ESN
EUROPEAN SOCIETY FOR NEUROCHEMISTRY

Virtual Mini-Conference

"MOLECULAR MECHANISMS OF COGNITIVE IMPAIRMENT AND INTELLECTUAL DISABILITY"

Programme and Abstract Book

Organized by

European Society for Neurochemistry (ESN)

In Collaboration with

Federation of European Neuroscience Societies (FENS)

Conference organizers
Co-Chairs:
Illana Gozes (Israel), ESN Secretary
Eva-Maria Blumrich E-M (UK) – ESN Council Member

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Natalia N Nalivaeva (UK/Russ) – ESN President;
Johannes Hirrlinger (Germany) - ESN Treasurer;
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Anthony J. Turner (UK) - Abstract Committee

DESCRIPTION OF THE TOPIC

Cognitive impairment and intellectual disability affect a large population of children suffering from neurodevelopmental diseases as well as the elderly population succumbing to age-associated cognitive impairments. Understanding the molecular mechanisms of these disorders will aid in better diagnosis and improved treatments. The Mini-Conference will feature some leading genes causing autism/intellectual disability syndromes, like ADNP and CHD8, as well as electrophysiology and molecular mechanisms of intellectual disability. The role of environmental factors as well as basic mechanisms of synaptic transmission and neuro-glial interactions will also be elucidated. Finally, innovative drug development will be discussed toward better cognitive functioning both in children and the elderly. A collaborative effort between the European Society for Neurochemistry (ESN) and the UK-based Simons Initiative for the Developing Brain will underpin this event.

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PROGRAMME

Saturday, 11th of July 2020
09:00-12:30 (GMT+1)

Prerecorded talks

Development and Intellectual disabilities

L1
9:00-9:20
Gozes Illana (Tel Aviv University, Israel)
ADNP autism and mild cognitive impairment

L2
9:20-9:40
McKinney R Anne (McGill University, Montreal, Canada)
Insight from Christianson syndrome on how deficits of endosomal pH impair cognition

L3
9:40-10:00
Nalivaeva Natalia N (Institute of Evolutionary Physiology and Biochemistry, St Petersburg, Russia)
Role of prenatal stress in development of cognitive disorders and search for therapy

Key mechanisms and drug development

L4
10:00-10:20
Hirrlinger Johannes (Carl-Ludwig-Institute, Leipzig, Max-Planck-Institut Göttingen, Germany) Neuronal cell energy metabolism – the glial aspect

L5
10:20-10:40
Michetti Fabrizio (Catholic University, Rome, Italy)
The S100B protein as a biomarker and effector in neural disorders: a potential novel therapeutic target

L6
10:40-11:00
Mothet Jean-Pierre (CNRS, Marseille, France)
Emerging roles of D-amino acids in the healthy and diseased brain

Simons Initiative for the Developing Brain (https://www.sidb.org.uk/)
Young investigator lectures (electrophysiology and molecular mechanisms of intellectual disability)

L7
11:00-11:20
Booker Sam A (SIDB, Edinburgh, UK)
Overcompensation of cellular excitability in the Fmr1-/y mouse

L8
11:20-11:40
Ribeiro dos Louros Susana - Perturbed proteostasis in ID/ASD

Open Live Virtual Discussion (11:40-12:30)

Moderators:

Gozes Illana (ESN Secretary) – Conference Chair
Nalivaeva Natalia N. (ESN President) – Conference Committee Member
Hirrlinger Johannes (ESN Treasurer) – Conference Committee Member
Blumrich Eva-Maria (ESN Council Member) – Conference Co-Chair

Posters of ESN travel award winners (11:40-12:00)

P1
Hadar Adva (Rehovot and Tel Aviv, Israel)
Genomic biomarkers for Alzheimer disease
P2
Li Catherine (Sydney, Australia)
Changes in cerebral glucose metabolism in chemotherapy-induced cognitive impairment
P3
Pershina Ekaterina (Pushchino, Russia)
Metabotropic glutamate receptors in the hippocampus and the prefrontal cortex in rats during neurodegeneration caused by trimethyltin chloride
P4
Shcherbitskaia Anastasiya (Saint Petersburg, Russia)
Gestational hyperhomocysteinemia affects development of the nervous system in rat fetuses and offspring

Open Discussion highlighting E- posters
12:00-12:30

P5
Ahmad Muddasir Khan Saara (Karachi, Pakistan)
The efficacy of herbal interventions in the pathogenesis of diabetes and neuropsychological deficits on Streptozotocin-induced diabetic rats.
P6
Árabe Laila Blanc (Belo Horizonte, Brazil)
Effects of maternal separation on microglia profile and anxiety-like behavior of male and female mice
P7
Baker Kate (Cambridge, UK)
Gene functional networks influence autism spectrum characteristics in young people with intellectual disability
P8
Gigliucci Valentina (Milan, Italy)
Region-specific effects of IGF-1 and oxytocin on KCC2 in MeCP2 KO mice
P9
Kozlova Daria (Saint Petersburg, Russia)
Effect of Prenatal Hypoxia on Cholinesterase Activity in Blood Serum of Rats
P10
Nikitina Veronika (Saint Petersburg, Russia)
Neonatal bacterial endotoxin exposure exacerbates stress-induced changes of NMDA and AMPA receptor expression in the rat brain
P11
Parodi Chiara (Milan, Italy)
Paving the way for future therapeutic strategies in Cornelia de Lange Syndrome modulating defective Wnt pathway
P12
Reiche Laura (Dusseldorf, Germany)
C21orf91 as a new regulator of gliogenesis and Down syndrome neuropathology
P13
Schultzberg Marianne (Solna, Sweden)
Studies on the resolution of inflammation in Alzheimer's disease
P14
Trofimov Alexander (Saint Petersburg, Russia)
Prolonged treatment with medium chain triglycerides (C8, C10) induces positive effect on cognitive abilities of intact rats
P15
Vasilev Dmitrii (Saint Petersburg, Russia)
The caspase-3 inhibitor Ac-DEVD-CHO normalizes neprilysin expression in brain tissue of rats subjected to prenatal hypoxia
P16
Zakharova Elena (Moscow, Russia)
Spatial contextual memory consolidation: key dopaminergic and cholinergic functional connections and their vanishing under brain hypo-perfusion

P17
Zhuravin Igor (Saint Petersburg, Russia)
Histone deacetylase inhibitor sodium valproate restores cognitive and olfaction impairments in rats subjected to prenatal hypoxia

Abstracts without posters:

A1
Basson M Albert (London, UK)
CHD8 autism and intellectual disability
A2
Benbenishty Amit (Tel Aviv, Israel)
Longitudinal in vivo imaging of perineuronal nets in fragile-X syndrome
A3
Gabrielli Martina (Milan, Italy)
Microglia-derived extracellular vesicles propagate early synaptic dysfunction in Alzheimer's Disease
A4
Rimpi Arora (Punjab, India)
Embelin negated the development of intracerebroventricular streptozotocin and β-amyloid induced Alzheimer's Dementia (AD) model in Rats

Also see the posters of ESN awardees at the FENS Forum:

1477
Pershina Ekaterina (Pushchino, Russia)
Expression of TGF-β1 and its receptors in rat brain after trimethyltin intoxication
1702
Hadar Adva(Tel Aviv, Israel)
Discovery of autism/intellectual disability somatic mutations in Alzheimer's brains: mutated ADNP cytoskeletal impairments and repair as a case study
2021
Li Catherine (Sydney, Australia)
Nicotinamide mononucleotide may be able to ameliorate chemotherapy-induced cognitive impairment
2144
Shcherbitskaia Anastasiya (Saint Petersburg, Russia)
Maternal hyperhomocysteinemia leads to the neural tissue development delay in rat fetuses and offspring


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ABSTRACTS

L1

ADNP autism and mild cognitive impairment

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In search for glial proteins protecting the brain, we discovered activity-dependent neuroprotective protein (ADNP). *De novo* mutations in ADNP result in the autism/intellectual disability ADNP syndrome (e.g. 1). With ADNP associated with stem cell differentiation and with Alzheimer's disese (AD) exhibiting reduced ability of neural stem cell renewal, we hypothesized that de novo mutations controlling embryonic development in ADNP and related genes, in the form of brain somatic mutations instigate the disease. By RNA sequencing of postmortem olfactory bulbs and datamining of multiple brain regions, we discovered somatic mutations in hundreds of genes converging on autism/intellectual disabilities/cytoskeleton with further increased rate/number/subject in AD. Mechanistically, major cytoplasmic targets for ADNP are the microtubule (MT) end-binding proteins, EB1 and EB3, key to synapse formation, enlisting Tau to MTs and protecting against tauopathy, a major pathology in AD. ADNP mutation load correlated with AD tauopathy. Treatment with the ADNP snippet, drug candidate NAP (CP201) increased Tau-MT association and protected against ADNP-mutation inflicted MT disruption (2). While regulating the neuronal synapse EB1 also regulates the immune synapse, with T cell activation requiring EB1-mediated MTs growth. As such, ADNP/NAP modulate the immune response, linked with microbiota composition. We have now shown that ADNP deficiency is associated with changes in commensal gut microbiota compositions, potentially serving as a sex-dependent biomarker for the ADNP syndrome and beyond. Strikingly, we discovered rapidly detected NAP (CP201) treatment-dependent biomarkers within the gut microbiota, toward clinical development (3).

Supported: ERA-NET Neuron, ISF, AMN Foundation, Dr. Ronith & Armand Stemer, French Friends of Tel Aviv University

Selected references:

1] Levine J, Cohen D, Herman C, Verloes A, Guinchat V, Diaz L, Cravero C, Mandel A, Gozes I. Developmental Phenotype of the Rare Case of DJ Caused by a Unique ADNP Gene De Novo Mutation. J Mol Neurosci. 2019 Jul;68(3):321-330

2] Ivashko-Pachima Y, Hadar A, Grigg I, Korenková V, Kapitansky O, Karmon G, Gershovits M, Sayas CL, Kooy RF, Attems J, Gurwitz D, Gozes I. Discovery of autism/intellectual disability somatic mutations in Alzheimer's brains: mutated ADNP cytoskeletal impairments and repair as a case study. Mol Psychiatry. 2019 Oct 30

3] Kapitansky O, Giladi E, Jaljuli I, Bereswill S, Heimesaat MM, Gozes I. Microbiota changes associated with ADNP deficiencies: rapid indicators for NAP (CP201) treatment of the ADNP syndrome and beyond. J Neural Transm (Vienna). 2020 Feb 18.

Conflict of Interest: Chief Scientific Officer of Coronis Neurosciences, developing CP201 for the ADNP syndrome.

L2

Insight from Christianson syndrome on how deficits of endosomal pH impair cognition

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Neurodevelopmental disorders comprise a heterogeneous group of conditions that result from altered early brain development. Christianson Syndrome (CS) is one such neurodevelopmental disorder that presents with intellectual disability (ID), epilepsy, ataxia, autistic behaviour, and progressive neurodegeneration. It is possibly one of the more common forms of X-linked ID, but little is known of its underlying etiology. CS arises from mutations in the *SLC9A6* gene encoding for sodium/proton exchanger isoform 6 (NHE6). We were the first to show the developmental profile of NHE6 in CNS, where NHE6 is localized in the synapse and that it is modulated by activity. NHE6 primarily localizes to the membranes of early and recycling endosomes, intracellular vesicles that function in receptor processing, cargo sorting, membrane protein recycling, and functions to alkalinize the internal pH of these structures, which must be tightly regulated to allow their proper function. If they become overacidified, this results in their cargo being trafficked towards lysosomes, acidic compartments involved in protein degradation.

Recently we have been investigating how lack of functioning NHE6 can result in learning and cognition deficits. We will present our latest findings showing that patient-derived NHE6 mutations, resulting in non-functioning NHE6 neurons, impairs glutamate AMPAR trafficking and structural plasticity at the cellular and circuit levels, which may be the cause of learning and memory impairments in CS patients. We will also report findings of novel therapeutic interventions using repurposed drugs which rescued learning deficits in CS animal model and could potentially improve cognition in CS patients.

Acknowledgments: NSERC, CIHR, The Norman Zavalkoff Family Foundation

L3

Role of prenatal stress in development of cognitive disorders: molecular mechanisms and search for therapeutic targets

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Stress factors of different modality and strength to which the maternal organism is exposed during pregnancy affect epigenetic regulation of fetal brain development and its functions in postnatal life. As a result, the individuals subjected to prenatal stress are predisposed in later life to development of neurodegenerative disorders, including Alzheimer's disease (AD). The pathogenesis of the sporadic form of AD is closely connected with impaired amyloid-β (Aβ) clearance from the brain which, in the healthy brain, is maintained by a group of amyloid-degrading enzymes (ADEs) and transport proteins. However, their expression and activity changes with age or earlier in life after prenatal stress. As we have demonstrated in our studies, prenatal hypoxia impairs expression of such neuronal genes participating in Aβ clearance as neuropeptidases neprilysin (NEP) and insulin-degrading enzyme (IDE), and transport protein transthyretin (TTR), which correlated with impaired memory of experimental animals. Deficit of NEP expression in the olfactory bulbs and entorhinal cortex of rats caused by prenatal hypoxia or natural ageing also resulted in impaired olfactory functions of rats. Translating the results of cell culture studies on the epigenetic mechanisms of regulation of ADEs into animal models of prenatal hypoxia in rats we have demonstrated that treatment with a histone-deacetylase (HDAC) inhibitor valproic acid or a caspase inhibitor Ac-DEVD-CHO was able to restore the decreased levels of NEP and TTR expression via the Amyloid Precursor Protein Intracellular Domain (AICD)-dependent mechanism which resulted in improved memory of animals. Treatment of neuronal cells in culture and animals with epigallocatechin gallate, which can act both as an antioxidant and HDAC inhibitor, also resulted in increased NEP expression and activity and improved memory of rats subjected to prenatal hypoxia. Further studies of the effect of prenatal stress on expression of neuronal genes will help to design new strategies for prevention of AD and other neurodegenerative diseases.

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Key words: prenatal hypoxia, learning, memory, amyloid-degrading enzymes, neprilysin, Alzheimer's disease

L4

Neuronal cell energy metabolism – the glial aspect

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Axonal pathology in neurological disorders may be caused by impaired oligodendrocyte-to-axon supply of energy substrates. To study the energy metabolism in white matter tracts, we established a transgenic mouse line with neuronal expression of a genetically encoded, fluorescent nanosensor for ATP, which allows monitoring of the cytoplasmic concentration of ATP within axons in real time and at high spatial resolution. These mice were crossbred to *Plp*$^{null/y}$-mice, a model of the neurological disorder X-linked spastic paraplegia type-2 (SPG2). Axons in optic nerves of these mice have impaired basal ATP levels and smaller compound action potential amplitudes. Unexpectedly, upon reperfusion after glucose deprivation, ATP levels in axons from *Plp*$^{null/y}$-mice recover faster than in control nerves. Structurally, myelin from *Plp*$^{null/y}$-mice shows increased numbers of cytosolic channels and higher expression of transporters of energy substrates, suggesting a higher accessibility of these substrates to the axon in *Plp*$^{null/y}$-mice. In summary, these data provide evidence for complex alterations of metabolic oligodendrocytes-axon coupling in this SPG2 mouse model.

L5

The S100B protein as a biomarker and effector in neural disorders: a potential novel therapeutic target

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S100B is a Calcium-binding protein mainly concentrated in astrocytes. Its levels in biological fluids (cerebrospinal fluid, peripheral and cord blood, urine, saliva, amniotic fluid, feces) are recognized as a reliable, even predictive, biomarker of active neural distress. Mounting evidence now points to S100B as a Damage-Associated Molecular Pattern molecule which, when released at high concentration, triggers tissue reaction to damage in various neural disorders, including neurodegenerative diseases such as Alzheimer's disease and psychiatric disorders. In many cases, overexpression/administration of the protein induces worsening of the disease, whereas its deletion/inactivation produces amelioration, both for clinical and neuropathological/biomolecular parameters (1). In particular, our results indicated a role of S100B in experimental models of amyotrophic lateral sclerosis, including correlation of astrocytic S100B levels with neurodegeneration, increase of S100B synthesis/release in astrocytes transfected with SODG93A, downregulation of proinflammatory genes after S100B silencing in SODG93A-derived astrocytes (2). Our current studies also indicated a role of the protein in pathogenic processes occurring in an *in vivo* model of multiple sclerosis (relapsing remitting experimental autoimmune encephalomyelitis in mice): the S100B inhibitor pentamidine induced amelioration of disease scores and coherent variation of neuropathological/biomolecular parameters such as demyelination, inflammatory cell infiltrates and cytokines. More in general, our results indicated the participation of S100B in processes leading to the activated neuroinflammatory phenotype in astrocytes. This scenario opens the perspective that S100B may be regarded as a therapeutic target for different neural disorders, even exhibiting different origin and clinical features, appearing to share some common pathogenic features, reasonably attributable to neuroinflammation.

Supported: Nando Elsa Peretti Foundation, Fondazione Italiana Sclerosi Multipla

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2.Serrano A, Donno C, Giannetti S, Peric M, Andjus P, D'Ambrosi N, Michetti F, *Mediators Inflamm* 2017, 1626204

L6

Emerging roles of D-amino acids in the healthy and diseased brain

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Amino acids serve important functions in most biological processes. All common amino acids, except for glycine, exhibit a chiral center resulting theoretically in the occurrence of L- and D-amino acids. However, the right-handed amino acids have been long assumed to be 'unnatural' and not bearing physiological functions in higher living organisms. D-amino acids are now emerging as a novel and important class of signaling molecules in many organs including brain and endocrine systems. There has been considerable progress in our understanding of the fundamental role of these novel messengers with implications for their widespread involvement in the pathophysiology of multiple human diseases including brain disorders. Considerable efforts have enabled the discovery that D-serine, D-aspartate and more recently D-cysteine are essential for the healthy development and function of the central nervous system. During this presentation, I will discuss recent progress that have profoundly transformed our vision of basic synapse physiology and brain functioning but also show how D-amino acids are now offering therapeutic promise in clinics for several brain diseases and for drug discovery.

Acknowledgements: I would like to thank my outstanding colleagues and collaborators who have contributed to advance the frontiers of knowledge on D-amino acids.
Funding: Fondation pour la Recherche Médicale,
Conflict of interests: The author declares no competing interests.

L7

Overcompensation of cellular excitability in the *Fmr1*$^{-/y}$ mouse

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Increased brain excitability is a pertinent feature of Fragile X Syndrome, and in the mouse model too. The cellular basis of this increased excitability and its responsiveness to altered activity states is not understood. I report recent findings that implicate the axon initial segment (AIS) length of pyramidal cells of the hippocampus in the Fmr1-/y mouse model that lead to increased cellular excitability. Further, we assess the ability of neurons to modify their structure and function in response to prolonged depolarisation in vitro and following sensory deprivation in vivo. Finally, I examine the circuit level mechanisms which may account for altered cellular activity in the Fragile X mouse, notably reduced synaptic input strength arising from extrinsic afferents to the hippocampus. Together, I propose that altered cell excitability in CA1 of the Fragile X mouse arises due to homeostatic alteration to cell function.

Supported: This work was funded by generous support from: The Simons Foundation Autism Research Initiative (529085), The Patrick Wild Centre, Medical Research Council UK (MR/P006213/1), and the Shirley Foundation and the RS Macdonald Charitable Trust.

L8

Perturbed proteostasis in ID/ASD

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In neurons, the ubiquitin proteasome system (UPS) has been implicated in several fundamental processes including morphogenesis, dendritic spine structure, synaptic activity, and the regulation of synaptic strength. Disruption of *de novo* protein synthesis or UPS function results in significant impairments in synaptic plasticity and memory formation. In fact, several genes encoding regulators of mRNA translation and members of the UPS have been associated with an increased risk for the development of intellectual disability and autism spectrum disorders (ASD). Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability and the leading identified genetic cause of autism. In the Fmr1 KO mouse model of FXS, protein synthesis is exaggerated, and this contributes to multiple disruptions in neurological function. However, a number of proteomic studies failed to identify the pool of proteins that is over-expressed in the Fmr1 KO brain. This raises the intriguing possibility that steady-state protein levels are maintained in the Fmr1 KO mouse due to an elevation in protein breakdown. Unlike protein synthesis, the role of protein degradation in the pathophysiology of FXS has received little attention. Here, we investigate the role of the ubiquitin proteasome system (UPS) in the Fmr1 KO mouse and rat. Using a combination of biochemical and functional approaches we find changes in UPS function and protein degradation that may be linked to the pathology observed in the Fmr1 KO brain. These findings suggest that disruptions in FXS may be due to altered proteostasis, including changes in both protein synthesis and protein degradation.

P1

Genomic biomarkers for Alzheimer disease

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Alzheimer disease (AD) is the most frequent cause of dementia. It has been suggested that some individuals are more prone than others to the neurotoxic effects of amyloid-β (Aβ) that accumulate in the aged human brain. To identify novel AD biomarkers, we initially applied genome-wide transcriptomics of human lymphoblastoid cell lines (LCLs) correlating gene expression levels with in-vitro Aβ sensitivity. We found lower *RGS2* and *DLGAP1* in healthy LCLs exhibiting higher Aβ sensitivity and in LCLs from AD patients compared to appropriate controls. Comprehensive datamining revealed that *RGS2* exhibited lower expression levels in AD and MCI blood. We then explored LCLs gene expression profiles of centenarians compared with AD patients. *SIRT1* expression levels were significantly higher in centenarians compared with AD LCLs, while the opposite was observed for the SIRT1 regulating micro RNA species, miR-132 and miR-212. In parallel, the expression levels of miR-212 and miR-132 in the postmortem hippocampus and the olfactory bulb were downregulated in AD patients. RNA sequencing of postmortem olfactory bulbs (19 AD, 20 controls) revealed somatic aging/AD-linked mutations converging on tauopathy, including mutations in the autism-intellectual disability linked activity-dependent neuroprotective protein (ADNP). The number and average frequencies of AD-related mutations per subject were higher in AD subjects compared to controls. Taken together, our results demonstrate an additional complexity of sporadic AD, already recognized as a multifactorial disease. The transcriptional changes could take part in neuroprotection, while subsequent somatic mutations accumulation lead to further neuronal damage.
Supported: ERA-NET Neuron, ISF, AMN Foundation, Dr. Ronith & Armand Stemer, French Friends of Tel Aviv University

Selected references:

1] Hadar A, Milanesi E, Squassina A, Niola P, Chillotti C, Pasmanik-Chor M, Yaron O, Martásek P, Rehavi M, Weissglas-Volkov D, Shomron N, Gozes I, Gurwitz D. RGS2 expression predicts amyloid-β sensitivity, MCI and Alzheimer's disease: genome-wide transcriptomic profiling and bioinformatics data mining. Transl Psychiatry. 2016 Oct 4;6(10):e909.
2] Hadar A, Milanesi E, Walczak M, Puzianowska-Kuźnicka M, Kuźnicki J, Squassina A, Niola P, Chillotti C, Attems J, Gozes I, Gurwitz D. SIRT1, miR-132 and miR-212 link human longevity to Alzheimer's Disease. Sci Rep. 2018 May 31;8(1):8465.
3] Ivashko-Pachima Y, Hadar A, Grigg I, Korenková V, Kapitansky O, Karmon G, Gershovits M, Sayas CL, Kooy RF, Attems J, Gurwitz D, Gozes I. Discovery of autism/intellectual disability somatic mutations in Alzheimer's brains: mutated ADNP cytoskeletal impairments and repair as a case study. Mol Psychiatry. 2019 Oct 30

P2

Changes in cerebral glucose metabolism in chemotherapy-induced cognitive impairment

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Cancer survival has improved due to new treatment regimens, with the use of chemotherapy leading to a population of patients experiencing chemotherapy-induced cognitive impairments (CICI) that persist after cessation of chemotherapy, for which currently there are no available treatments. Chemotherapy drugs such as doxorubicin (DOX) induce DNA damage, which activates enzymes that consume nicotinamide adenine dinucleotide (NAD^+), a vital metabolite required for a range of important processes such as DNA repair and glucose metabolism. Changes in glucose metabolism have been shown to interfere with normal brain function and can trigger behavioural deficits. We speculated that DOX treatment may cause changes in glucose metabolism in the brain that could be related to CICI, and to address this we tested the ability of the NAD^+ precursor nicotinamide mononucleotide (NMN) to prevent this. Using proton (1H) and carbon (13C) nuclear magnetic resonance spectroscopy with 13C-labelled glucose and acetate, we found that DOX treatment significantly reduced the incorporation of labelled glucose into lactate C3 in the cortex, and increased the total pool size of aspartate in the hippocampus. Although NMN co-treatment did not rescue this effect, NMN treatment alone increased overall total metabolic pool size of nearly all metabolites in the cortex. These findings suggest that DOX treatment may potentially increase oxidative phosphorylation as a compensatory mechanism, and NMN alone may increase cerebral blood flow.

P3

Metabotropic glutamate receptors in the hippocampus and the prefrontal cortex in rats during neurodegeneration caused by trimethyltin chloride

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The metabotropic glutamate receptors (mGluRs) play an important role in the development of the nervous system, in synaptic plasticity, cognitive activity and other brain functions. In the present work, mGluRs were studied using a neurotoxic model of neurodegeneration based on the influence of trimethyltin chloride (TMT).

Adult male Wistar rats were treated with a single injection of TMT at a dose of 7.5 mg/kg subcutaneously; rats in the control group were treated with saline. Histological analysis and behavioral studies confirmed that TMT caused hippocampal injury and cognitive impairments in rats. The mRNA level of mGluRs in the hippocampus and prefrontal cortex was determined by RT-qPCR 21 days after TMT injection. In this period of TMT-intoxication active neuroinflammation develops both in the hippocampus and prefrontal cortex, as is indicated by increased COX-2 expression.

Analysis of gene expression revealed, that among varies subtypes of mGluRs the expression of mGluR4, mGluR5 and mGluR7 in the hippocampus and in the prefrontal cortex is different. After TMT treatment, the expression of the presynaptic mGluR4 gene is upregulated in the hippocampus, remaining at the control level in the prefrontal cortex. Conversely, mGluR7 is upregulated in the prefrontal cortex and does not change in the hippocampus. The reason for this is possibly due to the brain distribution of receptors. The density of mGluR4 in the neocortex is lower than in the hippocampus, and the density of mGluR7 in the neocortex is high, therefore, the effect of TMT on the expression level of these receptors is more significant. In addition, it should be emphasized that TMT leads to the death of neurons to the greatest extent in the hippocampus, therefore, a difference in the expression of receptors may mean a different contribution of individual mGluR subtypes to neuroprotection.

P4

Gestational hyperhomocysteinemia affects development of the nervous system in rat fetuses and offspring

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Prenatal hyperhomocysteinemia (PHHC) is one of the common complications of pregnancy that causes cognitive deficits in the offspring during postnatal development. We aimed at identification of some markers of fetal CNS developmental disorders in the «mother-placenta-fetus» system and studying the effects of PHHC on rat nervous tissue during postnatal ontogenesis.
Our study demonstrated that increased levels of homocysteine led to oxidative stress in pregnant rats and caused activation of their immune system. Studying the neuroactive factors synthesized in the placenta, which can penetrate the fetoplacental barrier and influence the development of the fetal brain, we found that PHHC led to accumulation in the placenta of pro-BDNF and pro-NGF, which have the opposite effect on the survival and proliferation of neurons, compared to their mature forms. Moreover, PHHC affected the content of these pro-neurotrophins and expression and activity of caspase-3 in the fetal brains.
At the structural level, PHHC caused a disruption in neuroblast generation and migration in the parietal cortex of rat pups accompanied by an increased number of cells with such features of neuronal death as chromatolysis. We have also observed an increase in the number of glial cells and IL-1β content in the cortex of pups after PHHC.
The data obtained indicate that PHHC causes changes in the placental content of IL-1β, BDNF and NGF, which might underlie the changes in brain development and maturation through impaired cell migration and increased apoptosis, as well as induce neuroinflammation in the postnatal period.
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P5

The efficacy of herbal interventions in the pathogenesis of diabetes and neuropsychological deficits on Streptozotocin-induced diabetic rats

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Diabetes is one of the most common metabolic disorders with severe concerns associated with many neurophysiological comorbidities including depression, a most common psychiatric illness with altered serotonergic receptors mechanism including 5-HT 2C which induces the anxiogenic effects and leads to depressive symptoms followed by cognitive impairment. The bioactive components of chamomile and saffron are known to induce therapeutic effects on diabetes and depression. **Objective:** Therefore, the present study was designed to evaluate the effects of saffron, chamomile and their co-administration on neuropsychological deficits following streptozotocin (STZ) induced diabetes in rats. **Methodology:** Fifty rats were randomly divided (n=10) into five groups DC; disease control, HC; healthy controls, S; saffron (10mg/kg), C; chamomile (30 mg/kg) and SC; combined saffron and chamomile (5 mg/kg and15 mg/kg respectively) administrated diabetic rats and made diabetic by the intra-peritoneal administration of 160 mg/kg STZ prior to the experiment. The exploratory activity in elevated plus maze test (EPM) and depression-like symptoms were assessed in Forced swim test (FST). Memory assessment was done by Morris water maze test (MWM). **Results:** The Results of present study showed that the treatment of saffron and chamomile enhanced the performance in EPMT and FST, thus produce anxiolytic and antidepressant effects. Likewise, the rats that received saffron and chamomile showed the improved cognitive activity in MWM significantly as compared to DC rats. **Conclusion:** The present study concluded that STZ-induced diabetes alters the brain functions and induced psychoneurological deficits, which may reverse by the therapeutic action of saffron, chamomile and their combination in low doses to treat diabetes and its associated neuropsychological deficits.

Keywords: Depression, Diabetic Rats, Neurophysiological changes, Herbal drugs

P6

Effects of maternal separation on microglia profile and anxiety-like behavior of male and female mice

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Childhood abuse and neglect are associated with a higher risk of developing psychiatric disorders. Once symptoms start at adolescence, it is important to point at this or to previous developmental windows. Microglia cells participate in both synaptic pruning and neuronal survival and its profile is modified in neurodevelopmental disorders. Thus, we aim to evaluate the effects of early-life stress on behavior and microglia morphophysiology in pre-pubertal male and female mice. For this, the litter of C57BL6 mice was randomly distributed between the control and maternal separation groups. The birthday was designed postnatal day 1 (PD1) and pups were separated from their mother 3h/day between PD2 and PD14. Between PD28 to PD31 the anxiety-like behavior was evaluated by locomotor activity box (LAB), open field (OF), dark-light box (DLB), elevated plus maze (EPM) and novelty suppressed feeding test (NSF). In order to investigate the microglia profile, we used C57BL6 CX3CR1:GPF mice. The animals went through the same protocol described and were euthanized at PD15 and at PD30. Microglia of the ventral hippocampus was assessed by confocal microscopy. In all tests, significance was set at $p<0.05$. Females, but not males, increased their distance traveled and the number of rearings on LAB and the time in extremity on OF. In contrast, only males decreased time in light zone and number of transitions on DLB and decreased head dipping on EPM. Preliminary results don't show a significant difference in microglia density of ventral HIP at P15. Our results showed an increase in anxiety-like behavior on males and suggest that females are more resilient to maternal separation protocol, even before hormonal influence.

P7

Gene functional networks influence autism spectrum characteristics in young people with intellectual disability

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Genes associated with Intellectual disability (ID) converge on cellular functional networks, for example chromatin regulation and neuronal communication, but it is not known whether functional networks can predict behavioural characteristics. This study asked whether functional network membership of ID-associated variants predicts autism spectrum characteristics (ASC). Participants with ID were allocated to two groups defined by functional annotations of their pathogenic variants: synaptic physiology (n=29) or chromatin regulation (n=23). We applied principal components analysis to the Social Responsiveness Scale to map the structure of ASC in this population. This identified three ASC components – Inflexibility, Social Understanding and Social Motivation. We then used Akaike Information Criterion (AIC) to model relationships between ASC dimensions and demographic factors (age, gender), non-ASC behavioural factors (adaptive function, anxiety, hyperactivity, inattention) and gene functional networks. We found that, when other factors are accounted for, the chromatin regulation group showed higher levels of inflexibility. We also observed contrasting associations between ASC and non-ASC features within each network group: within the chromatin group, social understanding was associated with inattention, and social motivation was predicted by hyperactivity; within the synaptic group, social understanding was associated with hyperactivity, and social motivation was linked to anxiety. In conclusion, we found that gene functional networks can predict some (but not all) ASC dimensions, and can predict behaviours co-occurring with ASC. Further work is warranted to define the cognitive and neurobiological basis for inflexibility in disorders of chromatin regulation and elucidate network-specific developmental pathways from genomic variation to social understanding and social motivation.

P8

Region-specific effects of IGF-1 and oxytocin on KCC2 in MeCP2 KO mice

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The K+/Cl- cotransporter 2 (KCC2) is involved in the transition in polarity of GABAergic response, critical for brain development and maturation. During early postnatal development, KCC2 is modulated by the neuropeptide oxytocin (OXT) through its OXT receptor (OXTR), thus exerting a neuroprotective effect. Early developmental dysregulation of KCC2 expression is found in male mice carrying loss of function mutations in the gene Methyl-CpG binding protein 2 (Mecp2) (MeCP2-KO mice), which recapitulate many symptoms of Rett Syndrome (RTT). Recombinant human insulin-like growth factor-1 (rhIGF-1) treatment ameliorates the phenotype of MeCP2-KO mice and normalizes the E/I balance by restoring KCC2 expression.
We hypothesized that MeCP2-KO mice may have alterations in an IGF-1/OXT signaling cross-talk that modulates KCC2. To test this, we mapped and quantified KCC2, OXTR and IGF-1 receptor (IGF-1R) levels in several brain regions of MeCP2-KO male mice treated with vehicle, recombinant human IGF-1 (rhIGF-1), or OXT and compared their levels to littermate control mice. With a main focus on brain olfactory regions, we found that MeCP2-KO mice displayed alterations of IGF-1R and OXTR levels in all the regions analyzed, however these changes were not necessarily accompanied by KCC2 alterations. Indeed, we found that KCC2 deficits and the effects of treatments on KCC2 levels in MeCP2-KO are region-specific.
This suggests possible complementary contributions of the IGF-1 and OXT signaling in early brain development. Moreover, the strong region-specificity of KCC2 alterations, and of rhIGF-1 and OXT effects, in our model indicates that region-selective innovative therapeutic strategies are most desirable, aiming at normalizing the E/I balance only in key brain regions subtending the RTT symptomatology.

P9

Effect of Prenatal Hypoxia on Cholinesterase Activity in Blood Serum of Rats

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Analysis of age-dependent dynamics of acetylcholine- and butyrylcholinesterase (AChE, BChE) in blood serum of rats demonstrated that their enzyme activities significantly decrease during ageing. Moreover, in mature rats (5 and 8 months) subjected to prenatal hypoxia during the period of active formation of the brain (E14, 7% O_2, 3 h) there was a two-fold decrease in the activity both of AChE and BChE compared to controls. Prenatal hypoxia at a later stage of pregnancy (E18) also resulted in decreased activity of BChE (down to 30% of the controls) in the blood serum of mature rats. However, the activity of AChE in the serum of such animals was significantly higher (by 80%) than in controls. Levels of cholinesterase activity in blood serum also correlated with the motor activity of rats. In active mature rats, AChE activity was, on average, 20% and BChE 70% higher than in passive rats. Administration to animals of a natural antioxidant L-carnitine or a synthetic tyrosine kinase inhibitor imatinib (gleevec), which affects expression of some neuronal genes including AChE, resulted in an increase in the activity of both cholinesterases in the serum. In addition to our previous data on the prolonged effects of prenatal stress on the cholinergic brain system and impaired cognitive functions in the postnatal life, this study suggests that prenatal hypoxia also affects the activities of AChE and BChE in the blood which might underlie changes in the peripheral reactions of animals to different types of stressors.

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Key words: prenatal hypoxia, the cholinergic brain system, cognitive functions, amyloid-degrading enzymes, neprilysin, Alzheimer's disease

P10

Neonatal bacterial endotoxin exposure exacerbates stress-induced changes of NMDA and AMPA receptor expression in the rat brain

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Deregulated glutamatergic transmission may be implicated in neurological disorders including post-traumatic stress disorder (PTSD). Structural changes of glutamate receptors can affect glutamatergic transmission. Long-term changes of gene expression of NMDA and AMPA receptor subunits after vital stress are not clear yet, while it seems important for understanding the mechanisms of PTSD. Neonatal pro-inflammatory activation can affect brain maturation by making it more vulnerable to stressful events later in life and increasing risk of PTSD.
We aimed to investigate NMDA-R and AMPA-R subunit gene expression in the rat brain in a model of vital stress alone or combined with neonatal lipopolysaccharide exposure.
Male Wistar rats 3 m.o. were subjected to stress by 40-min contact with a predator (black-tailed python) either without neonatal manipulation (Study I) or after LPS treatment, 25 or 50 μg/kg, i.p., at P15, P18, P21 (Study II). qRT-PCR analysis of mRNA expression of NMDA (GluN1, GluN2a, GluN2b) and AMPA (GluA1, GluA2) glutamate receptor subunits was performed in brain structures 6, 24 hrs, 3, 9, 25 days after stress (Study I), and 7 days after stress (Study II).

Study I. Most pronounced gene expression alterations were observed 25 days after stress: GluN2a mRNA increased in the amygdala, GluN2b increased in the ventral hippocampus (VH) and medial prefrontal cortex (mPFC) and decreased in the dorsal hippocampus (DH), GluA1 and GluA2 decreased in DH and increased in VH of stressed rats compared with control.

Study II. Stress-induced changes were more prominent in animals injected with 50 μg/kg LPS. In mPFC of stressed LPS-treated rats, GluN1, GluN2a, GluN2b, GluA1, GluA2 mRNA, as well as GluN2a/GluN2b ratio increased; in DH, GluN2a and GluA1 mRNA and GluN2a/GluN2b ratio decreased compared with vehicle-treated control groups.
Observed LPS-evoked disturbances of NMDA-R and AMPA-R subunit expression may contribute to severe stress-induced mental illnesses.
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P11

Paving the way for future therapeutic strategies in Cornelia de Lange Syndrome modulating defective Wnt pathway

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Cornelia de Lange Syndrome (CdLS) is a rare developmental disorder affecting almost any organ including the Central Nervous System (CNS), inducing a variable – i.e. mild to severe – neurodevelopmental delay. The underestimated prevalence is 1: 10.000-30.000 newborns. CdLS is characterized by slow growth, abnormalities of bones and disorders in gastro-intestinal tract, and they present distinctive facial features. CdLS patients are characterized by intellectual disabilities and behavior of the autism-spectrum disorder.

CdLS is caused by mutations in *NIPBL, SMC1A, SMC3, RAD21,* and *HDAC8* genes encoding for proteins of the cohesin complex, a conserved multimeric structure which plays a pivotal role in gene expression regulation and is involved in chromatin organization. Our previous studies uncovered a correlation between cohesins alterations and impairment of the canonical Wnt pathway.

First, we have explored possible ameliorative effects of chemical activation of Wnt pathway with lithium chloride (LiCl) and other activators in lymphoblastoid cell lines from healthy donors and CdLS patients. Normally, proliferation is reduced in CdLS cells. These treatments restored cellular proliferation rate and induced the expression of *CyclinD1*. Then, mammalian Neural Stem Cells CdLS models (CdLS-NSCs) showed a significant reduction in proliferation rate and differentiation capabilities toward the neuronal lineage, compared to controls. Interestingly, when CdLS-NSCs were exposed to LiCl, such defects were rescued restoring physiological levels, underlying a protective effect of LiCl. Then, the importance of the canonical Wnt pathway has been validated in a D. melanogaster CdLS model. Upon feeding on LiCl, *Nipped-B407* mutants show, in the offpring, a significant rescue of development of the mushroom body morphology, a CNS structure involved in learning and memory.

Overall, our data confirm that the canonical Wnt pathway is impaired in CdLS models, possibly explaining the neurodevelopmental alterations of CdLS patients. In addition, our rescue experiments could pave the way for future therapeutic strategies.

P12

C21orf91 as a new regulator of gliogenesis and Down syndrome neuropathology

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Neuropathological diseases of the central nervous system (CNS) are frequently associated with impaired differentiation of the oligodendroglial cell lineage and subsequent alterations in white matter structure and dynamics. Down syndrome (DS), or trisomy 21, is the most common genetic cause for cognitive impairments and intellectual disability (ID) and is associated with a reduction in the number of neurons and oligodendrocytes, hypomyelination and astrogliosis. Recent studies mainly focused on neuronal development in DS and underestimated the role of glial cells as pathogenic players. This also relates to C21orf91, a protein considered a key modulator of aberrant CNS development in DS. We investigated the role of C21orf91 in terms of oligodendrogenesis and myelination using primary oligodendroglial progenitor- (OPCs) and primary neural stem cells (NSCs). We found that upon modulation of C21orf91 gene expression, this factor is important for accurate oligodendroglial differentiation in that for example gene suppression restricts morphological maturation. On the other hand, C21orf91 overexpression, which accelerates morphological maturation, is still resulting in a diminished oligodendroglial capacity to myelinate axons. In addition, overexpression initiates a cell population co-expressing astroglial- and oligodendroglial markers such as for example glial fibrillary acid protein (GFAP) together with myelin basic protein (MBP). This observation indicates that elevated C21orf91 expression levels induce a gliogenic shift towards the astrocytic lineage reflecting observations in DS brains. Current investigations aim at confirming C21orf91 dependent cell fates *in vivo* using suitable transplantation experiments.

P13

Studies on the resolution of inflammation in Alzheimer's disease

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Alzheimer's disease (AD) is the most common type of dementia and the number of AD-patients is growing fast worldwide. In addition to the classical hallmarks, extracellular amyloid beta (Aβ) in amyloid plaques and neurofibrillary tangles (NFTs), there is an ongoing inflammation in the AD brain. Normally, inflammation ends by the resolution process, the final stage that results in return to homeostasis in the tissue. However, there is evidence that this process is disturbed in AD, resulting in chronic inflammation and the ensuing deleterious effects on neurons caused by pro-inflammatory cytokines and cytotoxic molecules such as reactive oxygen species and proteolytic enzymes. Our studies aim to investigate the resolution of inflammation in Alzheimer's disease and the role of the specialized pro-resolving mediators (SPMs). We use morphological and biochemical methods to investigate the effects of the SPMs on microglia and neurons as well as the levels of the receptors and synthetic enzymes of SPMs in human and mouse brain. Our results indicate the decrease in SPMs in the human brain and CSF and that the receptors to resolvin E1 (RvE1), ChemR23 and BLT1, are increased in AD. We show that SPMs are able to modulate the response of microglia towards Aβ by decrease in pro-inflammatory markers and an increased uptake of Aβ.
Our studies provide evidence for a disturbed resolution of inflammation in AD, and of this process as a possible treatment target.

P14

Prolonged treatment with medium chain triglycerides (C8, C10) induces positive effect on cognitive abilities of intact rats

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Cognitive impairment often occurs as a result of the brain glucose hypometabolism and insufficient energy supply. Ketone bodies (KB), the by-products of fatty acid beta-oxidation, represent an alternative source of energy for the brain with high energetic potential. A number of studies have demonstrated a broad neuroprotective effect of the KBs. However, achieving an increase of the KB concentration in the body by removing carbohydrates from the diet is not acceptable because of the metabolic disturbances it can cause. It is possible to intensify the KB generation even in the presence of carbohydrates by treatment with medium-chain saturated fatty acids (C8, C10) or their triglycerides (MCT).
We aim to develop a model to gain in-depth knowledge about the mechanisms of effects of MCT-treatment on cognitive abilities of animals in various conditions.
The work was performed on adult Wistar male rats. The animals were tested in Y-maze and Open field test. Then, the animals were divided into 2 groups: MCT (chow excluded for 6 h/day, MCT oil intragastric, 2 ml/kg) and control (equivolume water intragastric). After 2 weeks of such everyday treatment, the tests were repeated, adding the Morris water maze. Statistical analysis was performed by rm-ANOVA, *post hoc* Sidak; Student's and Mann-Whitney tests, $p < 0.05$.
In the Y-maze, MCT group demonstrated more spontaneous alternations compared to control, indicating better working memory. In the Open field, MCT animals showed decreased exploration than control group when normalized to pre-treatment trials, indicating better memory of the environment. In the probe trial of Morris water maze, MCT animals spent more time in the target quadrant than control group, indicating better spatial memory.
Thus, MCT-treatment is shown to be a promising non-drug approach to improve cognitive functioning that is worth further physiological and biochemical investigations.
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P15

The caspase-3 inhibitor Ac-DEVD-CHO normalizes neprilysin expression in brain tissue of rats subjected to prenatal hypoxia

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The major amyloid-degrading enzyme neprilysin (NEP) is known to be one of the crucial enzymes related to the pathogenesis of neurodegenerative disorders. However, little is known about the regulatory mechanisms of NEP expression in brain structures of laboratory rodents which are frequently used as a zootropic model of human neurodegenerative diseases. Acute hypoxia in pregnant female rats as shown in our studies leads to impaired embryonic brain development in the offspring. It was shown to decrease the level of NEP expression and change normal metabolism of the amyloid precursor protein (APP) in pups' brains. The structural changes of axo-spinal synapses in the cortical and hippocampal tissues of "hypoxic" pups were accompanied by impaired cognitive functions. The APP intracellular domain (AICD), which was shown to interact with the NEP promoter upregulating its expression, is one of the substrates of caspases. In the first month of postnatal ontogenesis of rat pups subjected to prenatal hypoxia the level of active caspases in the cortical areas was found to be significantly increased. At the same time, the content of AICD and NEP as revealed by Western blotting was decreased. As such we suggested the caspases might be involved in AICD degradation and hence reduced NEP expression after prenatal hypoxia. When we treated the pups subjected to prenatal hypoxia with an intraventricular injection of the caspase-3 inhibitor Ac-DEVD-CHO during the first month of development (P18), we found that the levels of AICD peptide in the cortical areas was normalized, as were the levels of NEP protein expression. Inhibition of caspase activity also prevented structural abnormalities and cognitive deficit caused by prenatal hypoxia. As such, we can conclude that modulation of caspase activity in early postnatal development of rats subjected to prenatal stress via regulation of neuronal gene expression, in particular of neprilysin, can affect neuronal plasticity and cognitive functions of animals in adulthood.

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Key words: prenatal hypoxia, neuronal plasticity, memory, amyloid-degrading enzymes, neprilysin, Alzheimer's disease.

P16

Spatial contextual memory consolidation: key dopaminergic and cholinergic functional connections and their vanishing under brain hypo-perfusion

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Aims. A study of dopaminergic (DA) and cholinergic (ChE) mechanisms of consolidation of spatial contextual memory (SCM) in an intact brain and the reasons for its delayed disturbance under chronic cerebral hypo-perfusion conditions (2VO model). **Methods**. 2VO and sham (control) rat operations were induced. 6-8 days after surgery, a long-term memory was studied in spatial contextual model of learning in Morris water maze. The SCM consolidation was evaluated in a first attempt of 2nd day of training. Two days after learning, the sub-synaptic fractions were isolated from the "light" and "heavy" synaptosomal fractions of neocortex and hippocampus, in which an activity of tyrosine hydroxylase (TH) and choline acetyltransferase (ChAT) (markers of DA and ChE synapses, respectively) was estimated.

Results. Control rats were divided into sub-groups of high (HCRs), medium and low capable (LCRs) for SCM consolidation. In all sub-groups, the correlations of TH-T and / or ChAT-T were revealed, as well as inter-fractional and inter-structural connections of TH-TH, TH-ChAT and ChAT-ChAT were revealed in pre-synapses of fractions involved in consolidation.

In sub-group of HCRs, DA pre-synapses of heavy synaptosomal fraction of hippocampus (presumably projections from locus coeruleus) were key in conjugation of different DA and ChE elements of functional network. In sub-group of LCRs, ChE pre-synapses of projection neurons into hippocampus (light fraction) played a key role. Under hypo-perfusion, TH activity decreased significantly and the value of DA system in SCM consolidation was completely lost, while the value of ChE system was reorganized. 2VO group practically consisted of LCRs whose functional network retained only ChAT-T connections of cortical interneurons (heavy fraction).

Conclusion. SCM consolidation is carried out with different efficiency through different functional networks. Under hypo-perfusion, a loss of DA link led to a loss of ability to maintain the SCM consolidation at a high level.

P17

Histone deacetylase inhibitor sodium valproate restores cognitive and olfaction impairments in rats subjected to prenatal hypoxia

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The data accumulated to date indicate that disturbances in the olfactory system and its connections with other parts of the brain are an attribute both of normal aging and early signs of the development of many neurodegenerative diseases. A large number of studies testify to the important role of the olfactory system in the development of dementia and in the pathogenesis of AD. In particular, a number of models have been developed using bulbectomized rodents in which accelerated amyloidogenesis and the development of neurodegeneration take place. In our studies it was shown that impaired embryonic development in rats, as a result of prenatal hypoxia, leads to changes in the normal metabolism of the amyloid peptide and its precursor protein, to alterations of the morphological and functional properties of the nervous tissue of the parietal cortex and hippocampus and to impaired cognitive functions and olfaction. Therefore, prenatal hypoxia in rats can be considered as a zootropic model of the early stages of human neurodegenerative diseases. Investigating the ways to restore the impaired brain functions, we have tested the effects of a histone deacetylase inhibitor sodium valproate which is known to regulate expression of neuronal genes related to neurodegenerative disorders, in particular, of the neuropeptidase neprilysin (the major amyloid-degrading enzyme). We have found that a series of intraperitoneal injections of sodium valproate leads to the restoration of cognitive functions in the radial maze and the novel object recognition test, as well as to the improvement of the sense of smell when testing the odor preference and the ability to search for food. As such, we can conclude that the behavioral disorders observed after prenatal hypoxia can be attenuated by epigenetic regulation of gene expression, in particular, of neprilysin.

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Key words: prenatal hypoxia, learning, memory, amyloid-degrading enzymes, neprilysin, Alzheimer's disease

A1

CHD8 autism and intellectual disability

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Heterozygous, loss-of-function mutations in the gene *CHD8*, which encodes Chromodomain Helicase DNA-binding factor 8, an ATP-dependent chromatin remodelling factor, are some of the highest confidence autism risk factors identified to date. More than 95% of individuals with *CHD8* haploinsufficiency are diagnosed with autism, >65% have macrocephaly and approximately 50% have intellectual disability. We have established a number of *Chd8*-deficient mouse lines to investigate how *Chd8* deficiency affects brain development and function. Reductions in CHD8 protein levels by 50% and 25% resulted in brain hyperplasia, but no convincing autism-associated behaviours. *Chd8* haploinsufficient mice exhibited abnormalities in functional connectivity, pre-figured by altered expression of synaptic and axon guidance genes in the early postnatal period. These findings show that *Chd8* haploinsufficiency disrupts normal postnatal brain development and connectivity.

To determine if *Chd8* haploinsufficient mice exhibit learning and memory phenotypes and may serve as a useful model to understand the basis of intellectual disability in *CHD8* patients, we tested mice in the contextual fear conditioning paradigm. These mice showed a clear deficit in short term memory consolidation in this test, compared to wildtype control littermates. As CHD8 controls transcription by regulating chromatin structure, we compared the hippocampus transcriptome in $Chd8^{+/-}$ and $Chd8^{+/+}$ mice during learning. The initial results from these studies will be presented.

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A2

Longitudinal *in vivo* imaging of perineuronal nets in fragile-X syndrome

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Fragile X syndrome (FXS), engendered by silencing of the fragile X mental retardation (FMR1) gene, is the most common monogenic cause of autism spectrum disorder (ASD) and intellectual disability. Perineuronal nets (PNN), specialized extracellular matrix (ECM) structures ensheathing inhibitory parvalbumin cells, were implicated in many processes related to phenotypes presented in FXS, including neuronal processing, synaptic plasticity, learning, and memory. Unfortunately, lack of tools for monitoring PNNs *in vivo* limited studies to (i) *ex-vivo* labeling and electrophysiological recordings, which are performed on partial neuronal systems with incomplete microenvironments; or to (ii) enzymatic degradation studies with inability to monitor dynamic processes such as activity and synthesis. Here we introduce a straightforward approach for direct *in vivo* imaging and quantification of PNNs in awake and behaving mice using two-photon microscopy. This approach allows, for the first time, to longitudinally image PNNs, segregate and monitor neuronal activty of PNN-positive cells, as well as to observe the dynamics of PNN breakdown and de-novo synthesis; all with high specificity and with subcelluar resolution in a minimally invasive manner. Implementing this novel tool combined with calcium imaging, we point to hyperexcitability of the excitatory neurons in a mouse model of FXS (fmr1-KO), in line with impaired activity of parvalbumin neurons. Using enzymatic degradation, we point to the specific roles of PNNs in mediating this effect and to altered synthesis of PNNs in FXS. Finally, using widefield calcium imaging we study the abnormalities in synchronization and connectivity between brain regions in FXS.

A3

Microglia-derived extracellular vesicles propagate early synaptic dysfunction in Alzheimer's Disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by pathogenic amyloid-β (Aβ) accumulation. Extensive literature implicates synaptic dysfunction as an early mechanism affected in AD, that involves increasingly larger areas of the brain over time. However, how synaptic dysfunction rises and propagates throughout the brain is largely unclear. In this study, we tested the hypothesis that EV released by microglia and carrying Aβ (AβEV) may induce synaptic alteration and spread it among connected brain regions. We first analysed spine morphology and synaptic plasticity expression in cultured hippocampal neurons exposed to AβEV or EV from untreated microglia (ctrlEV), finding that AβEV, but not ctrlEV, affect dendritic spines and impair synaptic plasticity. Then, we tested the possibility that AβEV may propagate synaptic dysfunction from the entorhinal cortex (EC), the starting point of AD degeneration, to its main target region, the dentate gyrus (DG). To this aim, we stereotaxically injected AβEV or ctrlEV into the mouse EC and measured LTP both in the EC and the DG through extracellular recordings on cortico-hippocampal slices. 1h after the injection, LTP was impaired only in the EC of AβEV injected brains. While 24h after AβEV injection, LTP was impaired also in the DG, indicating a spreading of synaptic dysfunction between the two connected regions. Next, by combining optical manipulation to time-lapse imaging, we gained insights into EV-neuron interaction dynamics, finding that Aβ-EV drift on the neuron surface and that their motility can be impaired by coating EV with annexin-V. Importantly, when Aβ-EV motion was limited, no propagation of LTP impairment occurred, indicating that EV motility at the neuron surface is involved in the spreading of synaptic dysfunction. Our data provide strong evidence of the involvement of EV from microglia in the start and propagation of synaptic dysfunction in early AD, paving the way for novel therapies.

A4

Embelin negated the development of intracerebroventricular streptozotocin and β- amyloid induced Alzheimer's Dementia (AD) model in Rats

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Although Alzheimer's Dementia (AD) is the most common age-related neurodegenerative disease and characterized by memory impairment, only symptomatic treatments are available. In recent years there has been increasing interest towards identification of novel leads from natural sources considering their safety profile under clinical development. Because Embelin (2, 5-dihydroxy-3-undecyl-1,4-benzoquinone) is a naturally occurring alkyl substituted hydroxy benzoquinone and a major constituent of *Embelia ribes* BURM. (*Myrsinaceae*) has various neuroprotective effects and improves cognitive function in animal models of neurodegenerative disorders (Gupta et al., 2013, Afzal et al., 2012). In the present study, we investigated the therapeutic effects of embelin in an intracerebroventricular (ICV)-streptozotocin (STZ) and amyloid β (Aβ) induced animal models of Alzheimer's Dementia (AD).

Methods:

STZ and β amyloid $_{1\text{-}42}$ oligomers were infused bilaterally at the dose of 3 mg/kg/icv (STZ) on day 1st, 3rd and 3nmol/3 µL/icv (β amyloid $_{1\text{-}42}$ oligomers) on day 0 after surgery respectively. Rats were treated with embelin (2.5, 5 and 10 mg/kg i.p.) for 14 days from 7th day onwards after ICV-STZ and Aβ infusion. Spatial and non-spatial memory was evaluated using Morris water maze (MWM) and object recognition task (ORT) in rats. On day 22 rats were sacrificed and hipoocampal brain regions were used to identify biochemical, neurochemical and neuroinflammatory alterations.

Results:

ICV-STZ and Aβ was found to significantly shorten the latency time on the MWM and ORT which was associated with increase in oxidative stress (lipid peroxidation and nitrite), compromised antioxidant defense (reduced glutathione), neurotransmitter alteration (AChE, DA, NA, 5-HT, GABA and glutamate) and elevation in neuroinflammatory cytokine (IL-1 β, IL-6 and TNF- α) levels. On the other hand, embelin significantly attenuated all these detrimental effects induced by STZ and Aβ.

Conclusions: Embelin dose dependently attenuated STZ and Aβ-induced cognitive deficits, biochemical alterations and restored hippocampal neurochemical levels. The observed protective effect might be attributed to the antioxidant and anti-inflammatory potential of embelin and its ability to restore hippocampal neurochemistry. Thus, the outcomes of the current study suggest therapeutic potential of embelin in cognitive disorders such as AD.

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