Session 14: New Biomarkers in Neurodegenerative Diseases

Lectures

L14.1

Astroglia in health and pathology

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Astrocytes are the major glial cells in the central nervous system (CNS). They play pivotal roles in many processes including neurogenesis, synaptogenesis, synaptic plasticity, brain blood flow, ionic and neurotransmitter homeostasis. Astrocytes are also responsible for metabolic support of neurons and participate in synaptic transmission. Such varied and important roles can be carried out due to complex interactions of astrocytes with other types of cells of CNS and the vasculature. Mounting evidence indicates that dysfunctional astrocytes contribute to the pathogenesis of several brain disorders including neurological, neurodegenerative and psychiatric diseases as well as brain tumors. A better understanding of biology and the role of astrocytes in the pathogenesis of CNS disorders may lead to novel strategies to treat these diseases.

L14.2

Regulatory effects of acetyl-CoA distribution in cellular compartments of healthy and diseased brain

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Brain neurons, to support their neurotransmitter functions require a several times higher supply of glucose than non-excitable cells. Pyruvate, the end product of glycolysis, through pyruvate dehydrogenase complex reaction, is a principal source of acetyl-CoA, which is a direct energy substrate, in all brain cells. Several neurodegenerative conditions result in the inhibition of pyruvate dehydrogenase and decrease of acetyl-CoA synthesis in mitochondria. This attenuates metabolic flux through TCA, yielding energy deficits, and inhibition of diverse synthetic acetylation reactions in all neuronal subcompartments. The acetyl-CoA concentrations in neuronal mitochondrial and cytoplasmic compartments are in the range of 10 and 7 μmol/L, respectively. They appear to be from 2 to 20 times lower than its Km values for carnitine acetyltransferase, acetyl-CoA carboxylase, aspartate acetyltransferase, choline acetyltransferase, sphingosine kinase1 acetyltransferase, acetyl-CoA hydrolase, and acetyl-CoA acetyltransferase, respectively. Therefore, alterations in acetyl-CoA levels alone may significantly change the rates of metabolic fluxes through multiple acetylation reactions in brain cells in different physiologic and pathologic conditions. Such substrate-dependent alterations in cytoplasmic, endoplasmic reticulum or nuclear acetylations, may directly affect ACh synthesis, protein acetylations and gene expression. The excitotoxicity-evoked intracellular zinc excess hits several intracellular targets, yielding the collapse of energy balance and impairment of the functional and structural integrity of postsynaptic cholinergic neurons. Acute disruption of brain energy homeostasis activates slow accumulation of amyloid-β_{1-42} (Aβ). Extra and intracellular oligomeric deposits of Aβ affect diverse transporting and signaling pathways in neuronal cells. Different neuro-glial and neuronal cell types display differential susceptibility to similar pathogenic insults depending on individual proportions between rates of acetyl-CoA provision and utilization in their energy producing and diverse synthetic acetylations compartments. Thereby, alterations in acetyl-CoA availability may regulate functional and adaptative properties of neuronal and non-neuronal brain cells in diverse physiologic and pathologic conditions.

Oral presentations

O14.1

Plant's compounds modulate GABA-shunt enzymes activity

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Many neurodegenerative and affective diseases are characterized by disorders of gamma-aminobutyric acid (GABA) and three enzymes involved in its metabolism (GABA-shunt enzymes): glutamate decarboxylase (GAD), GABA aminotransferase (GABA-T) and succinic semialdehyde dehydrogenase (SSADH). Neurological diseases are also often accompanied by disturbances of calcium homeostasis. Traditional drugs are not always efficient and may be are associated with adverse side effects. Chemicals naturally occurring in plants can provide an attractive alternative target in modulating neurotransmission of GABA *via* affecting activity of GABA-shunt enzymes. The purpose of this study is to investigate an impact of one of natural plant's compounds: genistein, on activity of GABA-shunt enzymes. In this study we use pseudoneuronal PC12 cell line with reduced expression of calcium membrane pumps PMCA2 or PMCA3 Cells were incubated with 10 uM genistein during 10 minutes. After that activity of particular enzymes was determined by measurment of products level. Our preliminary findings indicate that genistein can modulate activity of glutamate decarboxylase and this way can change balance between to oppositely (reversely) acting neurotransmitters.

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O14.2

Altered PMCA composition in differentiated PC12 cells causes changes in CCL5 – induced response

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Impaired calcium homeostasis is one of the factors contributing to neurodegeneration induced by pro-inflammatory chemokines. One of the paths triggered by chemokine receptors stimulation is phospholipase C activation and formation of IP_3, with subsequent Ca^{2+} mobilization from endoplasmic reticulum stores. Calcium signal is terminated mainly by plasma membrane Ca^{2+}-ATPase (PMCA), the most sensitive calcium detector. The enzyme exists in four isoforms. PMCA1 and PMCA4 are ubiquitous, but PMCA2 and PMCA3 are specific for excitable cells, including neurons. In our study on pseudo-neuronal PC12 cells we assayed whether the change in PMCA isoform composition due to down-regulation of neuron-specific PMCA isoforms affects cell response to pro-inflammatory CCL5 chemokine. Presence of CCL5 sensitive receptors was confirmed by WB and confocal microscopy. Experiments in calcium-free buffer showed that calcium releasing mediated by PLC/IP_3 pathway was higher in modified cell lines. Further analysis showed that PMCA2 and PMCA3 down-regulation changed the IP_3 receptors expression on both, mRNA and protein level. Since lowered Ca^{2+} extruding potency due to lowered PMCA amount and activity is observed in aging neurons, more intense response on CCL5 may underlie the neurodegeneration processes.

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Posters

O14.3

Correlation between the concentration of fibrinogen in blood platelets and the degree of platelet aggregation in multiple sclerosis

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Introduction: Multiple sclerosis (MS) is a chronic, demyelinating immune-mediated disease of the central nervous system with axonal degeneration.
Blood platelets have increased pro-thrombotic properties in the course of MS and are present in active inflammation demyelinating lesions. However, the exact determination of platelet significance in MS pathology still needs to be clarified.
Our previously study indicates the increased level of fibrinogen in blood platelets in MS, which probably may cause augmented pro-thrombotic platelet activity. The aim of presented study was to establish a correlation between the degree of platelet aggregation and the concentration of platelet fibrinogen in MS in relation to control group.
Methods: The level of platelet aggregation in non-stimulated whole blood was measured by flow cytometry method, while the level of fibrinogen in platelets was determined using commercial enzyme immunoassay ELISA kit.
Results: The obtained results univocally indicate the existence of a statistically significant positive correlation (p=0.0018; R=0.791) between degree of platelet aggregation and the concentration of platelet fibrinogen in MS. Whereas, there is no statistical significant correlation in control group.
Conclusion: We suggest that one of the potential mechanism of elevated aggregation properties of blood platelets in MS may be their ability to synthetize and/or storage of fibrinogen.