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The role of ASCT-1 in the pathophysiology of schizophrenia

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Bernhard Mitterauer Joined: 07 Jun 2005 Posts: 11	Posted: Wed Sep 13, 2006 1:02 pm Post subject: The role of ASCT-1 in the pathophysiology of schizophrenia quote edit

Possible role of neutral amino acid transporter (ASCT-1) in the pathophysiology of schizophrenia

Bernhard J. Mitterauer

Dysfunctions in neurotransmission modulated by the excitatory amino acid glutamate may play a decisive role in the pathophysiology of schizophrenia (Auld, Robitaille, 2003). Recently, Weiss et al. (2006) identified in the human brain ASCT-1 which is a transporter protein responsible for the uptake of glutamate into glial cells and neurons, with the bulk of glutamate uptake occurring in glial cells (Danboldt, 2001). With regard to the pathophysiology of schizophrenia, a global decrease of astroglial ASCT-1 has been found in schizophrenic brains, but not in bipolar disorder and major depression (Weiss et al., 2006).

These authors pose the question if the observed findings, especially in schizophrenia, result secondarily from disturbed glutamatergic transmission, or if they are primarily encoded by astrocytes as well as the pattern of and relationship between ASCT-1 protein and mRNA expression. According to my "gliocentric" hypothesis on the pathophysiology of schizophrenia, the latter may be the case (Mitterauer, 2003; 2005).

For the understanding of the possible role of ASCT-1 in the pathophysiology of schizophrenia, let me summarize my hypothesis. Schizophrenia could be the phenomenological manifestation of the brain's inability to constrain neuronal information processing among neuronal modules, since the glial system (especially astrocytes) does not establish boundaries between them. This could be attributed to mutations in glial cells. The glia will then lose their inhibitory boundary-setting function

(Mitterauer, 1998). Thus, neuronal flux is unconstrained by normal glial boundaries in tripartite synapses, as is the flux of thought on the phenomenological level.

Originally, I focussed on a (undisturbed) model of a tripartite synapse as proposed by Smit et al. (2001). Here, a neurotransmitter is released from the presynaptic terminal ready for occupancy of glial binding proteins and postsynaptic receptors. In parallel, glial receptors are occupied by neurotransmitters which increase the production and secretion of soluble glial binding proteins into the synapse. The increased levels of soluble binding proteins in the synapse reduce that amount of free neurotransmitter that can bind to postsynaptic receptors, and neurotransmission is inactivated by this form of negative feedback. Once the neurotransmitter levels have returned to baseline, the glial binding protein levels will drop because the glial cells are no longer stimulated to produce binding proteins; the synapse will return to its initial state and synaptic information processing can start again. Unfortunately, up to now glial binding proteins have not been identified in human brains.

However, ASCT-1 proteins may exert a comparable function to glial binding proteins in glutamatergic tripartite synapses. Here, the astrocyte does not use binding proteins, but produces ASCT-1 mediating glutamate that negatively feeds back on the presynaptic element of the synapse. Supposing that astrocytes are incapable of producing functional ASCT-1 proteins or even any such proteins at all, glutamate cannot negatively feed back on the presynapse. So the flux of synaptic information transmission is unconstrained. This may be the basic fault in schizophrenia (Mitterauer, 2005).

Admittedly, the findings of Weiss and coworkers (2006) that astroglial ASCT-1 is decreased in various brain areas only allows for the interpretation that astrocytes are involved in the pathophysiology of schizophrenia. However, this result should be further investigated. To test my hypothesis one should start out with searching for faulty molecular mechanisms responsible for non-functional ASCT-1 proteins in single astrocytes of schizophrenic brains.

Of course, other transporter proteins produced by astrocytes could also be involved, for example ASCT-2 proteins. Generally speaking, any substance (proteins, neurotransmitters, D-serine, etc.) that is produced by astrocytes and which is involved in the negative feedback mechanism temporarily interrupting synaptic information processing, may be responsible for the pathophysiology of schizophrenia, if for various reasons (mutations, etc.) it is non-functional or even not produced at all.

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