September 30th, 13:00 [Computational Neuroscience]

Inferring coupling functions of brain regions from synthetic EEG data by using graph neural networks

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Electroencephalographic (EEG) measurements are a valuable tool for investigating the intricate dynamics of large-scale brain activity in humans. The theoretical aspects of such dynamics, however, like explaining observed oscillations and their interactions, remain elusive. Numerous large-scale brain models have been developed to address this, some of which focusing on explaining coupling functions by using coupled phase oscillators.

In our study, we first generate synthetic EEG data based on the Desikan-Killiany atlas. Each of the 68 cortical regions is represented by five oscillators operating within distinct frequency brainwave bands. To create a diverse dataset, we randomly phase-couple these oscillators, with only a small subset of oscillator pairs exhibiting strong coupling. Finally, we sum the oscillatory activity of the relevant oscillators to obtain a single time series per region and project it to the EEG electrodes using a forward model and a template anatomical atlas.

At the conference, we will present the outcomes of our ongoing analysis, which aims to infer the source regions exhibiting phase-coupled dynamics within the scalp EEG data. Our analysis uses a graph neural network (GNN) approach. Initially, we transform each multivariate time series into a graph representation using Markov modeling. The resulting graphs serve as input to the GNN, which is used to obtain a representation of the connections between regions. With such analysis, we strive towards discerning and classifying the information flow between the regions with respect to time, frequency, and phase. In the future, we plan to test the proposed approach on real EEG data.

Keywords: electroencephalography, coupling functions, phase coupling, graph neural networks

MET.01 Friday, September 29th, 13:00 [Neuroscience Methods]

Smart probes for ex vivo assessment of Alzheimer disease conformational pathology

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Therapeutic interventions' lackluster performance in Alzheimer dementia (AD) may in part be due to the irreversibly advanced stage of the pathological process underlying cognitive decline once the latter is diagnosed. Currently, clinical diagnosis of AD is supported by in vivo molecular imaging of disease-related Aβ and Tau aggregates in the brain, and analysis of cerebrospinal liquid. Positron Emission Tomography, Single Photon Emission Computed Tomography, and Magnetic Resonance imaging are the most common methods used. They are costly, which limits their use in routine screening. We used fluorecent microscopy to examine and compare the selectivity and optical properties of four small fluorescent molecules, designed to translate subtle changes in their environment to their optical properties upon binding to AD biomarkers including amyloid-beta and Tau protein. In addition, we investigated their affinity for other targets, including Lewy and Pick bodies, using brain tissue samples obtained post mortem from patients with confirmed AD, a familial tauopathy with Tau mutation, PD, and Pick disease, and cross-referenced our findings with immunofluorescence staining. We found that several probes, primarily designed to bind AD biomarkers, also exhibit affinity for intra- and extracellular Tau deposits, as well as Lewy and Pick bodies, and can be used to distinguish various types of pathology based on emission spectra. While our long-term goal is the development of reliable and cost-effective molecular probes to detect conformational pathology in blood samples, our presentation will focus on comparative characteristics of the four canditate probes in fluorescent microscopy of post mortem brain tissue samples.

Keywords: fluorescent microscopy, biomarkers, neurodegeneration

MOL.01 Friday, September 29th, 13:00 [Molecular Neuroscience A]

Switch of rat dorsal root ganglia macrophages to M2 phenotype after cyto skeleton alteration reduces SNL-induced neuropathic pain

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Traumatic nerve injury such as SNL (spinal nerve ligations) is accompanied by clustering of Iba1 (+) macrophages around DRG (dorsal root ganglia) neurons, presumably activating them and facilitating neuropathic pain development. Previously we have shown that intra-ganglionic L5 injection of naked siRNA directed against Iba1 significantly inhibited spinal nerve ligation- induced mechanical and cold allodynia, 5 days after the lesion. In this study we investigated whether the siRNA-induced analgesia is due to a switch in the activation phenotype of macrophages from M1 pro-inflammatory to M2 anti-inflammatory accompanied by a reduced mobility of macrophages, and complemented by a pro-regenerative profile of DRG neurons with reduced excitability. The results have shown that the analgesic effect of Iba1 silencing in DRG macrophages is due to their functional switch towards an M2, anti-inflammatory state accompanied by an increased secretion of anti-inflammatory cytokines and pro-regenerative mediators which, however, doesn't seem to alter significantly the electrophysiological properties of L5 DRG neurons. This data are in line with a reduced contribution of L5 DRG neurons to pain pathogenesis after SNL, and suggest an extended influence of the immune mechanism to neighboring non-lesioned DRG neurons, possibly responsible for the Iba1 siRNA-induced analgesia.
This research was funded by the Romanian Government via Executive Agency for Higher Education, Research, Development and Innovation Funding (UEFISCDI), grant number 374/2020, PN-III-P2-2.1-PED-2019-3103, and by the ICGEB (International Center for Genetic Engineering and Biotechnology), Grant CRP/ROU16-04 (2017-2020).

MOL.03 Friday, September 29th, 13:00 [Molecular Neuroscience A]

Axonal and myelin recovery after traumatic spinal cord compression mediated via AT2 receptor stimulation

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In the present study, we tested pharmacological AT2 receptor stimulation in an experimental model of severe spinal cord compression in adult female Wistar rats using selective AT2 receptor agonist CGP42112 (0.1 mg/kg per day) continuously administrated by osmotic minipumps (s.c.). On the 28th post-injury day, the RT-PCR and WB analysis revealed the increased expression of axonal and myelin structural markers such as neurofilaments, myelin basic protein and CNPase, and marker of axonal regeneration GAP43 after AT2 stimulation compared to trauma. The histopathological changes were analysed by using a histological Luxol fast blue staining combined with Cresyl violet. A statistically significant amount of spared spinal cord tissue was observed after AT2 stimulation, especially in the injury epicentre. Besides, the AT2 stimulation also reduced the formation of microcysts and cystic cavities, predominantly in caudal regions. The acquired results correlated with functional recovery. During the 28-day posttraumatic period, the motor function recovered rapidly, and the improvement was more profound after AT2 receptor stimulation compared to spinal cord injury alone (BBB locomotor score: 10.4 points vs 9 points) and strongly negatively correlated (Pearson r= -0.908) with evidently shorter latency (7.03 ms vs 10.8 ms). Many of these positive effects were partially or completely prevented by the AT2 receptor blocking. Our results suggested that posttraumatic AT2 receptor stimulation promotes axonal recovery resulting in improved functional neurological outcomes; thus, it could be considered promising therapeutic approach for spinal cord injury.
Supported by APVV-18-0163, APVV-22-0248 and VEGA No. 2/0123/23.

Keywords: spinal cord injury, AT2 receptor, axonal regeneration

MOL.05 Friday, September 29th, 13:00 [Molecular Neuroscience A]

Circular RNAs in association with amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a rapidly progressive fatal adult-onset neurodegenerative disease affecting both upper and lower motor neurons. Here, we investigated the potential association of circRNAs and ALS. CircRNAs represent a class of non-coding RNAs that are formed during precursor mRNA processing via back-splicing events. Among the versatile functions of circRNAs are also miRNA sponging and RNA-binding protein (RBP) sequestration, both linked to gene regulation. We first performed a microarray analysis of circRNAs on peripheral blood mononuclear cells of a subset of ALS patients and controls. For further analyses, we selected two approaches. In one approach we collected only circRNA with a host gene that harbors any evidence of genetic constraints, which could hypothetically have a significant role in determining a trait or disease. In another approach, we used different clustering algorithms to find the smallest dataset of circRNA which have the best True positive rate and True negative rate in identifying cases and controls. In both approaches, hsa_circ_0060762 and its host gene CSE1L were detected. Further analysis in larger sets of patients and controls revealed significant differences in expression levels for both hsa_circ_0060762 and CSE1L and receiver operating characteristics curve analysis showed diagnostic potential for CSE1L and hsa_circ_0060762. CSE1L is a member of the importin β family and mediates inhibition of TDP-43 aggregation, the central pathogenicity in ALS, and hsa_circ_0060762 has binding sites for several miRNAs that have been connected to ALS.

Keywords: Amyotrophic lateral sclerosis

MOL.07 Friday, September 29th, 13:00 [Molecular Neuroscience A]

Exosomal miRNA alterations in rotenone models of Parkinson's Disease

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Parkinson's Disease (PD) is a debilitating, progressive neurodegenerative disease. The loss of dopaminergic neurons in the substantia nigra is a hallmark pathology responsible for many of the motor deficits. While the etiology of most cases is unknown, a variety of environmental and genetic risk factors have been explored. Rotenone is an organic pesticide that primarily acts though mitochondrial complex I inhibition. It has been identified as a PD risk factor and is widely used to study PD in models. The current study aimed to test the hypothesis that specific exosomal miRNA changes can serve as biomarkers in in rotenone PD models. The importance of exosomal changes in PD has received much attention, but there is much yet to learn. Exosomal content can potentially serve as both biomarkers and key mediators of pathogenesis. Preliminary studies in primary cortical and midbrain neurons treated with rotenone (60nM and 25nM, respectively) for 24h demonstrated that several specific exosomal miRNAs were differentially expressed. Further, 3-month-old Sprague Dawley male rats were acutely dosed with rotenone (3 mg/kg) for 8h and 24h, and serum and CSF were extracted. Exosomal miRNAs were differentially expressed in both serum and CSF, notably miR-181c-5p and miR-93-5p; these miRNAs are important in modulation of mitochondrial functions and inflammation respectively. Further, neuronal cultures treated with isolated serum exosomes from rotenone treated rats showed selective dopaminergic toxicity. Taken together, our findings show changes in exosomal miRNAs may be early diagnostic markers for PD and that show changes could be important in. pathogenesis.

Keywords: Parkinson's disease; exosome; rotenone

MOL.09 Friday, September 29th, 13:00 [Molecular Neuroscience A]

hnRNPH localizes to G4C2 nuclear foci and cytoplasmic stress granules of C9orf72 amyotrophic lateral sclerosis

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The most common genetic cause of ALS is hexanucleotide G4C2 repeat expansion in the first intron of C9orf72. One of the hallmarks is the formation of RNA G4C2 foci in the nucleus, which contain aberrant repeat transcripts and various RNA-binding proteins (RBP). hnRNPH is a member of a large RBP family involved in the regulation of alternative splicing, mRNA stabilization, transcription, and translation. In ALS brain tissue, hnRNPH colocalizes with nuclear G4C2 foci, whereas under cellular stress conditions, it is localized in cytoplasmic stress granules. Sequestration of hnRNPH in insoluble RNA aggregates correlates with dysregulation of splicing and may contribute to neurodegeneration. Our goal was to reveal the domains of hnRNPH that determine its localization to G4C2 foci and stress granules. We designed a series of hnRNPH1 protein constructs based on its domain structure and introduced mutations into individual qRRM domains to disable their RNA-binding activity. Quasi (q)RRM2 and qRRM3, but not qRRM1, were sufficient for localization of hnRNPH to stress granules. Localization of hnRNPH to G4C2 foci was independent of the RNA-binding activity of any individual qRRM domain. Using RBDmap, we demonstrated that

the putative ZnF domain of hnRNPH may have RNA-binding activity. Surprisingly, hnRNPH localized to G4C2 foci even after the removal of the RNA-binding activity of the qRRM and ZnF domains. This result suggest that RNA-binding activity may not be the only driving force for the sequestration of hnRNPH into the G4C2 foci associated with C9orf72 ALS.

Keywords: ALS, C9orf72, hnRNPH, G4C2 foci, stress granules

MOL.11 Friday, September 29th, 13:00 [Molecular Neuroscience A]

Molecular factors that implicate involvement of human retrotransposon LINE1 in neurodegeneration

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Neurodegenerative diseases present a growing problem for the ageing global population. By 2050 more than 2 billion people will be 60 years or older. Therefore, it is crucial to develop a better understanding of molecular mechanisms of neurodegeneration. A growing number of research links mobile genetic elements, namely retrotransposons, to Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). The human genome consists of many copies of retrotransposons, of which LINE1 is the most prevalent. It represents up to 17 % of the human genome and is still active today. Full-length LINE1 element includes 3 open reading frames for ORF1p, ORF2p, and ORF0p. In our work we analysed the protein interactome of ORF1p with biotin identification. Mass spectrometry results revealed that potential ORF1p interaction partners, like ORF1p, localize in stress granules, cytoplasm, nucleus, and nucleoli. Potential interactors are mainly RNA-binding proteins involved in various steps of RNA metabolism, translation and its regulation, and stress granule assembly. By immunodetection, we confirmed 5 ORF1p interactors (TDP-43, IGF2BP1, ELAVL1, FUS, and hnRNPK), all of which are distinct RNA-binding proteins. IGF2BP1 and ELAVL1 also colocalized with transiently expressed Flag-ORF1p in unstressed HEK293T cells. Among confirmed ORF1p interactors, TDP-43 and FUS are already strongly implicated in different neurodegenerative diseases. Moreover, aberrant RNA metabolism is emerging as a significant mechanism in neurodegeneration. Our results provide insight into the ORF1p-protein interaction network, which may help us understand the role of ORF1p in health and disease.

Keywords: retrotransposon LINE1, ORF1p, BioID, neurodegeneration

MOL.13 Friday, September 29th, 13:00 [Molecular Neuroscience A]

Potential therapeutic effects of dehydroepiandrosterone and its sulfate in mouse models of Alzheimer´s disease

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Alzheimer's disease (AD), the most common form of dementia, comprises 60-70% of all dementia cases. This neurodegenerative disorder involves the accumulation of amyloid beta (Aβ) peptide in amyloid plaques and hyperphosphorylated tau protein in neurofibrillary tangles. These contribute to neuronal loss, brain atrophy and cognitive deterioration. Unfortunately, there is currently no effective therapy to treat AD or prevent its onset. Therefore, extensive research is underway to explore the therapeutic potential of different compounds.

Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), abundant steroids in human circulation, decline with age and in neuropsychiatric disorders like AD. They are produced in the adrenal gland, ovaries and testes, crossing the blood-brain barrier. Engaging in neurogenesis, neurite growth, survival, neurotransmission, synaptic plasticity and inflammation, they play significant roles in various brain processes.

Our study included both genetic and pharmacologically induced mouse models of AD. In the genetic AD model, the 3xTg-AD and 3xTg (+/+) control mice were chronically treated with DHEAS using the subcutaneously intrascapulary implanted osmotic pumps. In the pharmacological AD model, C57BL/6 mice were chronically intraperitoneally treated with DHEA or the vehicle, after the stereotaxic intracerebroventricular administration of Aβ oligomers.

The results suggest that a longer period of Aβ treatment or a higher dose of DHEA might be necessary to effectively induce and treat AD pharmacologically. However, the administration of DHEAS yielded only modest effects in the genetic AD model. Further investigation in this domain is warranted and it is crucial to replicate and validate these results in studies encompassing a larger sample size.

Keywords: Alzheimer's disease, DHEA, DHEAS, 3xTg-AD, C57BL/6, Aβ oligomers

MOL.15 Friday, September 29th, 13:00 [Molecular Neuroscience A]

The role of insulin and glucose in regulation of neuropathy target esterase-related esterase in primary human myotubes

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In murine skeletal muscle, expression of neuropathy target esterase-related esterase (NRE), also known as patatin-like phospholipase domain containing protein 7 (PNPLA7), a lysophospholipase, is increased by fasting and decreased by feeding, indicating NRE is regulated by metabolic hormones and/or nutrients. Consistent with this notion, insulin reduced NRE expression in cultured murine adipocytes. Here we examined whether NRE is functionally expressed in primary human skeletal muscle cells and whether its expression is modulated by insulin and/or glucose. Primary human myoblasts and myotubes expressed NRE mRNA and protein. Gene silencing of NRE in myoblasts reduced the activity of the mTOR pathway as well as the abundance of α1-subunit of Na^+,K^+-ATPase and acetyl-CoA carboxylase, indirectly suggesting a functional role for NRE in these cells. In myotubes, insulin reduced NRE mRNA levels at normal glucose concentration (1 g/L), but not at low (0.5 g/L) or high (4.5 g/L) glucose concentrations. The NRE protein levels were inversely correlated with the glucose concentrations. Conversely, treatment with dexamethasone, a synthetic glucocorticoid, and forskolin, an activator of adenylyl cyclase, did not affect NRE expression regardless of glucose concentration. In conclusion, NRE expression in human myotubes was regulated by insulin in a glucose-dependent manner, implicating a role for NRE in skeletal muscle energy metabolism.

Keywords: NRE, PNPLA7, insulin, glucose, cultured human myotubes

MOL.17 Friday, September 29th, 13:00 [Molecular Neuroscience A]

The involvement of Angiotensin II receptors in posttraumatic recovery of severe injured spinal cord

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Most of the known physiological as well as pathological effects of Angiotensin II are mediated via AT1 receptors. The AT2 receptor was considered as "enigmatic" for very long time, but intensive research in recent decades has determined it as potential therapeutic target. Many scientific results in recent decades clearly demonstrated beneficial effects of the AT1 receptor blockage and the AT2 receptor stimulation. The appropriate timing of receptor blockade or stimulation after specific lesion is a one of crucial factors affecting the efficiency of therapeutic approach. Based on measured physiological parameters and the time-dependent receptor expression analysis in injured spinal cord, we specified an appropriate timing of pharmacologic intervention for AT1 receptor blockage and AT2 receptor stimulation. Neurological dysfunction, motor evoked potentials, bladder function, blood pressure and heart rate, body weight changes, post-traumatic tissue sparing and cystic cavitation, axonal structural proteins and vascular markers have been evaluated. Our experimental results suggested a promising therapeutic potential of pharmacologic intervention aimed to these major Angiotensin II receptors after severe spinal cord injury.

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Keywords: Angiotensin II, AT1 receptor, AT2 receptor, neuroprotection, spinal cord injury

MOL.02 Saturday, September 30th, 13:00 [Molecular Neuroscience B]

ALS/FTD-associated C9orf72 C4G2 repeat RNA binds to FARS protein and affect the rate of phenylalanine-tRNA aminoacylation

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The most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) is the C9orf72 gene mutation, which results in expanded hexanuleotide repeat – GGGGCC. It transcribes in sense (G4C2)n and antisense (C4G2)n direction and leads to the formation of nuclear RNA foci. We have identified proteins that bind to antisense transcripts. These include proteins involved in protein synthesis, cytoskeleton stability and mRNA processing. For the first time we observed the interaction with phenylalanine-tRNA synthetase (FARS). To determine the interactors, we performed RNA-pull down assay from mouse and human brain lysates followed by mass spectrometry. We validated the interaction using WB, FISH/ICC and developed modified RNA-protein proximity ligation assay to observe cytoplasmic interactions of the repeats. To evaluate the impact of antisense RNA-FARS interaction on tRNA aminoacylation, protein synthesis and cellular stress we used two aminoacylation assays, western blot analysis and Click-chemistry.Antisense RNA-FARS interaction resulted in significant decrease in aminoacylation rate in in vitro assay and

lower charged tRNAphe levels in patient derived lymphoblasts compared to controls. Additionally, we observed a decreased expression of phenylalanine-containing proteins at the whole protein level and of five individual proteins with high phenylalanine content. We also evaluated the effect of the lower aminoacylation level on cellular stress and autophagy. In the presented study we investigated and confirmed protein interactions with the biologically relevant 32×C4G2 RNA repeats and how this affects cellular processes. Our discovery highlights the role of aminoacyl-tRNA synthetases in C9orf72 ALS/FTD where they may be important contributors to the development of these diseases. This is important because studies have linked irregularities in aminoacyl-tRNA synthetases to other neurodegenerative disorders.

Keywords: ALS C9orf72 FARSA

MOL.04 Saturday, September 30th, 13:00 [Molecular Neuroscience B]

Muscle-specific microRNAs as spinal muscular atrophy biomarkers

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Introduction: Spinal muscular atrophy (SMA) is a debilitating neurodegenerative disease characterized by the progressive degeneration of motor neurons, leading to muscle weakness and paralysis. The primary cause of SMA is the survival motor neuron (SMN) protein deficiency, which is attributed to homozygous deletions in the survival of motor neuron (SMN1) gene. To address this underlying gene deficiency, three drugs (nusinersen, risdiplam, and onasemnogene abeparvovec) have been approved that aim to increase SMN protein production in SMA patients. However, accurately assessing the efficacy of SMA therapy presents challenges in identifying reliable measures. Recently, circulating microRNAs (miRNAs) have emerged as potential biomarkers for assessing disease progression and predicting and monitoring treatment response in various diseases, including SMA.

Results: To investigate miRNAs associated with the pathogenesis of SMA and their potential use as biomarkers, we conducted an extensive literature search. Among the miRNAs studied, four muscle-specific miRNAs (myomiRs) have shown promise as potential SMA biomarkers. These myomiRs include hsa-miR-1-3p, hsa-miR-133a-3p, hsa-miR-133b, and hsa-miR-206, and were found to be frequently elevated in SMA patients compared with healthy controls, and their levels demonstrated a decrease following nusinersen treatment. Moreover, their target genes were found to be involved in neurological inflammatory processes, further highlighting their relevance to SMA.

Conclusions: Further studies with larger cohorts of healthy individuals and SMA patients, both pre- and post-treatment, are needed to validate the use of myomiRs as biomarkers for SMA. Ultimately, the identification of reliable biomarkers will enable more effective clinical management and personalized treatment strategies for SMA patients.

Keywords: spinal muscular atrophy, microRNA, biomarkers

MOL.06 Saturday, September 30th, 13:00 [Molecular Neuroscience B]

Examining the impact of TDP-43 mislocalization on its protein network

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TDP-43 is a DNA/RNA-binding protein located mainly in the nucleus. In amyotrophic lateral sclerosis and frontotemporal dementia, it becomes mislocalized and is the main component of cytoplasmic protein aggregates. In the present study, we investigated the interactome of wild-type TDP-43 and TDP-43dNLS that mimics a pathological condition. We established inducible mammalian cell lines stably expressing the recombinant fusion protein TDP-43wt or TDP-43dNLS with the biotin ligase BioID2. We performed the BioID method and isolated biotinylated proteins from the cell lysates. The isolated proteins were detected by mass spectrometry (MS), resulting in a list of unique TDP-43wt and TDP-43dNLS interactors that were further validated. The cellular localization and function of the interactors were investigated using bioinformatics analyses. It revealed that TDP-43wt interacts mainly with proteins of the ribonucleoprotein and spliceosome complexes and with paraspeckles, whereas the mutant TDP-43dNLS interactors are components of cytoplasmic stress granules and P-bodies. Validation of selected interacting proteins (NONO, SFPQ, FUS, MAML1, PUM1, and ATXN2L) revealed that MAML1 is unique TDP-43wt interactor, whereas NONO, SFPQ, and FUS are common interactors of TDP-43wt and TDP-43dNLS and are more abundant in the TDP-43wt fraction. ATXN2L and PUM1 are unique interactors of mutant TDP-43. Our results suggest that the development of ALS may involve impaired regulatory functions related to transcription/paraspeckle function and a potential link to stress granules and P-bodies due to their increased association with mutant TDP-43. In addition, the newly identified interactors of TDP-43 in this study may contribute to the understanding of the aggregation process.

Keywords: TDP-43, interactome, BioID, ALS

MOL.08 Saturday, September 30th, 13:00 [Molecular Neuroscience B]

Expression of disease-associated mRNAs in platelets: a potential new biomarkers of ALS pathology?

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Loss of nuclear TAR DNA-Binding Protein of 43 kDa (TDP-43) and cytoplasmic TDP-43 accumulation are widely recognized as major

neuropathologic features in Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal lobar degeneration (FTLD) cases. Particularly, neuropathologic forms of TDP-43 arise from disease-associated changes in splicing and post-translational modification. Although, all these aberrant TDP-43 forms can be detected in post-mortem tissue of ALS and FTLD patients, few literatures are currently available regarding their quantification in biological fluids. Recently, it has been reported that more than 90% of plasma TDP-43 arises from platelets, as well as an increase of TDP-43 phosphorylated forms in platelets of ALS patients compared to healthy donors. Moreover, platelets express a large number of neurotransmission-related proteins and although they are anucleate cells, they contain mitochondria and all the machinery to carry on signal-dependent RNA processing and de novo protein synthesis. Therefore, the aim of this work is to establish new bioassays for detecting pathological TDP-43 species in ALS platelet samples, as well as to define their significance as potential biomarkers. Our preliminary results identified several neurodegenerative-related targets commonly regulated among healthy control platelets and brain-derived cells depleted for TDP-43, including PDGFRB, COL6A2, ANXA2, FOXO4 and CEND1. Overall, these results strongly support our hypothesis of similarity in RNA expression pattern of platelets and neurons, and they may contribute to set the stage for an early detection of TDP-43 neuropathology in ALS.

Keywords: Platelets, TDP-43, RNAseq

MOL.10 Saturday, September 30th, 13:00 [Molecular Neuroscience B]

Hyperglycemic zebrafish exposed to chronic unpredictable mild stress display oxidative damage in the brain: mitigation by chlorogenic acid

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Hyperglycemia, a core feature of diabetes, is speculated to be injurious to brain health. Diabetes often involves chronic stress, termed diabetic distress. Chronic stress is explored with reference to psychiatric disorders such as depression and anxiety. However, extensive literature addressing concurrently occurring hyperglycemia and chronic stress is unavailable. Diabetes-associated brain pathology studies are now including the zebrafish (Danio rerio) as a disease model. It has been repeatedly demonstrated that oxidative stress is associated with the pathophysiology of various chronic diseases. The nuclear factor erythroid 2-related factor 2 (NRF2) is a transcription factor that influences the expression of several cytoprotective antioxidant genes. Consequently, studies are exploring the therapeutic effects of NRF2-targeting compounds to mitigate disease progression. For instance, chlorogenic acid (CGA), a polyphenol, has shown promise against oxidative damage but whether it works through NRF2 is undetermined. We performed an exploratory study on adult zebrafish wherein they were exposed to simultaneous chronic unpredictable mild stress and hyperglycemia (111mM dextrose) for 14 days. This was followed by intraperitoneal injection with 50, 100, and 200 mg/kg of CGA on the 15th day. Fasting blood glucose levels were measured and brain tissue was extracted. Blood glucose levels were dramatically elevated in stressed-hyperglycemic fish compared to control. Furthermore, there were alterations in NRF2 protein and gene levels and also of its downstream target genes. Therefore, CGA may operate via NRF2 signaling in this context. This study paves a path for neuroscience researchers to model metabolic diseases in the adult zebrafish to explore its neurobiological implications.

Keywords: diabetes, hyperglycemia, chronic stress, NRF2, chlorogenic acid

MOL.12 Saturday, September 30th, 13:00 [Molecular Neuroscience B]

Neural agrin has an age-dependent stimulatory effect on the proliferation of cultured human myoblasts

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Neural agrin, a heparan-sulphate proteoglycan secreted by the α-motor neurons, promotes formation and maintenance of the neuromuscular junction via Lrp4 and the muscle-specific kinase (MuSK). By enhancing differentiation and maturation of myotubes neural agrin also promotes myogenesis. Here we determined whether and how neural agrin affects proliferating human myoblasts, which are often considered to be unresponsive to agrin. In cultured human myoblasts, neural agrin induced transient dephosphorylation of ERK1/2, while c-Abl, STAT3, and focal adhesion kinase were unresponsive to agrin treatment. Gene silencing of Lrp4 and MuSK markedly reduced the BrdU incorporation, suggesting the Lrp4/MuSK complex is functionally important for myoblast proliferation. Acute and chronic treatments with neural agrin increased the proliferation of myoblasts of old donors, but they did not affect the proliferation of myoblasts of young donors. The C-terminal fragment of agrin which lacks the Lrp4-binding site and cannot activate MuSK had a similar age-dependent effect, indicating that the age-dependent signalling pathways activated by neural agrin involve the Lrp4/MuSK receptor complex as well as a Lrp4/MuSK-independent pathway. Taken together, our results highlight an age-dependent role for neural agrin in regulation of myoblast proliferation.

Keywords: neural agrin, Lrp4, MuSK, myoblasts, ageing

MOL.14 Saturday, September 30th, 13:00 [Molecular Neuroscience B]

Crosstalk of Optineurin and TDP-43 in ALS and FTD

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are neurodegenerative diseases marked by neuronal loss, chronic inflammation, and protein aggregation. TAR DNA- binding protein 43 (TDP-43) is present in neuronal and glial aggregates in >95% of ALS

and >45% of FTD patients. Its aggregation is closely linked to its nuclear depletion and loss-of-function. Moreover, TDP-43 aggregates trigger chronic inflammation and vice versa, chronic inflammation further exacerbates TDP-43 aggregation. The autopsies of ALS and FTD patients carrying the mutations in the OPTN gene, encoding for optineurin, also show TDP-43 aggregates. As optineurin has been proposed to act as the adaptor protein in autophagy and inflammatory signaling, here we tested if optineurin ALS-linked mutations lead to impaired TDP-43 proteostasis and/or altered immune responses. To address this, we used (1) optineurin deficient microglial BV2 cells made using CRISPR/Cas9 technology (BV2 KO) and (2) optineurin insufficiency mouse model (Optn470T) that mimics loss-of-function Q398X truncation found in ALS patients. We found elevated basal TDP-43 protein levels in BV2 KO cells and Optn470T primary microglia but without differences in TDP-43 mRNA levels at basal state, arguing that TDP-43 is post-translationally regulated. Moreover, our results demonstrated that optineurin was dispensable as an adaptor in the process of TDP-43 turnover via autophagy. To test the role of inflammation on TDP-43 levels, we stimulated BV2 microglia cells and primary microglia with lipopolysaccharide (LPS) to mimic bacterial infection and observed a significant increase in TDP-43 protein levels in WT cells, which was absent in optineurin deficient and insufficient cells. In the latter, TDP-43 remained at the same elevated state as in the basal conditions. We did not detect a difference in TDP-43 mRNA levels upon LPS in optineurin deficient BV2 KO cells, but RNASeq analyses showed increased expression of inflammatory genes arguing that lack of functional optineurin could lead to chronically activated cells that can consequently increase levels in TDP-43. However, in vivo experiments did not show TDP-43 aggregation and ALS/FTD-like neuropathology in the Optn470T mice up to two years of age, suggesting that ageing was insufficient to provoke the phenotype. In conclusion, we observed elevated TDP-43 levels in optineurin insufficient and deficient microglia, but additional stimuli are likely necessary to exacerbate the phenotype and to elucidate the role of optineurin in disease pathogenesis.

MOL.16 Saturday, September 30th, 13:00 [Molecular Neuroscience B]

Toxic potential of midazolam on rat cortical astrocytes

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Objective: Midazolam is frequently used for initial induction into general anaesthesia. Recently, several reports have emerged reporting anaesthetics' toxicity following their use. Data on their potential toxic impact on brain is scarce and no mechanism explaining the observed toxicity is currently defined. Simultaneously, the role of astrocytes has been shown to be crucial in preserving brain homeostasis. The viability of astrocytes directly affects the function of the entire central nervous system. The objective of this study is to examine the cytotoxic effects of midazolam on primary rat cortical astrocytes using flow cytometry.

Method: Primary cultures of cortical astrocytes obtained from new-born rats were used as the basis for the experimental model. Cells were exposed for 24 hours to increasing concentrations of midazolam, including clinically observed plasma concentrations during anaesthesia. Apoptosis, necrosis, and necroptosis as types of cell death were examined using flow cytometric analysis.

Results: Midazolam up to 1 μM concentration did not increase cell death in cultured astrocytes. Cytotoxic effects were dose dependent and observed only at concentrations 400-times higher compared to therapeutic (300 μM – 15-fold vs. control, $p < 0,0001$). Majority of cells died due to necrosis (300 μM - 90%), via apoptotic pathway. Necroptosis was not observed.

Conclusions: Midazolam in concentrations, attainable in plasma during general anaesthesia, does not express any cytotoxic effects on cultured astrocytes. Even though astrocytes are relatively resistant to apoptosis it seems that midazolam at high concentrations triggers apoptotic and not necroptotic pathway.

Keywords: midazolam, astrocytes, toxicity

OTH.02 Saturday, September 30th, 13:00 [Other B]

What has (not) been learnt from the COVID pandemics

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On March 11th 2020, World Health Organization (WHO) declared that the disease caused by a Coronavirus has the characteristics of pandemics. It was first identified as an outbreak of respiratory illness cases in Wuhan, China, initially reported to WHO on December 31st, 2019. On January 30th, 2020, the WHO declared the COVID-19 outbreak a global health emergency.

Due to mutations, we were facing ever-changing clinical pictures from severe first wave illness caused by alpha variant, then delta variant in winter 2020 and spring 2021. Then a more virulent but less dangerous omicron variant emerged. Understanding of disease, diagnostics, and measures changed over the time, which caused confusion among people not used to the scientific process. WHO and CDC were reluctant to some measures e.g.: public use of masks, but then changed their recommendations. Rapid development of vaccines was seen as an achievement among scientific communities while the general public remained sceptic, even more prone to anti-vaxxer theories. Physical distance became very important as a preventative measure. Many governments have restricted free movement and placed populations under lockdown to limit the spread of the pandemic. The delays of screening programmes, diagnostics, elective surgeries and cut numbers of physicians and nurses available to treat other diseases than Covid-19, were not contributing to the notion that Covid-19 was at that time more serious threat to public health than cancer. Many people lost their relatives. Fear and anxiety which helped to comply with the rules and contain the virus during the first wave was replaced by pandemic fatigue. A consistent decline in compliance with mitigation behaviors over time globally led to oblivion even of simple mitigation tasks such as hand washing or staying at home when ill with infection.

Digitalization of all sectors (distant schooling, cross border data analytics), took place. Children who were home-schooled showed certain behavioral problems; mental health problems which were on the rise for decades now became more apparent. In addition, long COVID (post-acute sequelae) persist in approx. 10 % of those affected, however most of the symptoms resolve within a year. Multiple organs (heart, vessels, lungs, immune system, pancreas, nervous system, kidneys,

GIT, reproductive system) are involved, pathologies are overlapping, which can exacerbate management challenges.

Pandemics showed the importance of scientific literacy. As a society we should educate and empower people to be literate citizens who are able to evaluate the quality of scientific information on the basis of its source and the methods used to generate it. If this were the lessons learnt and additional action taken in place, then we could maybe say that the toll, measured in lives and healthy-years lost, due to COVID were not completely wasted. With better scientific literacy we could face next pandemics efficiently and better equipped.

Keywords: Covid, Corona virus, mitigation measures, fear, scientific literacy

SYS.01 Friday, September 29th, 13:00 [Systems Neuroscience A]

Behavioral sensitization and tolerance induced by ketamine enantiomers in male Wistar rats

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Ketamine has gained significant attention for its therapeutic benefits as a fast-acting antidepressant. However, it is crucial to address its undesirable side effects. In our study, we aimed to explore the divergent side effects of ketamine enantiomers, namely S-ketamine and R-ketamine, at subanesthetic doses (15 mg/kg), with a particular focus on their abuse and psychotomimetic potentials during prolonged treatment. Our hypothesis was that R-ketamine will exhibit fewer unwanted effects compared to S-ketamine, because of its lower NMDA receptor binding affinity.

Male Wistar rats were treated with either R-ketamine, S-ketamine, or saline every third day for a total of three weeks. We evaluated the enantiomers' abuse potential by investigating their capacity to stimulate locomotion and induce locomotor sensitization. Additionally, we evaluated their psychotomimetic potential by measuring dissociative stereotypy, which is defined by ataxia-like abnormal behaviors, stereotypical behaviors, and a decrease in natural behaviors.

Our findings revealed that S-ketamine acutely induced concurrent locomotor stimulation and ataxia, and attenuated the expression of other natural behaviors, whereas R-ketamine did not. With repeated treatment, S-ketamine led to locomotor sensitization and tolerance to the ataxic effects. Repeated treatment with R-ketamine also led to locomotor sensitization, resulting in post-treatment locomotor stimulation that was not observed prior to repeated treatment.

We conclude that S-ketamine has a higher abuse and psychotomimetic potential than R-ketamine. However, their safety profiles in the prolonged treatment of depression remain to be determined.

Keywords: ketamine, enantiomers, side-effects, rats

SYS.03 Friday, September 29th, 13:00 [Systems Neuroscience A]

Effects of prayer on heart rate variability in resting sitting position in adults

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Background: Prayer is a common practice worldwide, but its effects on HRV (heart rate variability) are unclear. The aims of this study was were to examine the immediate and long term effects of prayer on HRV and to determine whether these effects differ from those of recitation.

Methods: In 78 subjects (49 females, age 37±11), who pray regularly and 50 controls (35 females, age 35±8) who do not pray at all, ECG and respiratory rate were recorded continuously for 60 minutes in sitting position during five phases: resting, silent prayer, resting, silent recitation of song lyrics, and resting. For a subgroup of subjects, the order of interventions was reversed. From the 5-minute intervals of each protocol phase, HRV parameters, reflecting parasympathetic heart rate modulation, RMSSD (root mean square of successive differences) and HF (high frequency) were calculated.

Results: During prayer, the mean of RMSSD decreased significantly ($p=0.001$), and mean of HF tended to decrease ($p=0.038$). The means of baseline HRV parameters and their decreases during the prayer did not differ significantly between prayers and controls. In males, the decrease in RMSSD tended to be greater during prayer than during recitation ($p=0.022$).

Conclusions: Parasympathetic modulation of heart rate decreased during silent prayer in a resting sitting position, but was unaffected by history of regular prayer. The trend of a greater decrease during prayer than during recitation suggests that this cannot be explained solely by language processing. Furthermore, the trend of a greater decrease in males than in females suggests sex differences in autonomic heart rate regulation.

Keywords: heart rate variability, prayer, autonomic nervous system, parasympathetic

SYS.02 Saturday, September 30th, 13:00 [Systems Neuroscience B]

Gut microbiota perturbations disrupts hippocampal serotonin bioavailability and anxiety behavior

Jazib Shafiq, Ayaz Ahmed

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Gut Microbiome-Brain axis is a dynamic trans-kingdom communication system linking the gut microbiome and host CNS through metabolites, hormones, and immune mediators. The composition of gut microbiome correlates with host behavior and its disruption is implicated in several neurological disorders. Germ free (GF) mice model is extensively used to study GMB axis, however, recent research reported the dysregulated serotonergic transmission in GF mice. To address this issue, we developed antibiotics-induced gut dysbiosis mice model and employing multi-omics approach to dissect the role of gut microbiota in modulation of hippocampal serotonin (5-HT) bioavailability and anxiety behavior. SPF mice were given combination of non-absorbable antibiotics for 14 days to induce dysbiosis before assessing anxiety using elevated plus maize and open field. After behavioral study, mice were euthanized, and organs/tissues were collected. Neurotransmitters and targeted genes transcripts were quantified in mice hippocampus using HPLC and RT-qPCR. DNA was extracted from mice cecum and subjected to shotgun metagenomic sequencing. Data was processed with standard bioinformatics pipelines and visualized using R Studio. Behavioral results showed dysregulated anxiety behavior in dysbiosis mice, and their hippocampus exhibited low levels of 5-HT, Trp, and 5-HIAA. Transcription level of 5-HT transporter was down-regulated in dysbiosis group, while expression of glucocorticoid, 5-HT, and GABA receptors, and TPH2 remains unchanged. Taxonomic analysis depicted increase in beta diversity between groups, and Shannon-Weaver index was significantly lower in dysbiosis group. Functional dominance in dysbiosis mice shifted from Firmicutes and Bacteroidetes to Proteobacteria. The dominant communities in control group were Muribaculum and Bacteroides, whereas Klebsiella and Enterobacter were dominant in dysbiosis group. 5-HT is the key regulator of anxiety, and our data suggest that gut microbiome perturbations disrupt hippocampal 5-HT bioavailability, leading to dysregulated host anxiety. We are further integrating metabolomics data to study the host/bacterial metabolites involved in 5-HT and anxiety regulation.

Keywords: microbiome gut brain axis, tryptophan metabolism, anxiety-like behavior

SYS.04 Saturday, September 30th, 13:00 [Systems Neuroscience B]

The individual differences in response to ketamine enantiomers: an exploratory preclinical approach

Anamarija Banjac, Kristian Elersič, Marko Živin, Maja Zorović

Institute of Pathophysiology, Faculty of Medicine, University of Ljubljana, Slovenia

Rodent ultrasonic vocalizations (USVs) in the 50-kHz range can be used as a measure of individual differences in positive hedonic response, hence bringing great value to preclinical antidepressant research. To test differential hedonic response to two enantiomers of ketamine, R- and S-ketamine, we performed an exploratory statistical analysis. 18 male Wistar rats received daily s.c. injections of either R-ketamine, S-ketamine or saline, for seven consecutive days. Their USVs were measured before treatment (baseline measures, dose 0) and after the 1st, 3rd, 5th, and 7th dose (10 minutes each measurement). After the experimental procedure, the animals were categorized as either high or low vocalizers based on the number of their baseline 50-kHz vocalizations. An exploratory paired-samples t-tests on square root transformed data showed significant differences in vocalizations only for high vocalizers. Following the 1st dose, those treated with S-ketamine displayed a significantly higher number of vocalizations compared to the baseline. The difference disappeared following the 3rd dose, equating high vocalizers treated with S-ketamine to low vocalizers. High vocalizers treated with R-ketamine displayed a significantly lower number of vocalizations compared to baseline, but only after 7 doses, also equating them to low vocalizers. The results indicate the importance of individual differences and dose quantity in antidepressant response. However, extreme caution should be applied to any further conclusions due to the exploratory nature of the analysis and a low sample size.

Keywords: rats, ultrasonic vocalizations, antidepressant, ketamine

CEL.12 Saturday, September 30th, 13:00 [Cellular Neuroscience B]

Paclitaxel-induced peripheral neuropathy: in vitro and in vivo study

Zuzana Michalová, Ivo Vanický

Institute of Neurobiology, Biomedical Research Center, Slovak Academy of Sciences, Košice, Slovakia

Paclitaxel induced peripheral neuropathy (PIPN) is a severe adverse effect observed in most cancer patients receiving paclitaxel. Although highly effective in blocking tumor progression, a major dose-limiting side effect of paclitaxel can persist for up to two years after completing treatment, greatly affecting both the course of chemotherapy and patients' quality of life. The main symptoms are numbness, paresthesia and burning pain in a glove-and-stocking distribution. In this study, dorsal root ganglion (DRG) dissociated primary cultures have been used as a neurotoxicity-screening model to evaluate the effect of paclitaxel on the neurite elongation in vitro. The neurotoxic effect of this drug was analyzed by measuring the neurite length of post-mitotic, non-dividing cells, such as neurons. Moreover, in DRG primary cultures, the morphological features of paclitaxel-induced cellular death were studied and the DRG neurons were observed to die by necrosis. In vivo, axonal degeneration was observed in sections of dorsal roots as well as caudal nerves in a rat model of PIPN. In adult rats, we have observed a dose-dependent large-fiber sensory neuropathy with no deleterious effects on overall health, using two intravenous injections of paclitaxel 2 days apart. Currently, there are no therapeutic options available for the prevention of PIPN and only few drugs are recommended for the treatment of existing neuropathies because the mechanisms of PIPN remain unclear. Our findings demonstrate a dose and time dependent neurotoxic effect of paclitaxel in DRG derived sensory neuron culture system as well as in rat in vivo model.

Acknowledgments: This work was supported by the Grant Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic (No. VEGA 2/0120/23, VEGA 2/0109/21) and ITMS 2014+: 313011V344.

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Abstracts

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Saturday, September 30th, 08:30

The search for pain biomarkers

Giandomenico Iannetti

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Functional brain imaging techniques are being used more than ever to investigate pain in health and disease, with the objective of finding new means to alleviate clinical pain and improve patient wellbeing. The observation that several brain areas are activated by transient painful stimuli, and that the magnitude of this activity is often graded with pain intensity, has generated excitement but also confusion. Indeed, researchers devise approaches to extract features of brain activity that could serve as biomarkers to measure pain objectively. However, most of the brain responses observed when pain is present can also be observed when pain is absent. For example, similar brain responses can be elicited by salient but non-painful auditory, tactile and visual stimuli, and such responses can even be recorded in patients with congenital analgesia. Thus, as I will show in my talk, there is still disagreement on the degree to which current measures of brain activity specifically relate to pain. Furthermore, whether more recent analysis techniques can be used to identify distributed patterns of brain activity selective for pain can be only warranted using carefully designed control conditions. In general, the clinical utility of current pain biomarkers derived from human functional neuroimaging is overstated, and evidence for their efficacy in real-life clinical conditions is scarce. Rather than searching for biomarkers of pain perception, several researchers are developing biomarkers to achieve mechanism-based stratification of pain conditions, predict response to medication and offer personalized treatments. Initial results with promising clinical perspectives need to be further tested for replicability and generalizability.

Saturday, September 30th, 09:30

Peripheral and spinal circuits

Carole Torsney

Centre for Discovery Brain Sciences, University of Edinburgh, United Kingdom

The pain network provides an important warning system to avoid injury. However if tissue injury occurs the somatosensory system is dynamically altered to increase sensitivity and ensure maximal protection to promote recovery and repair. If this adaptive response persists beyond tissue healing there is transition to chronic pain. This somatosensory plasticity that drives the symptoms of hyperalgesia (exaggerated pain) and allodynia (touch-evoked pain) will be reviewed with a focus on peripheral and spinal circuits. The advances made using techniques to genetically target, ablate or manipulate molecularly defined neuronal subtypes that has expanded understanding of nociceptor sensitisation and spinal circuit plasticity will be highlighted. Recent novel insights in to the amplified relay of nociceptive signals by peripheral sensory neurons and the regulation and unmasking of spinal circuits that manifest as hyperalgesia and allodynia will be presented.

Saturday, September 30th, 10:30

Pain and memory

Jelena Radulović

Departments of Neuroscience and Psychiarty, Albert Einstein College of Medicine, New York, USA
Department of Biomedicine, Aarhus University, Denmark

Negative experiences, including pain, negative emotions, moods, and memories, share a common feature in that they are all perceived as unpleasant, distressing, or aversive. Yet these experiences also have features that segregate them in discrete phenomena. This lecture will focus on the molecular and circuit mechanisms of the brain as the interface between pain and other negatively valenced states. We will discuss in more detail evidence linking pain to negative mood (i.e., depression), and negative memories (i.e., stress-related memories), while emphasizing the difference between acute and chronic pain. From the molecular standpoint, we will highlight how pain-inducing, relative to valence neutral stimuli shape the key intraneuronal signaling pathways mediating short- and long-term adaptation and plasticity through gene expression and epigenetic changes. At the circuit level, we will analyze findings on various input integration models leading to the generation of negative affective states. The lecture will conclude with the significance of the aforementioned analyses for devising novel pain therapeutics.

Saturday, September 30th, 11:00

Pain modulation and emotion

Volker Neugebauer

Texas Tech University Health Sciences Center, Lubbock, TX, USA

The amygdala and related limbic circuits have emerged as important players in pain modulation and in the affective dimension of pain. While pain-related neuroplasticity in this region is now well- established, the contribution of non-neuronal factors and mechanisms of chronic neuroplasticity are not clear. Evidence will be discussed to suggest a change of synapse- and cell type-specific mechanisms of amygdala neuroplasticity and pain behaviors in the transition from acute to chronic neuropathic pain. The focus will be on CRF neurons and neuro-immune signaling, their interactions, and mechanistic links to pain behaviors. Data from opto- and chemogenetic strategies combined with electrophysiology and behavior will be presented and the application of transcriptomics will be discussed for the identification of molecular mechanisms and factors of neuropathic pain-related changes in the amygdala.

Saturday, September 30th, 11:30

Early anti-inflammatory treatment of pain: beneficial or detrimental?

Massimo Allegri

Centre Lemanique d'antalgie et neuromodulation, Ensemble Hospitalier de la Cote, Morges, Switzerland

Pain is an intricate phenomenon with a complex neurophysiological basis. Recently, the definition of pain has undergone revision, accompanied by the proposal of a new classification to enhance its understanding, aiding in more accurate diagnosis. In fact, pain can manifest as a simple symptom of acute or chronic diseases, or it can evolve into a distinct disease itself with its own underlying pathophysiology. For instance, the emergence of "nociplastic pain" as a new entity encompasses various syndromes, including fibromyalgia, shedding light on how alterations in pain pathways can result in a distinct disease, where pain is a prominent symptom. Another significant concern lies in the persistence of pain after surgery, which can linger for up to 3-6 months post-surgery, affecting up to 20% of individuals. Understanding how acute pain transforms into chronic pain is vital for efficient treatment.

Recent research has unveiled the immune system's newfound role in this transition from a symptom to a chronic disease, not only in post-surgery pain but also in chronic conditions like low back pain and temporomandibular pain. Surprisingly, chronic pain is not an aberrant response to pain stimuli, as previously believed; instead, it represents the immune system's "non-response." This discovery underscores the intricate interaction between neurons and the immune system and how an inadequate immune response can lead to modifications in the nervous system, giving rise to chronic pain.

These revelations open up new avenues for prevention and treatment, with potential therapeutic targets that will be explored in the presentation.

Saturday, September 30th, 14:00

Pharmacogenetics of pain treatment

Vita Dolžan

Pharmacogenetics Laboratory, Institute of Biochemistry and Molecular Genetics, Faculty of Medicine, University of Ljubljana, Slovenia

Opioids are commonly used in the treatment of moderate to severe pain, particularly in oncology patients. Opioids such as codeine, oxycodone and tramadol are a preferable option to morphine as they provide a similar level of analgesia with a lower risk of side effects and opioid dependence. Contrary to morphine, these drugs need to be metabolically activated in the liver to their active metabolites that exhibits their analgesic activity by binding to μ opioid receptor (MOR). However some patients experience insufficient pain relief or adverse events when using standard therapeutic doses. Genetic variability of drug metabolizing enzymes, drug transporters as well as drug targets may influence the response to treatment. The most well studied gene involved in the metabolic activation of opioids, codeine and tramadol in particular, is cytochrome P450 2D6 (CYP2D6). The CYP2D6 gene is highly polymorphic with many important single nucleotide polymorphisms, haplotypes and copy number variants that may influence the capacity for drug metabolism. Carriers of two non-functional CYP2D6 variants are poor metabolizers (PMs) and are at risk for reduced treatment efficacy due to lower systemic concentrations active metabolite. On the other hand, carriers of multiple gene copies are ultrarapid metabolizers (UMs) and may be at increased risk of toxicity at therapeutic doses of tramadol and codeine due to elevated concentrations of active metabolites. The current level of pharmacogenetic evidence enabled the preparation of genotype-guided treatment recommendations that can support safer opioid prescribing and better outcomes for patients receiving pain management.

Saturday, September 30th, 14:20

Pharmaco-interventional treatment of non-oncological pain

Gorazd Požlep

Clinical Department of Anaesthesiology and Surgical **Intensive Therapy, University Medical Centre Ljubljana,** Slovenia

Over the last few decades our knowledge about pain has altered drastically. Traditionally pain has been understood as a consequence of a disease or an injury. The implication being that a proper treatment of the underlying disease or healing of the injury would relieve pain. But this is not always the case. In the latest international classification of diseases chronic pain has been described as an independent disease.

There are many different methods for pain treatment. So the approach we take is case specific and depends on the several factors including the underlying cause of the pain, its severity and patient's individual characteristics. Acute pain is normally treated with drugs such as broad spectrum of analgesics e.g. paracetamol and metamizole, non-steroidal anti-inflammatory drugs, opioids and adjuvant analgesics e.g. antidepressants, anticonvulsants and muscle relaxants. Often we can achieve better results with the combination of different drugs.

Interventional pain management involves the use of different procedures to diagnose and treat various types of pain. It can be used when traditional pharmacological methods have proven inadequate or have significant side-effects. These procedures are often performed by a pain management specialist with the aim to provide pain relief by directly targeting the source of pain. Some of the common used interventional pain management techniques include peripheral nerve blocks, epidural steroid injections, facet joint injections, radiofrequency ablation, spinal cord stimulation, intrathecal drug delivery, joint infiltrations and trigger point injections.

Psychological and social factors can play a significant role in shaping how pain is perceived tolerated and managed by the patient. Emotional state, cognitive factors e.g. , expectations, social support, social and cultural factors are some of the important psychosocial factors which can contribute to the experience of pain.
Thus, often an interdisciplinary approach is needed for patients with intractable pain. It involves a team of healthcare professionals from various disciplines working together to address the physical psychological and social aspects of pain.

Saturday, September 30th, 15:00

Pharmaco-interventional treatment of oncological pain

Iztok Potočnik, Branka Stražišar

University Medical Centre Ljubljana, Slovenia
Institute of Oncology, Ljubljana, Slovenia

Pain is very common in oncological patients. The intensity of the pain increases with the progression of the disease. At assessment, 60-90% of patients have significant pain. The cause of pain is complex and may be the result of tumor growth, metastasizing, or treatment (surgical, systemic and radiation). Patients may also have pain due to associated diseases (diabetes, peripheral arterial occlusive disease, degenerative joint diseases). The nature of the pain is usually mixed (nociceptive, neuropathic and nociplastic). Effective pain management is vital. Good pain management improves the quality and quantity of the patient's life. In the treatment of carcinoma pain, we use a multimodal approach, including both non-pharmacological and pharmacological measures (medication and intervention). Pharmacological treatment is based on the World Health Organization's analgesic grading ladder with a multimodal approach. History, examination and pain assessment are always required. Oncological pain is usually severe. Opioids are the basis of pain treatment. If there is a neuropathic component, adjuvant drugs are added (antiepileptics, antidepressants, local anesthetics, ketamine, corticosteroids). When the pain is very severe or additional symptoms are present, clonidine and dexmedetomidine are added. Radiation and bisphosphonates are most helpful in alleviating bone pain. Interventional techniques are necessary in a small proportion of patients (2-10%) when conservative methods fail. Nerve blocks, central nerve blocks and catheters are used. In Slovenia, subcutaneous application of drugs is common, especially towards the end of life, as it allows treatment of several symptoms of advanced disease. We must always adapt the treatment to the individual patient and use a multimodal approach.

Saturday, September 30th, 15:30

Non-pharmacological treatment of pain

Jasmina Markovič Božič, Alenka Spindler Vesel

Clinical Department of Anaesthesiology and Surgical **Intensive Therapy, University Medical Centre Ljublja**na, Slovenia
Department of Anaesthesiology and Reanimation, Faculty of Medicine, University of Ljubljana, Slovenia

Non-pharmacological treatment of pain is used when patients refuse pharmacological or interventional treatments, when such treatments prove unsuccessful, or mostly as part of an integrated multimodal pain approach. They may help decrease pain, give more control over pain, and improve quality of life. Evidence-based non-pharmacologic therapies are safe and effective components of comprehensive pain care that can be opioid-sparing and have additional benefits. They reduce anxiety and depression, reduce nausea and vomiting, facilitate restful sleep, increase a sense of well-being, and motivate patients to participate in their own recovery and commitment to self-care.

There are effective non-pharmacological therapies, such as physical (sensory) interventions that inhibit pain perception or behavioural and environmental approaches that activate pain control mechanisms. Some common non-pharmacological treatments are heat, cold, massage, positioning, acupuncture, transcutaneous electrical neurostimulation (TENS), physical therapy, and psychological support.

There are directed or self-engaged movement therapies and meditative movement therapies, as in yoga and tai chi. Psychological approaches, such as stress management, medical hypnosis, cognitive behavioural therapy, musical therapy, meditation, mindfulness, are also recommended. Other lifestyle approaches, including diet and sleep hygiene, have been shown to benefit health. These are low-risk, low-cost treatments that are well accepted by patients. They have different mechanisms of action that involve endogenous pain modulation systems, neuroplasticity, and nonspecific effects. We will give a review lecture on the topic and focus more on acupuncture and medical hypnosis.

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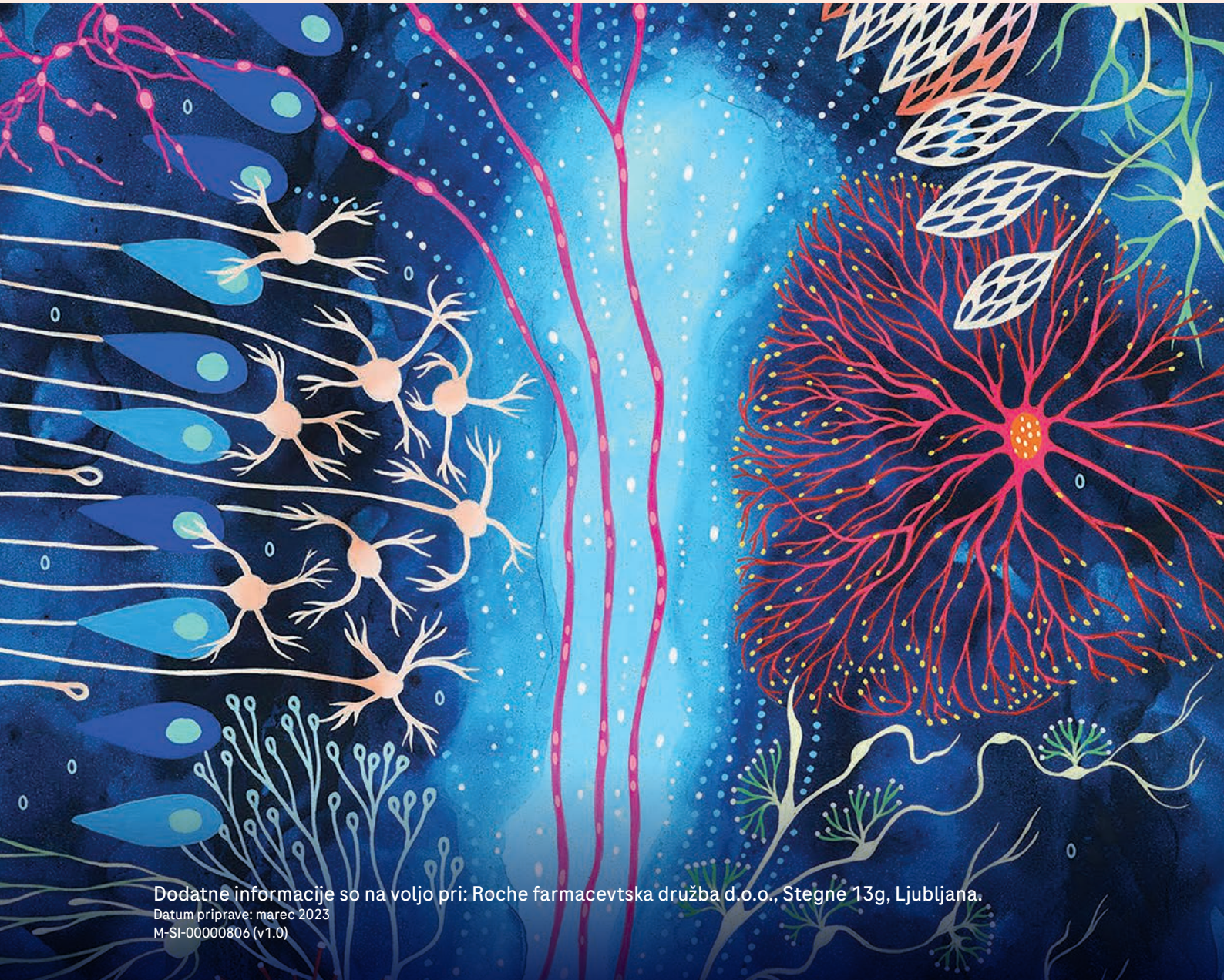

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Če je klinično indicirano, je možno odmerek kortikosteroida postopoma zmanjševati v korakih po največ 2,5 mg do najmanjšega odmerka 5 mg deksametazona (i.v.) ali enakovrednega zdravila. Bolnik mora pred vsakim zmanjšanjem odmerka kortikosteroida za premedikacijo prejeti vsaj 3 zaporedne i.v. infuzije zdravila Onpattro brez pojava reakcij, povezanih z infuzijo. *Izpuščeni odmerek* Po izpuščenem odmerku je treba zdravilo Onpattro dati čim prej. Če bolnik zdravilo Onpattro prejme v 3 dneh po izpuščenem odmerku, naj se zdravljenje nadaljuje po prvotnem načrtu za bolnika. Če bolnik zdravilo Onpattro prejme več kot 3 dni po izpuščenem odmerku, naj se odmerjanje nadaljuje vsake 3 tedne po tem dnevu. Posebne populacije *Starejši bolniki* Pri bolnikih, starih ≥ 65 let, prilagajanje odmerka ni potrebno. *Okvara jeter* Pri bolnikih z blago okvaro jeter prilagajanje odmerka ni potrebno. Zdravila Onpattro niso preučili pri bolnikih z zmerno ali hudo okvaro jeter in ga ti bolniki ne smejo prejemati, razen če pričakovana klinična korist odtehta možno tveganje. *Okvara ledvic* Pri bolnikih z blago do zmerno okvaro ledvic prilagajanje odmerka ni potrebno. Zdravila Onpattro niso preučili pri bolnikih s hudo ledvično okvaro ali končno odpovedjo ledvic in ga ti bolniki ne smejo prejemati, razen če pričakovana klinična korist odtehta možno tveganje. *Pediatrična populacija* Varnost in učinkovitost zdravila Onpattro pri otrocih ali mladostnikih, mlajših od 18 let, nista bili dokazani. Podatkov ni na voljo. Način uporabe Zdravilo Onpattro je za intravensko uporabo. Za bolj podrobna navodila o načinu uporabe glejte Povzetek glavnih značilnosti zdravila. **Kontraindikacije:** Huda preobčutljivost (npr. anafilaksa) na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Reakcije, povezane z infuzijo Pri bolnikih, zdravljenih z zdravilom Onpattro, so opazili reakcije, povezane z infuzijo. Pri bolnikih, ki imajo reakcije, povezane z infuzijo, se prva reakcija, povezana z infuzijo, običajno pojavi pri prvih 2 infuzijah. Najpogostejši simptomi reakcij, povezanih z infuzijo, o katerih so poročali v vseh kliničnih študijah (pri ≥ 2 % bolnikov) so bili zardevanje, bolečina v hrbtu, navzea, bolečina v trebuhu, dispneja in glavobol. Reakcije, povezane z infuzijo, lahko vključujejo tudi hipotenzijo in sinkopo. Za zmanjšanje tveganja reakcij, povezanih z infuzijo, je treba bolnike na dan infundiranja zdravila Onpattro vsaj 60 minut pred začetkom infundiranja premedicirati. Če se pojavi reakcija, povezana z infuzijo, je treba razmisliti o upočasnitvi ali prekinitvi infundiranja in uvedbi ustreznega zdravljenja (npr. s kortikosteroidi ali drugo simptomatsko zdravljenje). Pri prekinitvi infundiranja se infundiranje lahko ponovno začne z nižjo hitrostjo, ko simptomi izzvenijo. Infundiranje je treba prekiniti v primeru resnih ali smrtno nevarnih reakcij, povezanih z infuzijo. Pri nekaterih bolnikih, ki imajo reakcije, povezane z infuzijo, lahko upočasnitev hitrosti infundiranja ali dodatni oz. večji odmerki enega ali več zdravil za premedikacijo pri nadaljnjih infuzijah pomagajo zmanjšati tveganje reakcij, povezanih z infuzijo. Pomanjkanje vitamina A Zdravilo Onpattro z zmanjšanjem ravni beljakovine TTR v serumu povzroči zmanjšanje ravni vitamina A (retinol) v serumu. Ravni vitamina A v serumu, ki so pod spodnjo mejo normalnih vrednosti, je treba korigirati in pred uvedbo zdravljenja oceniti kakršne koli očesne simptome ali znake zaradi pomanjkanja vitamina A. Bolniki, ki prejemajo zdravilo Onpattro, morajo za zmanjšanje možnega tveganja toksičnosti za oči zaradi pomanjkanja vitamina A peroralno jemati nadomestek vitamina A v odmerku 2500 i.e na dan. V prvih 60 dneh nosečnosti so lahko previsoke ali prenizke ravni vitamina A povezane s povečanim tveganjem malformacije ploda. Zato je treba pred začetkom jemanja zdravila Onpattro izključiti nosečnost, ženske v rodni dobi pa morajo uporabljati učinkovito kontracepcijo. Če ženska namerava zanositi, je treba dajanje zdravila Onpattro in nadomestka vitamina A prekiniti in spremljati ravni vitamina A v serumu, ki se morajo vrniti na normalno raven, preden poskusi zanositi. V primeru nenačrtovane nosečnosti je treba zdravljenje z zdravilom Onpattro prekiniti. Pomožne snovi z znanim učinkom To zdravilo vsebuje 3,99 mg natrija na ml, kar je enako 0,2 % največjega dnevnega vnosa natrija za odrasle osebe, ki ga priporoča Svetovna zdravstvena organizacija, in znaša 2 g. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Formalnih kliničnih študij medsebojnega delovanja zdravil niso izvedli. Pri odmerkih, večjih od klinično pomembnega odmerka, so *in vitro* opazili indukcijo in časovno odvisno zaviranje CYP2B6. Neto učinek na substrate CYP2B6 (npr. bupropion in efavirenz) *in vivo* ni znan. Ne pričakuje se, da bi zdravilo Onpattro povzročalo medsebojno delovanje z drugimi zdravili ali da bi nanj vplivali zaviralci ali induktorji encimov citokroma P450. Preiskave vitamina A TTR v serumu je nosilec vezavne beljakovine za retinol, ki olajša prenos vitamina A v krvi. Zdravljenje z zdravilom Onpattro zmanjša ravni TTR v serumu, kar povzroči zmanjšanje ravni vezavne beljakovine za retinol in vitamina A v serumu. Vendar pa lahko v odsotnosti vezavne beljakovine za retinol prenos in privzem vitamina A v tkivo potekata s pomočjo alternativnih mehanizmov. Posledično laboratorijske preiskave ravni vitamina A v serumu med zdravljenjem z zdravilom Onpattro ne kažejo celotne količine vitamina A v telesu, zato se ne smejo uporabljati kot smernice za dodajanje vitamina A. **Plodnost, nosečnost in dojenje:** Ženske v rodni dobi Zdravljenje z zdravilom Onpattro zmanjšuje ravni vitamina A v serumu. Previsoke ali prenizke ravni vitamina A so lahko povezane s povečanim tveganjem malformacije ploda. Zato je treba pred uvedbo zdravljenja izključiti nosečnost, ženske v rodni dobi pa morajo uporabljati učinkovito kontracepcijo. Če ženska namerava zanositi, je treba dajanje zdravila Onpattro in nadomestka vitamina A prekiniti in spremljati ravni vitamina A v serumu, ki se morajo vrniti na normalno raven, preden poskusi zanositi. Nosečnost Podatkov o uporabi zdravila Onpattro pri nosečnicah ni. Ni dovolj študij na živalih o vplivu zdravila na sposobnost razmnoževanja. Zaradi možnosti tveganja za teratogenost, ki izhaja iz neuravnoteženih ravni vitamina A zdravila Onpattro ne smete uporabljati pri nosečnicah, razen če klinično stanje nosečnice zahteva zdravljenje. V primeru nenačrtovane nosečnosti je treba skrbno spremljati plod, zlasti v prvem trimesečju. Dojenje Ni znano, ali se zdravilo Onpattro izloča v materino mleko. Tveganja za dojenega novorojenca/dojenčka ne moremo izključiti. Odločiti se je treba med prenehanjem dojenja in prenehanjem/prekinitvijo zdravljenja z zdravilom Onpattro, pri čemer je treba pretehtati prednosti dojenja za otroka in prednosti zdravljenja za mater. Plodnost Podatkov o učinku zdravila Onpattro na plodnost pri človeku ni. Študije na živalih niso pokazale vpliva na plodnost samcev ali samic. **Vpliv na sposobnost vožnje in upravljanja strojev:** Zdravilo Onpattro nima vpliva ali ima zanemarljiv vpliv na sposobnost vožnje in upravljanja strojev. **Neželeni učinki:** Najpogostejši neželeni učinki, o katerih so poročali pri bolnikih, zdravljenih z zdravilom Onpattro, so bili periferni edem (29,7 %) in reakcije, povezane z infuzijo (18,9 %). En bolnik (0,7 %) je zdravljenje med kliničnimi študijami prekinil zaradi reakcije, povezane z infuzijo. Zelo pogosti (≥ 1/10): reakcije povezane z infuzijo, periferni edem. Pogosti (≥ 1/100 do < 1/10): bronhitis, sinusitis, rinitis, vrtoglavica, dispneja, dispepsija, eritem, artralgija, mišični krči. Občasni (≥ 1/1000 do < 1/100): ekstravazacija.
Način/režim predpisovanja/izdaje zdravila: ZZ - Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v javnih zdravstvenih zavodih ter pri pravnih in fizičnih osebah, ki opravljajo zdravstveno dejavnost.
Imetnik dovoljenja za promet z zdravilom: Alnylam Netherlands B.V., Antonio Vivaldistraat 150, 1083 HP Amsterdam, Nizozemska
Številka(-e) dovoljenja za promet z zdravilom: EU/1/18/1320/001
Datum zadnje revizije besedila: 05/2023

Pred predpisovanjem se seznanite s celotnim Povzetkom glavnih značilnosti zdravila.

hATTR: dedna transtiretinska amiloidoza; TTR: transtiretin

Reference:
1. Alnylam Pharmaceuticals. ONPATTRO® Povzetek glavnih značilnosti zdravila. **2.** Adams D, et al. N Engl J Med. 2018;379(1):11–21. **3.** Solomon SD, et al. Circulation. 2019;139(4):431–443.

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GENESIS pharma

Datum priprave materiala: september 2023. ONP-SI-AD-09.2023

VYVGART®
20 mg/ml koncentrat za raztopino za infundiranje
(efgartigimod alfa)

Zdravilo VYVGART: zdravljenje vzroka za viden učinek

Dokazano izboljšanje sposobnosti bolnikov za opravljanje vsakodnevnih aktivnosti[1]*

Prvi in edini odobreni fragment Fc, pridobljen iz IgG, za zdravljenje **generalizirane miastenije gravis** pri odraslih bolnikih, ki so pozitivni na protitelesa proti acetilholinskemu receptorju.[2,3]

Zdravilo Vyvgart je indicirano kot dodatek k standardni terapiji za zdravljenje odraslih bolnikov s splošno miastenijo gravis (gMG), ki so pozitivni na protitelesa proti acetilholinskim receptorjem (AChR).[2]

*Primarni cilj študije ADAPT: delež bolnikov, pozitivnih na protitelesa za AChR (AChR-Ab+), odzivnih na MG-ADL v ciklu 1; VYVGART 67,7 % (44/65), placebo 29,7 % (19/64); p < 0,0001.

Okrajšave: Ab, protitelo; AChR, acetilholinski receptor; Fc domena IgG; gMG, generalizirana miastenija gravis; IgG, imunoglobulin G; MG-ADL, lestvica aktivnosti vsakdanjega življenja, specifična za miastenijo gravis.

Reference: 1. Howard JF et al. Lancet Neurol 2021;20(7):526-536. **2.** VYVGART. Povzetek glavnih značilnosti zdravila, september 2023. **3.** Wolfe GI et al. J Neurol Sci 2021;430:118074.

Skrajšan povzetek glavnih značilnosti zdravila. Pred predpisovanjem preberite celoten Povzetek glavnih značilnosti zdravila.

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8, kako poročati o neželenih učinkih.

Vyvgart 20 mg/ml koncentrat za raztopino za infundiranje (efgartigimod alfa)

Kakovostna in količinska sestava: Ena viala z 20 ml vsebuje 400 mg efgartigimoda alfa (20 mg/ml). Efgartigimod alfa je fragment Fc, pridobljen iz humanega rekombinantnega imunoglobulina G1(IgG1), proizvedenega v ovarijskih celicah kitajskega hrčka s tehnologijo rekombinantne DNK. **Terapevtske indikacije:** Zdravilo Vyvgart je indicirano kot dodatek k standardni terapiji za zdravljenje odraslih bolnikov s splošno miastenijo gravis (gMG, generalised Myasthenia Gravis), ki so pozitivni na protitelesa proti acetilholinskim receptorjem (AChR, Acetylcholine Receptor). **Odmerjanje in način uporabe:** Efgartigimod alfa mora dajati zdravstveni delavec pod nadzorom zdravnika z izkušnjami pri zdravljenju bolnikov z živčno-mišičnimi motnjami. Odmerjanje: Priporočeni odmerek je 10 mg/kg v obliki 1-urne intravenske infuzije, ki jo je treba dajati v ciklih infundiranja enkrat na teden 4 tedne. Nadaljnje cikle zdravljenja aplicirajte v skladu s klinično oceno. Pogostnost ciklov zdravljenja se lahko razlikuje glede na bolnika. V kliničnem razvojnem programu je bil najzgodnejši čas za začetek naslednjega cikla zdravljenja 7 tednov od začetnega infundiranja prejšnjega cikla. Varnost uvedbe nadaljnjih ciklov prej kot 7 tednov po začetku prejšnjega cikla zdravljenja ni bila ugotovljena. Pri bolnikih s telesno maso 120 kg ali več je priporočeni odmerek 1200 mg (3 viale) na infundiranje. *Izpuščeni odmerek:* Če načrtovano infundiranje ni možno, se lahko zdravljenje izvaja do 3 dni pred načrtovano časovno točko ali po njej. Nato je treba nadaljevati s prvotnim režimom odmerjanja, dokler se cikel zdravljenja ne konča. Če je treba odmerek odložiti za več kot 3 dni, odmerka ne smete dajati, da zagotovite dajanje dveh zaporednih odmerkov v presledku najmanj 3 dni. *Starejši:* Pri bolnikih, starih 65 let ali več, odmerka ni treba prilagajati. *Okvara ledvic:* Podatki o varnosti in učinkovitosti pri bolnikih z blago okvaro ledvic so omejeni; prilagajanje odmerka pri teh bolnikih ni potrebno. Podatki o varnosti in učinkovitosti pri bolnikih z zmerno okvaro ledvic so zelo omejeni, za bolnike s hudo okvaro ledvic pa podatkov ni. *Okvara jeter:* Podatki za bolnike z okvaro jeter niso na voljo. Odmerka ni treba prilagajati. *Pediatrična populacija:* Podatkov ni na voljo. Način uporabe: Zdravilo se sme dajati samo z intravensko infuzijo. Zdravila ne dajajte kot intravensko potisno ali bolusno injekcijo. Pred uporabo ga je treba razredčiti z raztopino 9 mg/ml (0,9 %) natrijevega klorida za injiciranje. Zdravilo je treba dajati 1 uro. Pred dajanjem efgartigimoda alfa mora biti na voljo ustrezno zdravljenje infuzijskih reakcij in preobčutljivostnih reakcij. V primeru infuzijskih reakcij je treba infundirati počasneje, infundiranje prekiniti ali pa prenehati izvajati. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Sledljivost: Z namenom izboljšanja sledljivosti bioloških zdravil je treba jasno zabeležiti ime in številko serije uporabljenega zdravila. Bolniki z miastenijo gravis razreda V po merilih Ameriške fundacije za miastenijo gravis (MGFA): Zdravljenja z efgartigimodom alfa pri teh bolnikih niso proučevali. Upoštevati je treba zaporedje uvedbe zdravljenja med uveljavljenimi terapijami za MG-krizo in efgartigimodom alfa ter njihovo morebitno medsebojno delovanje. Okužbe: Ker efgartigimod alfa povzroči prehodno zmanjšanje ravni IgG, se lahko tveganje za okužbe poveča. Najpogostejše okužbe, opažene v kliničnih preskušanjih, so bile okužbe zgornjih dihal in okužbe sečil. Med zdravljenjem z zdravilom Vyvgart je treba bolnike spremljati glede kliničnih znakov in simptomov okužb. Pri bolnikih z aktivno okužbo je treba pretehtati razmerje med koristjo in tveganjem za ohranitev ali prekinitev zdravljenja z efgartigimodom alfa, dokler ni okužba odpravljena. Če se pojavijo resne okužbe, je treba razmisliti o odložitvi zdravljenja z efgartigimodom alfa, dokler ni okužba odpravljena. Infuzijske reakcije in preobčutljivostne reakcije: Pojavijo se lahko infuzijske reakcije, kot sta izpuščaj ali pruritus. V kliničnem preskušanju so bile infuzijske reakcije blage do zmerne in niso privedle do začasne ali trajne prekinitve zdravljenja. Bolnike je treba med dajanjem zdravila in še 1 uro po njem spremljati glede kliničnih znakov in simptomov infuzijskih reakcij. Če pride do reakcije, je odvisno od resnosti reakcije treba infundirati počasneje, infundiranje prekiniti ali prenehati izvajati, in uvesti ustrezne podporne ukrepe. Ko reakcija izzveni, se lahko zdravljenje previdno nadaljuje odvisno od klinične ocene. V obdobju po začetku trženja so poročali o primerih anafilaktične reakcije. Ob sumu na anafilaktično reakcijo je treba dajanje zdravila Vyvgart takoj prekiniti in začeti ustrezno zdravljenje. Bolnike je treba obvestiti o znakih in simptomih preobčutljivostnih in anafilaktičnih reakcij ter jim svetovati, naj se v primeru pojava teh reakcij takoj obrnejo na svojega zdravstvenega delavca. Imunizacije: Imunizacije s cepivi med zdravljenjem z efgartigimodom alfa niso proučevali. Varnost cepljenja z živimi ali živimi oslabljenimi cepivi in odziv na cepljenje s cepivi nista znana. Vsa cepiva je treba uporabiti v skladu s smernicami za cepljenje in vsaj 4 tedne pred začetkom zdravljenja. Pri bolnikih, ki se zdravijo, cepljenje z živimi ali živimi oslabljenimi cepivi ni priporočljivo. Vsa druga cepiva morajo biti uporabljena vsaj 2 tedna po zadnjem infundiranju v ciklu zdravljenja in 4 tedne pred začetkom naslednjega cikla. Imunogenost: Protitelesa proti efgartigimodu alfa niso imela opaznega vpliva na klinično učinkovitost ali varnost oziroma na farmakokinetične in farmakodinamične parametre. Imunosupresivi in antiholinesterazna zdravila: Pri zmanjšanju ali prekinitvi zdravljenja z nesteroidnimi imunosupresivi, kortikosteroidi in antiholinesteraznimi zdravili je treba bolnike skrbno spremljati glede znakov poslabšanja bolezni. Vsebnost natrija: To zdravilo vsebuje 67,2 mg natrija na vialo, kar ustreza 3,4 % največjega dnevnega vnosa 2 g natrija za odraslo osebo po priporočilih Svetovne zdravstvene organizacije (SZO). **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Študij medsebojnega delovanja niso izvedli. Efgartigimod alfa lahko zmanjša koncentracije spojin, ki se vežejo na humani neonatalni receptor Fc (FcRn), tj. imunoglobulinov, monoklonskih protiteles ali derivatov protiteles. Če je mogoče, je priporočljivo, da se začetek zdravljenja s temi zdravili preloži na 2 tedna po zadnjem odmerku katerega koli cikla zdravljenja z zdravilom Vyvgart. Bolnike je treba skrbno spremljati glede predvidenega odziva na učinkovitost teh zdravil. Zamenjava plazme, imunoadsorpcija in plazmafereza lahko zmanjšajo ravni efgartigimoda alfa v obtoku. Vsa cepiva je treba uporabiti v skladu s smernicami za cepljenje in vsaj 4 tedne pred začetkom cikla zdravljenja, vendar ne prej kot 2 tedna po zadnjem infundiranju v ciklu zdravljenja. Pri bolnikih, ki se zdravijo, cepljenje z živimi ali živimi oslabljenimi cepivi ni priporočljivo. **Plodnost, nosečnost in dojenje:** Nosečnost: Podatkov o uporabi efgartigimoda alfa pri nosečnicah ni. Znano je, da se protitelesa, vključno s terapevtskimi monoklonskimi protitelesi, aktivno prenašajo preko posteljice (po 30 tednihnosečnosti) z vezavo na FcRn. Efgartigimod alfa se lahko prenese z matere na razvijajoči se plod. Pričakuje se zmanjšanje pasivne zaščite novorojenca. Zato je treba razmisliti o tveganjih in koristih uporabe živih/živih oslabljenih cepiv pri dojenčkih, ki so bili *in utero* izpostavljeni efgartigimodu alfa. O zdravljenju nosečnic z zdravilom Vyvgart je treba razmisliti le, če klinične koristi odtehtajo tveganja. Dojenje: Ni podatkov o prisotnosti efgartigimoda alfa v materinem mleku, učinkih na dojenega otroka ali učinkih na proizvodnjo mleka. O zdravljenju žensk, ki dojijo, z efgartigimodom alfa je treba razmisliti le, če klinične koristi odtehtajo tveganja. Plodnost: Podatkov o vplivu efgartigimoda alfa na plodnost pri ljudeh ni na voljo. **Vpliv na sposobnost vožnje in upravljanja strojev:** Zdravilo Vyvgart nima vpliva ali ima zanemarljiv vpliv na sposobnost vožnje in upravljanja strojev. **Neželeni učinki:** Najpogosteje opaženi neželeni učinki so bile okužbe zgornjih dihal (10,7 %) in okužbe sečil (9,5 %). Pogosti (≥ 1/100 do < 1/10) neželeni učinki so bili še bronhitis, mialgija in proceduralni glavobol. V obdobju po začetku trženja so poročali o primerih anafilaktične reakcije. Pogostnost je neznana. Več informacij glede neželenih učinkov lahko najdete v Povzetku glavnih značilnosti zdravila. **Način in režim predpisovanja ter izdaje zdravila:** H - Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. **Imetnik dovoljenja za promet z zdravilom:** argenx BV, Industriepark-Zwijnaarde 7, 9052 Gent, Belgija **Številka dovoljenja za promet z zdravilom:** EU/1/22/1674/001 **Datum zadnje revizije besedila:** September 2023

Poročanje o neželenih učinkih
Poročanje o domnevnih neželenih učinkih zdravila po izdaji dovoljenja za promet je pomembno. Omogoča namreč stalno spremljanje razmerja med koristmi in tveganji zdravila. Od zdravstvenih delavcev se zahteva, da poročajo o katerem koli domnevnem neželenem učinku zdravila na Javno agencijo RS za zdravila in medicinske pripomočke (h-farmakovigilanca@jazmp.si).

Samo za strokovno javnost.
Zdravilo še ni razvrščeno na listo zdravil s strani ZZZS.
SI-MG-2023-98 I EU-VYV-22-00003 I Datum priprave: september 2023.

MEDISON | argenx

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KLINIČNE RAZISKAVE IN RAZISKAVE UPORABE V VSAKDANJI PRAKSI KAŽEJO

[VEČ JE MOGOČE] IS POSSIBLE

ZDRAVILO SPINRAZA™ POMAGA BOLNIKOM DOSEČI VEČ V PRIMERJAVI S KONTROLNO SKUPINO, KI JE PREJEMALA PLACEBO, IN NARAVNIM POTEKOM BOLEZNI[1,2]

Skrajšan povzetek glavnih značilnosti zdravila Spinraza
Ime zdravila: Spinraza 12 mg raztopina za injiciranje **Sestava:** En ml vsebuje 2,4 mg nusinersena. **Indikacije:** Zdravilo Spinraza je indicirano za zdravljenje 5q spinalne mišične atrofije. **Odmerjanje in način uporabe:** Zdravljenje z zdravilom Spinraza sme začeti le zdravnik, ki ima izkušnje z zdravljenjem spinalne mišične atrofije (SMA). • **Odmerjanje:** Priporočeni odmerek je 12 mg (5 ml) na vsako uporabo. Zdravljenje z zdravilom Spinraza je treba uvesti čimprej po postavitvi diagnoze s 4 začetnimi (polnilnimi) odmerki na dan 0, 14, 28 in 63. Nato je treba dati vzdrževalni odmerek enkrat na vsake 4 mesece. • ***Izpuščeni ali odloženi odmerki*** Za priporočila o izpuščenih ali odloženih odmerkih prosimo, glejte preglednico 1 v povzetku glavnih značilnosti zdravila Spinraza. • ***Okvara ledvic:*** Pri bolnikih z okvaro ledvic nusinersena niso proučevali. Varnost in učinkovitost pri bolnikih z okvaro ledvic nista bili dokazani in je treba te bolnike natančno opazovati. • ***Okvara jeter:*** Pri bolnikih z okvaro jeter nusinersena niso proučevali. Ne presnavlja se preko encimskega sistema citokroma P450, zato ni verjetno, da bo pri bolnikih z okvaro jeter potrebno prilagajanje odmerka. • **Način uporabe:** intratekalno z lumbalno punkcijo. **Kontraindikacije in interakcije:** • Preobčutljivost na učinkovino ali katero koli pomožno snov. • Študij medsebojnega delovanja niso izvedli. Študije in vitro so pokazale, da nusinersen ni induktor ali inhibitor presnove preko presnovne poti CYP450. Študije in vitro kažejo, da je medsebojno delovanje z nusinersenom malo verjetno zaradi kompeticije za vezavo na plazemske beljakovine ali zaradi kompeticije s prenašalci ali inhibicije prenašalcev. **Opozorila/previdnostni ukrepi:** • Obstaja nevarnost neželenih učinkov, ki se pojavljajo v okviru postopka lumbalne punkcije (npr. glavobol, bolečina v hrbtu, bruhanje). • Po dajanju drugih subkutano ali intravensko apliciranih protismiselnih oligonukleotidov so opazili trombocitopenijo in abnormalnosti koagulacije krvi, vključno z akutno hudo trombocitopenijo. Če je klinično indicirano, je pred dajanjem zdravila Spinraza priporočljivo laboratorijsko testiranje trombocitov in koagulacije krvi. • Po dajanju drugih subkutano ali intravensko apliciranih protismiselnih oligonukleotidov so opazili toksičnost za ledvice. Če je klinično indicirano, je priporočljivo testiranje beljakovin v urinu • Pri bolnikih, zdravljenih z nusinersenom v obdobju trženja, so poročali o komunikantnem hidrocefalusu, ki ni bil povezan z meningitisom ali krvavitvijo. Nekaterim bolnikom so vstavili ventrikulo-peritonealni spoj. Pri bolnikih z zmanjšano ravnijo zavesti je treba preveriti, ali imajo hidrocefalus. Trenutno so koristi in tveganja zdravljenja z nusinersenom pri bolnikih z ventrikulo-peritonealnim spojem neznana in nadaljevanje zdravljenja je treba skrbno pretehtati. • Zdravilo vsebuje manj kot 1 mmol (23 mg) natrija na 5 ml vialo, kar v bistvu pomeni 'brez natrija'. • Zdravilo vsebuje manj kot 1 mmol (39 mg) kalija na 5 ml vialo, kar v bistvu pomeni 'brez kalija'. **Neželeni učinki:** • ***Zelo pogosti:*** glavobol, bruhanje, bolečina v hrbtu (ti učinki se lahko upoštevajo kot manifestacija postpunkcijskega sindroma). • ***Neznana pogostnost:*** meningitis, preobčutljivost (npr. angioedem, urtikarija in izpuščaj), aseptični meningitis. • V obdobju trženja zdravila so opazili primere komunikantnega hidrocefalusa. • ***Poročanje o domnevnih neželenih učinkih:*** Poročanje o domnevnih neželenih učinkih zdravila po izdaji dovoljenja za promet je pomembno. Omogoča namreč stalno spremljanje razmerja med koristmi in tveganji zdravila. Od zdravstvenih delavcev se zahteva, da poročajo o katerem koli domnevnem neželenem učinku zdravila na Javna agencija Republike Slovenije za zdravila in medicinske pripomočke, Sektor za farmakovigilanco, Nacionalni center za farmakovigilanco, Slovenčeva ulica 22, SI-1000 Ljubljana, Tel: +386 (0)8 2000 500, Faks: +386 (0)8 2000 510, e-pošta: h-farmakovigilanca@jazmp.si, spletna stran: www.jazmp.si **Imetnik dovoljenja za promet:** Biogen Netherlands B.V., Prins Mauritslaan 13, 1171 LP Badhoevedorp, Nizozemska **Način izdajanja zdravila**: H **Opozorilo:** Pred predpisovanjem preberite celoten povzetek glavnih značilnosti zdravila. **Datum priprave informacije:** 01/2022

Prikazane slike so nastale po navdihu resničnih oseb, ki živijo s spinalno mišično atrofijo, in so namenjene zgolj ponazoritvi.

Vir: 1. Povzetek glavnih značilnosti zdravila SPINRAZA™. **2.** Coratti G, et al. Orphanet J Rare Dis. 2021;16:430.

Biogen

Podrobnejše informacije so na voljo pri: Biogen Pharma d.o.o., Ameriška ulica 8, 1000 Ljubljana, Slovenija
tel.: 01 511 02 90, faks: 01 511 02 99; www.biogen-pharma.si
Samo za strokovno javnost; Datum priprave materiala: avgust 2023; Biogen-216435

SPINRAZA™ (nusinersen) 12 mg raztopina za injiciranje

BOLNIKI V ZGODNJEM STADIJU

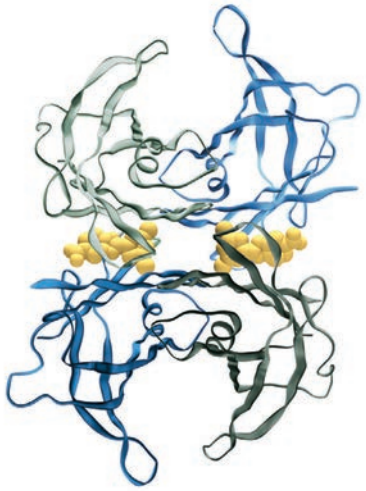
V zgodnjem stadiju polinevropatije zaradi ATTR ...

ZDRAVILO VYNDAQEL: ZA STABILIZACIJO TTR[1,2]

Zdravilo VYNDAQEL se selektivno veže na TTR, ga stabilizira in prepreči disociacijo – tako zavre amiloidno kaskado, ki ima pomembno vlogo pri napredovanju polinevropatije zaradi ATTR.[1,3,4]

V kliničnih in *ex-vivo* študijah pri bolnikih z *Val30Met* in brez *Val30Met* je zdravilo VYNDAQEL stabiliziralo **37 mutacij TTR.**[1, 4-7]

TTR je naravno prisotna beljakovina, ki jo zdravilo VYNDAQEL stabilizira v njeni nativni obliki[1,3,4]



Zdravilo VYNDAQEL na vezavnem mestu →

Stabilizacija TTR je dokazana pri številnih vrstah mutacij

98 % bolnikov z *Val30Met* po 1,5 leta[1†]

100 % bolnikov brez *Val30Met* po 1 letu[8‡]

†**Načrt študije:** 1,5-letna randomizirana, dvojno slepa, s placebom nadzorovana ključna študija. Bolniki z *Val30Met* so prejemali 20 mg zdravila VYNDAQEL na dan ali placebo. Soprimarna opazovana dogodka: analiza bolnikov, odzivnih po oceni nevropatske okvare v spodnjih okončinah (NIS-LL) (poslabšanje za < 2 točki) in razlika povprečne spremembe celotne norfolške ocene kakovosti življenja pri diabetični nevropatiji (TQOL) od izhodišča med terapevtskima skupinama v populaciji z namenom zdravljenja (ZNZ) (n = 125) in populaciji, ocenljivi za učinkovitost (n = 87). Sekundarni opazovani dogodki: sprememba nevrološkega delovanja, stanja prehranjenosti in stabilizacija TTR v populaciji ZNZ.[9]

‡**Načrt študije:** enoletna odprta študija z eno samo skupino. Bolniki brez *Val30Met* so prejemali 20 mg zdravila VYNDAQEL na dan. Primarni opazovani dogodek: stabilizacija TTR po 6 tednih (n = 19). Sekundarna opazovana dogodka: stabilizacija TTR po 6 mesecih (n = 18) in 12 mesecih (n = 17).[5]

TTR = transtiretin
ATTR = transtiretinski amiloid

Vyndaqel® (tafamidis)

ZGODNJE ZDRAVLJENJE, DOLGOROČNA ZANESLJIVOST[3]

BISTVENI PODATKI IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA

VYNDAQEL 20 mg mehke kapsule

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o kateremkoli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8 povzetka glavnih značilnosti zdravila, kako poročati o neželenih učinkih. **Sestava in oblika zdravila:** Ena mehka kapsula vsebuje 20 mg mikroniziranega tafamidis meglumina, kar ustreza 12,2 mg tafamidisa. Ena mehka kapsula vsebuje največ 44 mg sorbitola. **Indikacije:** Zdravljenje transtiretinske amiloidoze pri odraslih bolnikih s simptomatsko polinevropatijo stadija 1 za preprečevanje pojava perifernih nevroloških okvar. **Odmerjanje in način uporabe:** Zdravljenje je treba uvesti pod nadzorom zdravnika z izkušnjami pri zdravljenju bolnikov s transtiretinsko amiloidno polinevropatijo (ATTR-PN). Priporočeni odmerek je 20 mg peroralno enkrat na dan. Tafamidis in tafamidis meglumin nista medsebojno zamenljiva na podlagi mg. Če po odmerjanju pride do bruhanja in bolnik izbruha nepoškodovano kapsulo, naj vzame še en odmerek, če je mogoče. Če kapsule ne izbruha, dodaten odmerek ni potreben. Starejši bolniki: Prilagajanje odmerka ni potrebno. Okvara jeter in ledvic: Podatki pri bolnikih s hudo okvaro ledvic (očistek kreatinina 30 ml/min ali manj) so omejeni. Tafamidis meglumina pri bolnikih s hudo okvaro jeter niso preskušali, zato je pri teh bolnikih priporočljiva previdnost. Pediatrična populacija: Tafamidis ni namenjen za uporabo pri pediatrični populaciji. Način uporabe: Mehke kapsule je treba pogoltniti cele in se jih ne sme zdrobiti ali prerezati. Zdravilo Vyndaqel se lahko vzame s hrano ali brez nje. **Kontraindikacije:** Preobčutljivost na učinkovino ali katerokoli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Ženske v rodni dobi morajo med jemanjem tafamidis meglumina uporabljati ustrezno kontracepcijo in z njeno uporabo nadaljevati še 1 mesec po prenehanju zdravljenja. Tafamidis meglumin je treba uporabiti kot dodatek običajni skrbi za zdravljenje bolnikov z ATTR-PN. Bolnike je treba nadzirati in še naprej preverjati potrebo po dodatnem zdravljenju, vključno s potrebo po presaditvi jeter. Ker podatkov glede uporabe tafamidis meglumina pri bolnikih po presaditvi jeter ni, je treba pri teh bolnikih zdravljenje prekiniti. To zdravilo vsebuje največ 44 mg sorbitola na kapsulo. Sorbitol je vir fruktoze. Upoštevati je treba aditivni učinek sočasne uporabe zdravil, ki vsebujejo sorbitol (ali fruktozo), in sorbitola (ali fruktoze), ki ga vnesemo s hrano. Količina sorbitola v zdravilih za peroralno uporabo lahko vpliva na biološko uporabnost drugih zdravil za peroralno uporabo, ki se jemljejo sočasno. **Medsebojno delovanje z drugimi zdravili:** V klinični študiji pri zdravih prostovoljcih 20 mg tafamidis meglumina ni niti induciralo niti zaviralo encima citokroma P450 CYP3A4. Tafamidis *in vitro* zavira prenašalce BCRP, OAT1 in OAT3 ter lahko pri klinično pomembnih koncentracijah povzroči medsebojna delovanja s substrati teh prenašalcev. Študij medsebojnega delovanja, v katerih bi ocenjevali vpliv drugih zdravil na tafamidis meglumin, niso izvedli. Tafamidis lahko zmanjša koncentracije celokupnega tiroksina v serumu brez spremljajoče spremembe prostega tiroksina (T4) ali ščitnico spodbujajočega hormona (TSH). Spremljajočih kliničnih ugotovitev, skladnih z nepravilnim delovanjem ščitnice, ni bilo. **Plodnost, nosečnost in dojenje:** Ženske v rodni dobi morajo uporabljati ustrezno kontracepcijo med zdravljenjem s tafamidis megluminom in še en mesec po prenehanju zdravljenja, zaradi podaljšanega razpolovnega časa zdravila. Podatkov o uporabi tafamidis meglumina pri nosečnicah ni. Študije na živalih so pokazale škodljiv vpliv na razvoj. Tafamidis meglumina ne uporabljajte pri nosečnicah in ženskah v rodni dobi, ki ne uporabljajo učinkovite kontracepcije. Razpoložljivi podatki pri živalih kažejo na izločanje tafamidisa v mleko. Tveganja za dojenega novorojenčka/otroka ne moremo izključiti. Tafamidis meglumina se med dojenjem ne sme uporabljati. **Vpliv na sposobnost vožnje in upravljanja strojev:** Tafamidis meglumin naj ne bi imel vpliva ali naj bi imel zanemarljiv vpliv na sposobnost vožnje in upravljanja strojev. **Neželeni učinki:** Zelo pogosti: okužba sečil, okužba nožnice, driska, bolečine v zgornjem delu trebuha. **Preveliko odmerjanje:** Poročali so o enem neželenem dogodku blagega hordeola, povezanim z zdravljenjem. V primeru prevelikega odmerjanja je treba uvesti standardne podporne ukrepe. **Način in režim izdajanja zdravila:** Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. **Imetnik dovoljenja za promet:** Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgija. **Datum zadnje revizije besedila:** 15.02.2023.

Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

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9. Clinical Study Report for Protocol Fx-005. New York, NY: Pfizer Inc; May 2011.

Pfizer

Pfizer Luxembourg SARL, Grand Duchy of Luxembourg, 51, Avenue J. F. Kennedy, L-1855
Pfizer, podružnica Ljubljana, Letališka cesta 29a, 1000 Ljubljana, SLOVENIJA

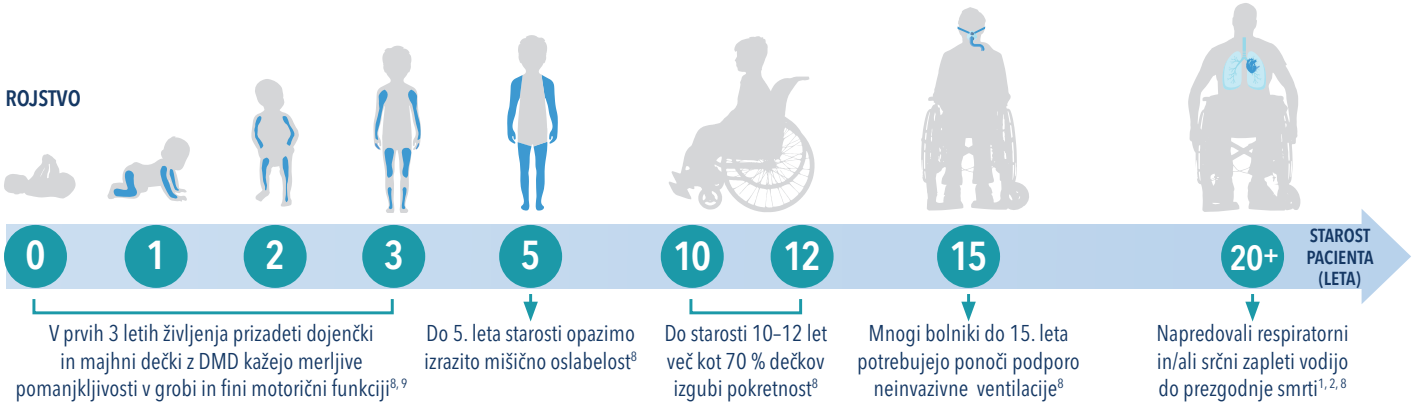
PP-VYN-SVN-0008 Marec 2023 SAMO ZA STROKOVNO JAVNOST.

DUCHENNOVA MIŠIČNA DISTROFIJA (DMD) JE REDKA GENETSKA MOTNJA[1, 2]

- DMD prizadene ~ 1 na 3600 do 6000 živorojenih dečkov[1–3]
- Za DMD je značilna progresivna mišična degeneracija, ki vodi do izgube pokretnosti, dihalnega in srčnega popuščanja ter kasnejše prezgodnje smrti[1, 2, 4, 5]

DMD JE POSLEDICA MUTACIJ V GENU ZA DISTROFIN NA X KROMOSOMU[2, 5]

- DMD povzročajo mutacije (delecije in duplikacije) v genu, ki kodira distrofin, pomembno komponento membrane mišične celice[5, 6]
- Mutacije v genu za distrofin vodijo do odsotnosti ali okvare distrofina[2, 5]
- Posledica tega je nenehna poškodba mišic in zamenjava mišičnih vlaken z brazgotinami in maščobo[6, 7]



ZGODNJE UKREPANJE LAHKO IZBOLJŠA IZID BOLEZNI[1, 2]

- Ko je mišica izgubljena, je ni mogoče obnoviti[7, 10]
- Zgodnja diagnoza je ključnega pomena za hitro obravnavo in zdravljenje[1, 2, 11]
- Vloga osebnih zdravnikov je ključnega pomena, saj so v idealnem položaju za odkrivanje zgodnjih znakov živčno-mišične bolezni[1, 11, 12]

PRAVOČASNA IN TOČNA DIAGNOSTIKA LAHKO PACIENTU IN DRUŽINI OMOGOČI, DA PREJEMA NEGO IN PODPORO, KI JO POTREBUJE[1, 2, 13]

Vir: 1. van Ruiten HJ, *et al. Arch Dis Child.* 2014;99:1074–1077. **2.** Birnkrant DJ, *et al. Lancet Neurol.* 2018;17:251–267. **3.** Bushby K. *et al. Lancet Neurol.* 2010;77–93. **4.** McDonald CM, *et al. Muscle Nerve.* 2013;48:343–356. **5.** Goemans N, *et al. Eur Neurol Rev.* 2014;9:78–82. **6.** Amato AA and Brown RH Jr. Muscular Dystrophies and other muscle diseases. In: Kasper DL, Fauci AS, Hauser SL, *et al.*, eds., Harrison's Principles of Internal Medicine, 19th Ed. **7.** Blake DJ, *et al. Physiol Rev.* 2002;82:291–329. **8.** Mendell JR, Lloyd-Puryear M. *Muscle Nerve.* 2013;48:21–26. **9.** van Dommelen P, *et al. Dev med Child Neurol.* 2020; doi: 10.1111/dmcn.14623. **10.** Laing NG, *et al. Clin Biochem Rev.* 2011;32:129–134. **11.** Noritz GH, *et al. Pediatrics.* 2013;131:e2016–e2027. **12.** Birnkrant DJ, *et al. Lancet Neurol.* 2018;17:445–455. **13.** McDonald CM, Fowler WM. *Phys Med Rehabil Clin N Am.* 2012;23:475–493.

Za več informacij se obrnite na lokalnega zastopnika:
Swixx Biopharma d.o.o., Pot k sejmišču 35, 1231 Ljubljana - Črnuče
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Humani polispecifični imunoglobulin (SCIg)
165 mg/ml raztopina za injiciranje

Novi SCIg namesto zdravila gammanorm®

Cutaquig® je vse, kar poznate pri gammanormu: odmerjanje, rutina in visoka kakovost, ki jo pričakujete

Cutaquig® ima dobro dokazano učinkovitost in prenašanje ter omogoča pacientom, da prilagodijo zdravljenje na domu svojemu individualnemu življenjskemu slogu[2,3]

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8, kako poročati o neželenih učinkih.

IME ZDRAVILA Cutaquig 165 mg/ml raztopina za injiciranje. **KAKOVOSTNA IN KOLIČINSKA SESTAVA:** Humani polispecifični imunoglobulin (s.c. Ig). 1 ml vsebuje: Humani polispecifični imunoglobulin 165 mg. Čistost vsaj 95% IgG. Največja vsebnost IgA je 300 mikrogramov/ml. **Terapevtske indikacije:** *Nadomestno zdravljenje odraslih ter otrok in mladostnikov (starih od 0 do 18 let)* pri sindromih primarne imunske pomanjkljivosti (PIP) z okvarjenim nastajanjem protiteles, sekundarnih imunskih pomanjkljivosti (SIP) pri bolnikih, ki trpijo zaradi hudih ali ponavljajočih se okužb, neučinkovitega protimikrobnega zdravljenja in bodisi dokazane odpovedi specifičnih protiteles (PSAF) ali serumske koncentracije IgG < 4 g/l. **Odmerjanje in način uporabe:** Nadomestno zdravljenje je treba uvesti in spremljati pod nadzorom zdravnika, izkušenega v zdravljenju imunskih pomanjkljivosti. Odmerek in shema odmerjanja sta odvisna od indikacije. Zdravilo je treba dajati po subkutani poti. Pri nadomestnem zdravljenju bo morda treba odmerek individualno prilagoditi posameznemu bolniku, odvisno od farmakokinetičnega in kliničnega odziva. Zdravilo Cutaquig se lahko daje v rednih časovnih presledkih od vsakodnevnega odmerka do odmerka vsak drugi teden. Naslednje sheme odmerjanja so podane kot smernice. *Nadomestno zdravljenje pri sindromih primarne imunske pomanjkljivosti:* S shemo odmerjanja je treba doseči najnižjo koncentracijo IgG najmanj 5 do 6 g/l in jo vzdrževati znotraj mej referenčnega intervala serumskih IgG glede na starost. Morda bo znašal začetni odmerek vsaj 0,2 do 0,5 g/kg (1,2 do 3,0 ml/kg) telesne mase. Le-tega je morda treba razdeliti na več dni; najvišji dnevni odmerek znaša med 0,1 in 0,15 g/kg. Ko je doseženo stanje dinamičnega ravnovesja ravni IgG, se dajejo vzdrževalni odmerki v ponavljajočih se presledkih, da se doseže kumulativni mesečni odmerek od 0,4 do 0,8 g/kg (2,4 do 4,8 ml/kg) telesne mase. Vsak posamezni odmerek bo morda potrebno injicirati v različna mesta na telesu. *Nadomestno zdravljenje pri sekundarni imunski pomanjkljivosti:* Priporočeni odmerek, ki se daje v ponavljajočih se presledkih, da se doseže kumulativni mesečni odmerek od 0,2 do 0,4 g/kg (1,2 do 2,4 ml/kg) telesne mase. Hitrost infundiranja in količino zdravila, infundiranega v določeno mesto, prilagodimo glede na prenašanje posameznega bolnika. Priporočena začetna hitrost infundiranja je 15 ml/h/mesto. Od sedmega infundiranja naprej, lahko hitrost infundiranja počasi povišate na 25 ml/h/mesto. Priporočene hitrosti infundiranja na uro skupaj za vsa mesta: 30 ml/h za prvih 6 infundiranj, potem počasi zvišujemo na 50 ml/h in, v primeru, da bolnik to dobro prenaša, na 80 ml/h. Pri dojenčkih in otrocih se lahko mesto infundiranja menja na vsakih 5-15 ml. Pri odraslih se odmerke nad 30 ml lahko razdeli na željo bolnika. Število mest infundiranja ni omejeno. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. Zdravila Cutaquig ne smete dajati intravensko. Prav tako zdravila ne smete dajati intramuskularno v primerih hude trombocitopenije in drugih motenj hemostaze. **Posebna opozorila in previdnostni ukrepi:** Priporočeno je, da ob vsakem dajanju zdravila Cutaquig bolniku zabeležite ime in številko serije zdravila. To zdravilo vsebuje največ 90 mg maltoze na ml kot pomožne snovi. Moteča prisotnost maltoze v testih ravni glukoze v krvi lahko povzroči lažno povečane odčitke koncentracije in posledično neustrezno odmerjanje inzulina, kar lahko povzroči smrtno nevarno hipoglikemijo in smrt. Prav tako lahko primeri dejanske hipoglikemije ostanejo nezdravljeni. Če se zdravilo Cutaquig po nesreči da v žilo, se lahko pri bolniku razvije šok. Priporočeno hitrost infundiranja, morate natančno upoštevati. Nekateri neželeni učinki se lahko pogosteje pojavijo pri bolnikih, ki prvič prejmejo humani polispecifični imunoglobulin, ali v redkih primerih, kadar se zdravilo s humanim polispecifičnim imunoglobulinom zamenja ali kadar je od zadnjega infundiranja minilo dalj časa. V primeru neželenih učinkov morate bodisi zmanjšati hitrost infundiranja ali infundiranje prekiniti. Potrebno zdravljenje je odvisno od vrste in resnosti neželenih učinkov. Če se razvije šok, je potrebno uvesti standardno medicinsko zdravljenje za šok. Prave alergijske reakcije so redke. Pojavijo se predvsem pri bolnikih s protitelesi proti IgA, ki jih je treba zdraviti posebej previdno. Pri bolnikih, ki imajo protitelesa proti IgA, pri katerih je zdravljenje s subkutanimi zdravili IgG edina možnost, je treba zdravljenje z zdravilom Cutaquig strogo nadzorovati. Redko lahko humani polispecifični imunoglobulin sproži padec krvnega tlaka z anafilaktično reakcijo tudi pri bolnikih, ki so prenašali predhodno zdravljenje s humanim polispecifičnim imunoglobulinom. Z uporabo imunoglobulinov so povezani arterijski in venski trombembolični dogodki, vključno z miokardnim infarktom, možgansko kapjo, globoko vensko trombozo in pljučno embolijo. Pred uporabo imunoglobulinov morajo biti bolniki ustrezno hidrirani. Pri bolnikih z obstoječimi dejavniki tveganja za trombotične dogodke je potrebna previdnost. V povezavi s subkutanim zdravljenjem z imunoglobulini so poročali o pojavu sindroma aseptičnega meningitisa. Pri bolnikih, ki so prejemali zdravljenje z imunoglobulini, so poročali o hudih neželenih učinkih na ledvicah, zlasti pri uporabi zdravil, ki so vsebovala saharozo (zdravilo Cutaquig ne vsebuje saharoze). Po injiciranju imunoglobulina lahko prehodno povečanje različnih pasivno prenesenih protiteles v bolnikovi krvi povzroči lažno pozitivne rezultate pri seroloških preiskavah. Pri dajanju zdravil, pripravljenih iz človeške krvi ali plazme, ni mogoče popolnoma izključiti prenosa povzročiteljev nalezljivih bolezni. To se nanaša tudi na doslej še neznane ali porajajoče se viruse in druge povzročitelje bolezni. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Uporaba imunoglobulinov lahko zmanjša učinkovitost cepiv z živimi oslabljenimi virusi, kot so cepiva proti ošpicam, rdečkam, mumpsu in noricam, za najmanj 6 tednov pa do 3 mesece. V primeru ošpic lahko opisano zmanjšanje učinkovitosti traja celo do enega leta. **Neželeni učinki** Občasno se lahko pojavijo neželeni učinki, kot so mrzlica, glavobol, omotica, povišana telesna temperatura, bruhanje, alergijske reakcije, navzea, artralgija, nizek krvni tlak in zmerna bolečina v križu. V redkih primerih lahko humani polispecifični imunoglobulini povzročijo nenadno zmanjšanje krvnega tlaka in v posameznih primerih anafilaktični šok, celo pri bolnikih, ki pri predhodnem zdravljenju niso pokazali znakov preobčutljivosti. Lokalne reakcije na mestih infundiranja so pogoste. **Posebna navodila za shranjevanje** Shranjujte v hladilniku. Ne zamrzujte. V času roka uporabnosti lahko zdravilo do 9 mesecev shranjujete pri sobni temperaturi (shranjujte pri temperaturi do 25 °C) ne da bi ga v tem času ponovno hranili v hladilniku. **Način in režim izdaje:** H/Rp **Imetnik dovoljenja za promet z zdravilom:** Octapharma (IP) SPRL, Allée de la Recherche 65, 1070 Anderlecht, Belgija. Datum prve odobritve: 19. 8. 2019 **Datum zadnje revizije besedila:** 28. 4. 2022

Reference: 1.Povzetek glavnih značilnosti zdravila Cutaquig. **2.** Kobayashi, R.H., et al., Clinical efficacy, safety and tolerability of a new subcutaneous immunoglobulin 16.5% [cutaquig®] in the treatment of patients with PID. Front Immunol, 2019. 10:40. **3.** Latysheva, E., et al., Efficacy and safety of cutaquig® in adults with PID: a prospective, open-label study. Immunotherapy, 2020. Epub, doi: 10.2217/ imt-2020-0012.

Samo za strokovno javnost. Pred predpisovanjem zdravila Cutaquig si preberite zadnji veljavni Povzetek glavnih značilnosti zdravil. Datum priprave informacije: avgust 2023

octapharma

XEOMIN®

Nevrotoksin bakterije *Clostridium botulinum* tipa A, brez beljakovin, ki tvorijo komplekse

TERAPEVTSKE INDIKACIJE[1]:

Pri odraslih: za simptomatsko zdravljenje blefarospazma in hemifacialnega spazma, cervikalne distonije, predvsem rotacijske oblike (spastični tortikolis), spastičnosti zgornjih udov ter kronične sialoreje, ki se pojavi zaradi nevroloških motenj.
Pri otrocih in mladostnikih, starih 2 do 17 let, ki tehtajo ≥ 12 kg, indicirano za simptomatsko zdravljenje kronične sialoreje, ki se pojavi zaradi nevroloških/razvojnih nevroloških motenj.

Skrajšan povzetek glavnih značilnosti zdravila XEOMIN / nevrotoksin bakterije Clostridium botulinum tipa A (150 kD), brez beljakovin, ki tvorijo komplekse

Ime zdravila: XEOMIN 50 enot prašek za raztopino za injiciranje: Ena viala vsebuje 50 enot nevrotoksina bakterije Clostridium botulinum tipa A (150 kD), brez beljakovin, ki tvorijo komplekse. XEOMIN 100 enot prašek za raztopino za injiciranje: Ena viala vsebuje 100 enot nevrotoksina bakterije Clostridium botulinum tipa A (150 kD), brez beljakovin, ki tvorijo komplekse. XEOMIN 200 enot prašek za raztopino za injiciranje: Ena viala vsebuje 200 enot nevrotoksina bakterije *Clostridium botulinum* tipa A (150 kD), brez beljakovin, ki tvorijo komplekse **Terapevtske indikacije:** Pri odraslih: za simptomatsko zdravljenje blefarospazma in hemifacialnega spazma, cervikalne distonije, predvsem rotacijske oblike (spastični tortikolis), spastičnosti zgornjih udov ter kronične sialoreje, ki se pojavi zaradi nevroloških motenj. Pri otrocih in mladostnikih, starih 2 do 17 let, ki tehtajo ≥ 12 kg, indicirano za simptomatsko zdravljenje kronične sialoreje, ki se pojavi zaradi nevroloških/razvojnih nevroloških motenj. **Odmerjanje in način uporabe:** Zaradi različnih enot v preskusih za določanje jakosti se odmerki enot zdravila XEOMIN ne smejo zamenjati z odmerki drugih zdravil botulinskega toksina tipa A. Zdravilo XEOMIN smejo dajati samo ustrezno usposobljeni zdravniki s potrebnimi izkušnjami z uporabo botulinskega toksina tipa A. Optimalni odmerek, pogostnost in število mest injiciranja mora zdravnik določiti za vsakega bolnika posebej. Odmerek je treba titrirati. Priporočenih posameznih odmerkov zdravila XEOMIN se ne sme preseči. Blefarospazem in hemifacialni spazem: Začetni priporočeni odmerek je 1,25 do 2,5 enot na mesto injiciranja. Začetni odmerek ne sme preseči 25 enot na oko. Skupni odmerek ne sme preseči 50 enot na oko pri posamičnem zdravljenju. Zdravljenja se v splošnem ne sme ponoviti pogosteje kot na vsakih 12 tednov. Razmik med posameznimi zdravljenji je treba določiti na osnovi dejanskih kliničnih potreb posameznega bolnika. Mediana časa opažanja pojava prvega učinka je do štiri dni po injiciranju. Učinek zdravljenja z zdravilom XEOMIN na splošno traja 3–5 mesecev, lahko pa tudi bistveno manj ali dlje. Ob ponovnem zdravljenju se lahko odmerek poveča do dvakrat, če je ocenjeno, da odziv na prvo zdravljenje ni bil zadosten. Vendar je videti, da ni dodatne koristi od injiciranja več kot 5,0 enot na mesto. Bolnike s hemifacialnim spazmom je treba zdraviti enako kot bolnike z enostranskim blefarospazmom. Po rekonstituciji se raztopina zdravila XEOMIN injicira intramuskularno z ustrezno sterilno iglo (npr. velikosti 27–30 G/ 0,30–0,40 mm premera/12,5 mm dolžine). Elektromiografsko vodenje ni nujno. Priporočen volumen injiciranega zdravila je približno 0,05 do 0,1 ml. Zdravilo XEOMIN se injicira v sredinsko in stransko očesno krožno mišico zgornje veke ter stransko očesno krožno mišico spodnje veke. Če spazmi ovirajo vid, se zdravilo lahko injicira v dodatna mesta v območju obrvi, stranske očesne krožne mišice in v zgornji predel obraza. V primeru enostranskega blefarospazma naj bo injiciranje omejeno na prizadeto oko. Bolnike s hemifacialnim spazmom je treba zdraviti enako kot bolnike z enostranskim blefarospazmom. Izkušenj z injiciranjem zdravila XEOMIN v spodnji predel obraza, ki bi bile pridobljene v kliničnih študijah, ni. Iz literature je razvidno, da se pri bolnikih s hemifacialnim spazmom, zdravila ne sme injicirati v mišice spodnjega dela obraza zaradi povečanega tveganja za lokalno šibkost mišic po injiciranju botulinskega toksina v ta predel. Spastični tortikolis: Pri obravnavanju spastičnega tortikolisa je treba odmerjanje zdravila XEOMIN prilagoditi posameznemu bolniku, glede na položaj njegove glave in vratu, mesto morebitne bolečine, mišično hipertrofijo, telesno maso in odziv na injiciranje. Pri prvem zdravljenju se lahko injicira največ 200 enot, pri nadaljnjih zdravljenjih pa se odmerek prilagaja glede na odziv bolnika. Skupni odmerek pri katerem koli posameznem zdravljenju naj ne bo večji od 300 enot. Na posamezno mesto injiciranja se ne sme dati odmerka, večjega od 50 enot. Mediana opažanja pojava prvega učinka je sedem dni po injiciranju. Učinek zdravljenja z zdravilom XEOMIN na splošno traja 3–4 mesece, lahko pa tudi bistveno manj ali dlje. Razmiki med posameznimi zdravljenji, krajši od 10 tednov, niso priporočljivi. Razmik med posameznimi zdravljenji je treba določiti na osnovi dejanskih kliničnih potreb posameznega bolnika. Za injiciranje v površinske mišice se uporablja ustrezna sterilna igla (npr. velikosti 25–30 G/ 0,30–0,50 mm premera/37 dolžine), za injiciranje v globlje mišice pa se lahko uporabi npr.igla velikosti 22 G/ 0,70 mm. Priporočen volumen injiciranega zdravila je približno 0,1 do 0,5 ml na mesto injiciranja. Pri zdravljenju spastičnega tortikolisa se zdravilo XEOMIN injicira v mišico obračalko glave, mišico dvigalko lopatice, mišico dvigalko reber, jermenasto mišico glave, in/ali trapezasto mišico/mišice. Seznam ni dokončen, saj je lahko vpletena katera koli mišica, odgovorna za nadzor položaja glave, in zato potrebuje zdravljenje. Če se pri izolaciji posameznih mišic pojavijo težave, je treba injiciranje opraviti z uporabo tehnik kot je elektromiografsko vodenjem ali ultrazvok. Pri izbiri ustreznega odmerka je treba upoštevati dejavnike, kot sta mišična masa in stopnja hipertrofije ali atrofije. Injiciranje na več mestih omogoča zdravilu XEOMIN enakomernejše pokritje oživčenih območij distoničnih mišic, zlasti pa je uporabno pri večjih mišicah. Optimalno število mest injiciranja je odvisno od velikosti mišice, ki jo želite kemijsko denervirati. Zaradi velikega tveganja za pojav neželenih učinkov (zlasti disfagije), se injiciranje v mišico obračalko glave ne sme opraviti bilateralno. To tveganje je veliko tudi pri dajanju odmerkov, ki so večji od 100 e. Spastičnost zgornjih udov: Odmerek in število mest injiciranja je treba natančno prilagoditi posameznemu bolniku, glede na velikost, število in položaj vključenih mišic, stopnjo spastičnosti in prisotnost lokalne mišične šibkosti. Največji skupni odmerek za zdravljenje spastičnosti zgornjih udov ne sme preseči 500 enot na cikel zdravljenja, v mišice ramena pa se ne sme dati več kot 250 enot. Bolniki so poročali, da so začetek delovanja zdravila opazili 4 dni po začetku zdravljenja. Največji učinek v obliki izboljšane napetosti mišic so opazili v štirih tednih. Na splošno so učinki zdravljenja trajali dvanajst tednov, lahko pa tudi bistveno manj ali dlje. Ponovno zdravljenje naj v splošnem ne sledi prej kot vsakih 12 tednov. Rekonstituirano zdravilo XEOMIN se injicira z ustrezno sterilno iglo (npr. velikosti 26 G/ premera 0,45 mm/ dolžine 37 mm za injiciranje v površinske mišice in daljšo iglo, npr. velikosti 22 G/ premera 0,7 mm/ dolžine 75 mm za injiciranje, v globlje mišice)..V primeru kakršnih koli težav pri izolaciji posameznih mišic je priporočljiva lokalizacija prizadetih mišic s tehnikami kot je elektromiografsko vodenje ali ultrazvok. Injiciranje na več mestih lahko pripomore, da ima zdravilo XEOMIN enakomernejši stik z oživčenimi območji mišic, zlasti pa je uporabno pri injiciranju v večje mišice. Kronična sialoreja (odrasli): Uporabiti je treba rekonstituirano raztopino v koncentraciji 5 enot/0,1 ml. Odmerek se razdeli v razmerju 3 (parotidna žleza) : 2 (submandibularna žleza). Mesto injiciranja naj bo blizu centra žleze. Priporočeni odmerek na posamezno zdravljenje je 100 enot. Najvišjega odmerka se ne sme prekoračiti. Interval zdravljenja je treba določiti na osnovi dejanskih kliničnih potreb posameznega bolnika. Ponovitev zdravljenja, ki je krajša od 16 tednov, ni priporočljiva. *Kronična sialoreja (otroci/mladostniki):* Uporabiti je treba rekonstituirano raztopino v koncentraciji 2,5 enot/0,1 ml. Zdravilo XEOMIN se injicira v parotidno in submandibularno žlezo na obeh straneh (skupaj štiri injekcije na posamezno zdravljenje). Odmerek, prilagojen telesni masi, se razdeli v razmerju 3 (parotidna žleza) : 2 (submandibularna žleza). Za otroke, ki tehtajo manj kot 12 kg, ni mogoče podati priporočil za odmerjanje. Mesto injiciranja naj bo blizu centra žleze. Interval zdravljenja je treba določiti na osnovi dejanskih kliničnih potreb posameznega bolnika. Ponovitev zdravljenja, ki je krajša od 16 tednov, ni priporočljiva. Po rekonstituciji se raztopina zdravila XEOMIN injicira intraglandularno z ustrezno sterilno iglo (npr. velikosti 27–30 G/ 0,30–0,40 mm premera/12,5 mm dolžine). Pri odraslih si je pri lokalizaciji prizadetih žlez slinavk mogoče pomagati z anatomskimi točkami ali z ultrazvokom. Prednostno se uporablja lokalizacija z ultrazvokom, ker so bili ob uporabi te metode opaženi boljši izidi zdravljenja. Pri zdravljenju otrok in mladostnikov je treba uporabiti ultrazvočno vodenje. Otrokom in mladostnikom, se lahko po skrbnem ovrednotenju razmerja med koristjo in tveganjem pred injiciranjem ponudi lokalna anestezija (na primer krema z lokalnim anestetikom), sedacija ali anestezija v kombinaciji s sedacijo. Vse indikacije: Če v enem mesecu od prvega injiciranja ni učinkov zdravljenja, je treba uvesti naslednje ukrepe: klinična potrditev učinka nevrotoksina na mišico, v katero je injiciran: npr. z elektromiografskim pregledom v specializirani ustanovi; analiza razlogov za odsotnost odziva, npr. slaba izolacija mišic, v katere naj bi zdravilo injicirali, premajhen odmerek, slaba tehnika injiciranja, fiksna kontraktura, prešibek antagonist, morebiten nastanek protiteles; ponovna ocena ustreznosti zdravljenja z botulinskim nevrotoksinom tipa A; če se med prvim zdravljenjem niso pojavili neželeni učinki, se lahko opravi naslednji cikel zdravljenja pod naslednjimi pogoji: 1) prilagoditev odmerka glede na analizo zadnje odsotnosti odziva, 2) lokalizacija prizadetih mišic s tehnikami kot so elektromiografsko vodenje, 3) upoštevanje priporočenega najmanjšega intervala med začetnim in ponovnim zdravljenjem. Pediatrična populacija: Varnost in učinkovitost zdravila XEOMIN za neodobrene indikacije še nista bili dokazani. Zdravilo Xeomin je namenjeno za intramuskularno in intraglandularno (injiciranje v žleze slinavke) uporabo. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov; splošne motnje mišične aktivnosti (npr. miastenija gravis, Lambert-Eatonov sindrom); okuženo ali vneto predvideno mesto injiciranja. **Posebna opozorila in previdnostni ukrepi:** Sledljivost: Z namenom izboljšanja sledljivosti bioloških zdravil je treba jasno zabeležiti ime in številko serije uporabljenega zdravila.Splošno: Pred dajanjem zdravila XEOMIN se mora zdravnik/zdravnica seznaniti z bolnikovo anatomijo in vsemi spremembami anatomije zaradi predhodnih kirurških posegov. Zdravilo XEOMIN se ne sme injicirati v žilo. Zdravilo XEOMIN je treba uporabljati previdno: v primeru kakršne koli krvavitve; če se bolniki zdravijo z zdravili proti strjevanju krvi ali drugimi zdravili, ki bi lahko zavirala strjevanje krvi. Klinični učinek botulinskega nevrotoksina tipa A se lahko s ponavljajočim injiciranjem poveča ali zmanjša. Možni razlogi za spremembe v kliničnih učinkih so lahko različne tehnike rekonstitucije, izbrani presledki med injiciranji, mesta injiciranja in mejna nihanja aktivnosti toksina zaradi biološke raznolikosti ali sekundarne neodzivnosti. Lokalno in oddaljeno širjenje učinka toksina: Neželeni učinki se lahko pojavijo zaradi injiciranja botulinskega nevrotoksina tipa A na napačno mesto, ki lahko povzroči začasno paralizo bližnjih mišičnih skupin. Večji odmerki lahko povzročijo paralizo mišic, ki so oddaljene od mesta injiciranja. Poročali so o neželenih učinkih, ki bi lahko bili povezani s širjenjem botulinskega toksina tipa A na mesta, oddaljena od mesta injiciranja. Nekateri izmed njih lahko ogrožajo življenje in poročali so o smrtnih primerih, ki so bili v nekaterih primerih povezani z disfagijo, pljučnico in/ali pomembno slabotnostjo. Pri bolnikih, ki prejmejo terapevtske odmerke, lahko pride do pretirane mišične šibkosti. Bolnikom in skrbnikom je treba svetovati, naj takoj poiščejo nujno zdravniško pomoč, če pride do težav pri požiranju, govoru ali dihanju. O disfagiji so poročali tudi po injiciranju v mesta zunaj vratne muskulature. Predhodna živčno-mišična obolenja: Bolniki z živčno-mišičnimi obolenji so lahko izpostavljeni povečanemu tveganju za pojav pretirane mišične šibkosti, zlasti, če so zdravljeni intramuskularno. Pri teh bolnikih mora zdravljenje z botulinskim toksinom tipa A spremljati zdravnik specialist, zdravljenje pa je dovoljeno samo v primerih, kadar pričakovana korist zdravljenja odtehta morebitno tveganje. V splošnem je treba bolnike z aspiracijo ali disfagijo v anamnezi zdraviti previdno. Izjemna previdnost je potrebna, kadar pri teh bolnikih poteka zdravljenje cervikalne distonije. Zdravilo XEOMIN je treba uporabljati previdno: pri bolnikih z amiotrofično lateralno sklerozo; pri bolnikih z drugimi boleznimi, ki povzročajo periferno živčno-mišično disfunkcijo; pri izrazito šibkih ali atrofičnih ciljnih mišicah. Preobčutljivostne reakcije: Pri uporabi zdravil, ki vsebujejo botulinski nevrotoksin tipa A, so poročali o preobčutljivostnih reakcijah. Če pride do resnih (npr. anafilaktičnih) reakcij in/ali reakcij takojšnje preobčutljivosti, je treba uvesti ustrezno zdravljenje. Tvorba protiteles: Prepogosti odmerki lahko povečajo tveganje za nastanek protiteles, kar lahko vodi v neuspešnost zdravljenja. Možnost tvorjenja protiteles se lahko zmanjša z injiciranjem najnižjega učinkovitega odmerka v najdaljših možnih presledkih med injiciranji kot je klinično indicirano. Pediatrična populacija: Pri drugih zdravilih z botulinskim toksinom tipa A so bila zelo redko podana spontana poročila o možnem oddaljenem širjenju toksina pri pediatričnih bolnikih, ki so imeli pridružene bolezni, predvsem cerebralno paralizo. V splošnem je v takšnih primerih uporabljeni odmerek presegal odmerke, ki so priporočeni za ta zdravila. Redko so bila po uporabi zdravil z botulinskim toksinom, vključno z uporabo izven navedenih indikacij (»*off label*« uporabo), na primer v predelu vratu, podana spontana poročila o smrtnih primerih pri otrocih s hudo obliko cerebralne paralize, ki je bila včasih povezana z aspiracijsko pljučnico. To tveganje je še posebej veliko pri pediatričnih bolnikih v slabem splošnem zdravstvenem stanju ali pri bolnikih s hudimi nevrološkimi težavami, disfagijo ali pri bolnikih, ki so nedavno preboleli aspiracijsko pljučnico ali imajo v anamnezi bolezen pljuč. Specifična opozorila vezana na posamezne: *Blefarospazem in hemifacialni spazem*: Da se zmanjša možnost pojava ptoze, se je treba izogibati injiciranju v bližini mišice dvigalke zgornje veke (levator palpebrae superioris). Zaradi difuzije botulinskega nevrotoksina tipa A v spodnjo poševno mišico (m. inferior oblique) lahko pride do diplopije. Izogibanje medialnim injekcijam v spodnjo veko lahko zmanjša pogostnost tega neželenega učinka. Zaradi antiholinergičnega učinka botulinskega toksina tipa A je treba zdravilo XEOMIN pri bolnikih, pri katerih obstaja tveganje za nastanek ozkokotnega glavkoma, uporabljati previdno. Z namenom, da se prepreči ektropij, se je treba izogibati injiciranju v območje spodnje veke, vsako okvaro epitelija pa je treba takoj intenzivno zdraviti. Za zdravljenje bodo morda potrebne zaščitne kapljice, mazila, mehke zaščitne kontaktne leče ali zaprtje očesa s povojem ali podobnim sredstvom. Zmanjšano mežikanje po injiciranju zdravila XEOMIN v krožno mišico lahko povzroči izpostavljenost roženice, stalne okvare epitelija in ulceracijo roženice, zlasti pri bolnikih z okvarami možganskih živcev (obraznega živca). Pri bolnikih s predhodnim kirurškimi posegi na očeh je treba previdno preskusiti kornealno zaznavo. V mehkih tkivih očesne veke lahko pride do ekhimoze. Takojšnji nežen pritisk na mesto injiciranja lahko zmanjša tveganje za njen pojav. *Spastični tortikolis:* Zdravilo XEOMIN je treba injicirati previdno, kadar so mesta injiciranja blizu občutljivih struktur kot so karotidna arterija, pljučni vršički in požiralnik. Predhodno akinetične bolnike ali bolnike, ki se ne gibajo, je treba opomniti, naj po injiciranju zdravila XEOMIN postopoma pričnejo z aktivnostmi. Bolnike je treba obvestiti, da injiciranje zdravila XEOMIN pri obravnavanju spastičnega tortikolisa lahko povzroči blago do hudo disfagijo s tveganjem za pojav aspiracije in dispneje. Morda bo potreben zdravniški poseg (npr. v obliki gastrične sonde za hranjenje). Omejitev odmerka, ki se injicira v mišico obračalko glave, na manj kot 100 enot lahko zmanjša pogostnost disfagije. Bolniki z manjšo maso vratnih mišic ali bolniki, pri katerih je potrebno bilateralno injiciranje v mišici obračalki glave, so izpostavljeni večjemu tveganju. Pojav disfagije se lahko pripiše širjenju farmakološkega učinka zdravila XEOMIN, ki je posledica širjenja nevrotoksina v mišice požiralnika. *Spastičnost zgornjih udov:* Zdravilo XEOMIN je treba injicirati previdno, kadar so mesta injiciranja blizu občutljivih struktur kot so karotidna arterija, pljučni vršički in požiralnik. Predhodno akinetične bolnike ali bolnike, ki se ne gibajo, je treba opomniti, naj po injiciranju zdravila XEOMIN postopoma pričnejo z aktivnostmi. Zdravilo XEOMIN so kot zdravilo za zdravljenje fokalne spastičnosti raziskovali v povezavi z običajnimi režimi standardne nege in ni namenjeno kot nadomestek teh načinov zdravljenja. Malo verjetno je, da je zdravilo XEOMIN učinkovito za izboljšanje obsega gibanja sklepov, ki jih je prizadela fiksna kontraktura mišice. *Kronična sialoreja (odrasli/otroci/mladostniki):* V primeru z zdravili povzročene sialoreje (npr. zaradi aripiprazola, klozapina, piridostigmina) je treba pred uporabo zdravila XEOMIN za zdravljenje sialoreje najprej razmisliti o zamenjavi, zmanjšanju odmerka ali celo ukinitvi zdravila, ki jo povzroča. Varnosti in učinkovitosti zdravila XEOMIN pri bolnikih, ki imajo z zdravili povzročeno sialorejo, niso raziskali. Če se pri zdravljenju z zdravilom XEOMIN pojavijo »suha usta«, je treba razmisliti o zmanjšanju odmerka. Priporočljivo je, da bolnik pred pričetkom zdravljenja obišče zobozdravnika. Zobozdravnik naj bo seznanjen z namenom zdravljenja sialoreje z zdravilom XEOMIN, da se bo lahko odločil o primernih ukrepih za preprečevanje kariesa. **Interakcije:** Študij medsebojnega delovanja niso izvedli. Teoretično se lahko učinek botulinskega nevrotoksina okrepi z aminoglikozidnimi antibiotiki ali drugimi zdravili, ki ovirajo živčno-mišični prenos, npr. tubokurarinskimi mišičnimi relaksanti. Pri sočasni uporabi zdravila XEOMIN in aminoglikozidov ali spektinomicina potrebna posebna previdnost. Periferne mišične relaksante je treba uporabljati previdno in po potrebi zmanjšati začetni odmerek relaksanta ali uporabiti hitro delujoča zdravila, npr. vekuronij ali atrakurij, namesto zdravil z dolgotrajnim učinkom. Dodatno lahko pri zdravljenju kronične sialoreje obsevanje glave in vratu vključno z žlezami slinavkami in/ali sočasna uporaba antiholinergičnih zdravil (npr. atropin, glikopironij, skopolamin) povečata učinek botulinskega toksina. Zdravljenje sialoreje z zdravilom XEOMIN v času zdravljenja z obsevanjem ni priporočljivo. 4-aminokinolini lahko zmanjšajo učinek zdravila XEOMIN. **Plodnost, nosečnost in dojenje:** Nosečnost: Ni zadostnih podatkov o uporabi botulinskega nevrotoksina tipa A pri nosečnicah. Zdravila XEOMIN se ne sme uporabljati med nosečnostjo, razen če je nujno in če morebitne koristi opravičijo tveganje. Dojenje: Zdravila XEOMIN se med dojenjem ne sme uporabljati. Plodnost: Ni kliničnih podatkov o uporabi botulinskega nevrotoksina tipa A. **Povzetek neželenih učinkov:** Neželeni učinki neodvisni od indikacije: lokalizirana bolečina, vnetje, parestezija, hipoestezija, občutljivost, otekanje, edem, eritem, srbenje, lokalizirana okužba, hematom, krvavitev in/ali modrice, vazovagalni odzivi, vključno s prehodno simptomatsko hipotenzijo, slabostjo, tinitusom in sinkopo, lokalizirana mišična šibkost, pretirana mišična šibkost, disfagija in aspiracijska pljučnica (zelo redko s smrtnim izidom), preobčutljivostne reakcije. Neželeni učinki na podlagi kliničnih izkušenj: *Blefarospazem*: Zelo pogosti: ptoza vek. Pogosti:, suhe oči, zamegljen vid, motnje vida, suha usta, bolečina na mestu injiciranja. *Hemifacialni spazem*: Pri hemifacialnem spazmu so pričakovani podobni neželeni učinki kot pri blefarospazmu. *Spastični tortikolis:* Zelo pogosti: disfagija. Pogosti: glavobol, občutek omedlevice, omotičnost, suha usta, navzea, hiperhidroza, bolečina v vratu, mišična šibkost, mialgija, mišični krči, togost mišic in skeleta, bolečina na mestu injiciranja, astenija, okužbe zgornjih dihal. *Spastičnost zgornjih udov:* Pogosti: suha usta. *Kronična sialoreja (odrasli):* Pogosti: parestezije, suha usta, disfagija. *Kronična sialoreja (otroci/mladostniki):* Občasni: disfagija. Izkušnje v obdobju trženja zdravila: Ob uporabi zdravila XEOMIN so po prihodu zdravila na trg z neznano pogostnostjo in ne glede na posamezne indikacije poročali o naslednjih neželenih učinkih: preobčutljivostne reakcije, kot so otekanje, edemi (tudi na mestih, oddaljenih od mesta injiciranja), eritem, pruritus, izpuščaj (lokaliziran in generaliziran) in zasoplost, mišična atrofija, gripi podobni simptomi. **Način in režim predpisovanja in izdaje zdravila:** Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v javnih zdravstvenih zavodih ter pri pravnih in fizičnih osebah, ki opravljajo zdravstveno dejavnost. **Imetnik dovoljenja za promet:** Merz Pharmaceuticals GmbH, Eckenheimer Landstraße 100, 60318 Frankfurt/Main, P.O. Box 11 13 53, 60048 Frankfurt/Main, Nemčija. **Pred predpisovanjem, prosimo, preberite povzetek glavnih značilnosti zdravila. Datum revizije besedila**: 02/2022

Literatura: Povzetek glavnih značilnosti zdravila Xeomin®.

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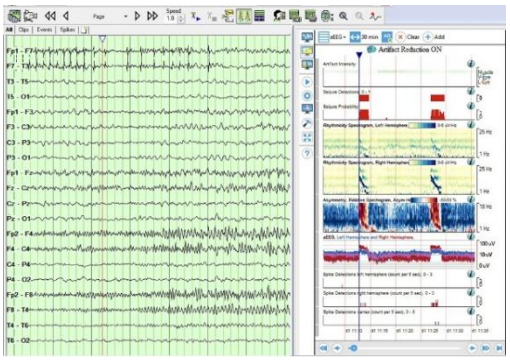

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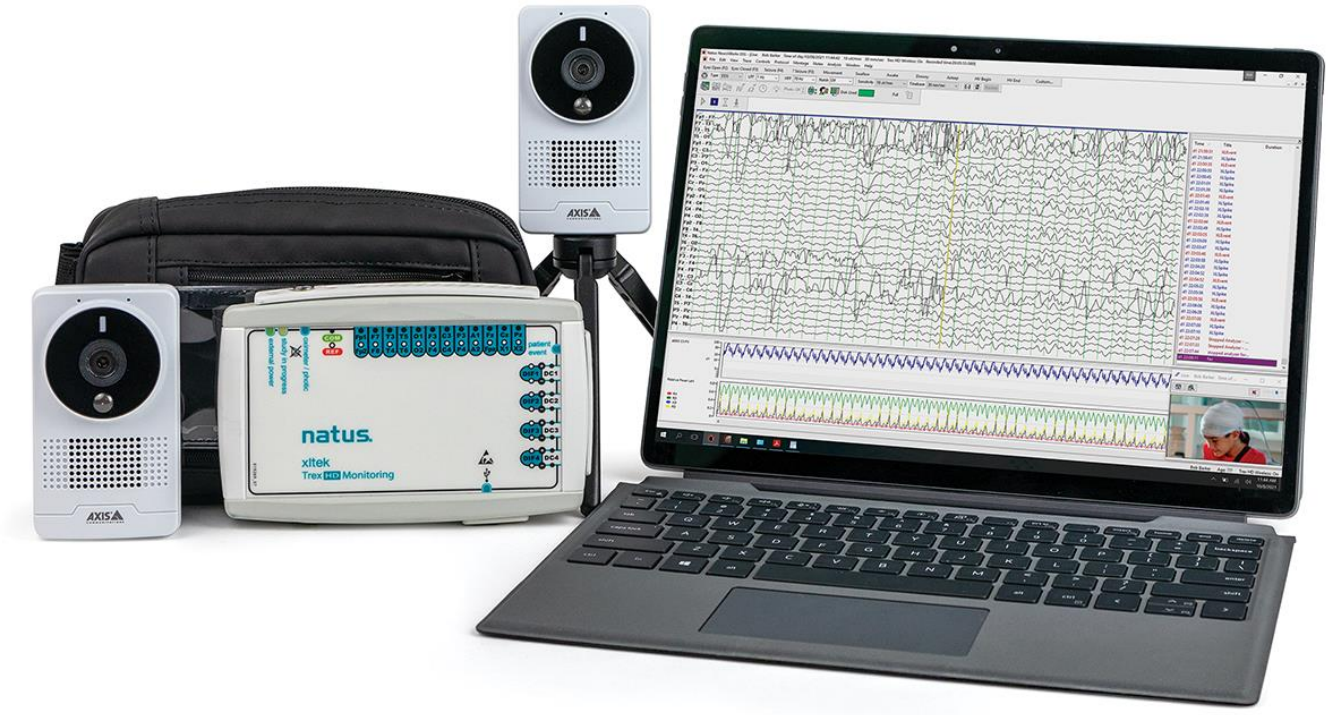

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