21.2 SYNAPTIC LIPID SIGNALING AT CENTRAL SYNAPSES: ROLE IN PSYCHIATRIC DISORDERS

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Background: Synaptic phospholipids were shown to regulate cortical excitability (E/I)-balance and to control sensory information processing in mice and man. However, altered synaptic LPA-signaling was suggested to be associated with psychiatric disorders.

Methods: In order to analyze the role of synaptic lipid signaling in psychiatric disorders, we performed electron microscopy, cell culture experiments, mass spectrometry and electrophysiological experiments on transgenic mouse lines, where different elements of cortical synaptic lipid signaling were deleted. These data were corroborated by in-vivo electrophysiological measurements in freely moving mice and by behavioral experiments.

Results: Our data show that the LPA-synthesizing enzyme autotaxin (ATX) is expressed in the astrocytic compartment of excitatory synapses and modulates glutamatergic transmission. In astrocytes, ATX is sorted towards synaptic membranes, and the enzymatic activity of astrocytes-metabolizing enzyme glutamate dehydrogenase (GDH), encoded by Glud1, is increased. GluN1-deficient mice displayed enhanced glutamate release, an elevated excitatory/inhibitory balance in cortex, and a reduced behavioral abnormalities in a battery of tests that assess different aspects of schizophrenia-like psychopathology. We further asked whether an environmental manipulation, i.e., stress exposure, would exacerbate the behavioral abnormalities and astrocytic-neuronal gene expression patterns in heterozygous and homozygous mice.

Conclusions: Collectively, these studies show that GDH-mediated glutamate metabolism in astrocytes impacts on neuronal glutamate transmission and release. GDH disruption, also demonstrated in post-mortem CA1 of patients with SZ, leads to SZ-like deficits in mice. GDH disruption and exposure to stress may cumulatively disrupt neuronal-astrocytic communication. These findings could lead to better understanding of the glutamate tripartite synapse and its contribution to SZ-like etiology.

21.3 NEURONAL-ASTROCYTIC REGULATION OF GLUTAMATE HOMEOSTASIS: RELEVANCE TO COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

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Background: Glutamatergic abnormalities are commonly observed in schizophrenia (SZ) and are hypothesized to play an important role in cognitive dysfunction. While the contribution of postsynaptic glutamate receptors to SZ psychopathology has been extensively examined, less is known about the role played by enzymes involved in glutamate metabolism and homeostasis. We examined mice with a brain-wide deficit in the glutamate metabolizing enzyme glutamate dehydrogenase (GDH), encoded by Glud1, which leads to glutamate excess due to reduced glutamate metabolism in astrocytes.

Methods: We investigated astrocytic and neuronal abnormalities in mice with a CNS-specific mutation in Glud1. We asked whether CNS-Glud1 deficient mice would display behavioral abnormalities in a battery of tests that assess different aspects of schizophrenia-like psychopathology. We further asked whether these behavioral abnormalities would exacerbate the behavioral abnormalities and astrocytic-neuronal gene expression patterns in heterozygous and homozygous mice.

Results: We found that mice with a homozygous mutation in CNS-Glud1, with a primarily astrocytic deficit in glutamate metabolism, display enhanced glutamate levels, an elevated excitatory/inhibitory balance in CA1, and a normally high mRNA expression of neuronal and astrocytic markers of glutamate transmission. In contrast, mice with a brain-wide deficit in Glud1 displayed several behavioral abnormalities, e.g., amphetamine-induced hyperlocomotion, nest building and social preference deficits, and abnormal reversal/extradimensional set shifting in the water T-maze. While heterozygous mice displayed no major behavioral or molecular abnormalities, their exposure to stress led to cognitive dysfunctions; these gene x environment interactions may be mediated by disrupted function of the neuron-ghi interface.

Conclusions: Collectively, these studies show that GDH-mediated glutamate metabolism in astrocytes impacts on neuronal glutamate transmission and release. GDH disruption, also demonstrated in post-mortem CA1 of patients with SZ, leads to SZ-like deficits in mice. GDH disruption and exposure to stress may cumulatively disrupt neuronal-astrocytic communication. These findings could lead to better understanding of the glutamate tripartite synapse and its contribution to SZ-like etiology.

21.4 CELL-TYPE SPECIFIC ALTERATIONS IN ADENOSINE-GENERATING PATHWAYS IN SCHIZOPHRENIA

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Background: Adenosine is a potent neuromodulator of glutamate and dopamine neurotransmission and abnormalities of adenosine metabolism are a possible pathophysiological mechanism postulated to underlie the signs and symptoms of schizophrenia. Extracellular adenosine is mainly generated in two ways. ATP is released into the extracellular space and converted to adenosine via a series of enzymatic steps. Alternatively, adenosine is directly released from cells via equilibrative nucleoside transporters (ENTs). Indirect generation of adenosine via conversion of ATP is more typical of glial cells, while direct adenosine release is more typical of neurons, although the enzymes required to generate adenosine and the ENT transporters are found in both cell types. The relative contributions of...