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Posted: Tue Jan 10, 2006 9:14 am Post subject: Decrease of oligodendroglia in schizophrenia

Decrease of oligodendroglia in schizophrenia. An explanatory attempt

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First let me start out with an abstract of my model of the pathophysiology of schizophrenia focusing on tripartite synapses. This "gliocentric" model is based on the hypothesis that astrocytes lose their controlling or modulatory function of neurotransmission in tripartite synapses (Mitterauer, 2003; 2005).

Normally, an astrocyte activated by a neurotransmitter produces the same transmitter substance into the synaptic cleft occupying cognate receptors, especially on the presynapse. Thus, the neurotransmission is temporarily interrupted in the sense of a negative feedback. One could also say that astrocytes have a temporal boundary-setting function structuring information processing. This negative feedback mechanism exerted by transmitters released from astrocytes is experimentally well established (Auld & Robitaille, 2003). Here I will focus on glutamate. Supposing that astrocytes cannot produce functional glutamate because of mutations, their controlling function or negative feedback mechanism in tripartite synapses is lost. As a consequence of this disorder the synaptic neurotransmission may be unconstrained leading to a permanent information flux. Such flooding of glutamate may disturb both the astrocyte-synaptic based compartmentalization and the oligodendrocitic-axonic based compartmentalization in neuronal networks. How could the latter disorder occur?

There is growing evidence for white matter abnormalities in brains with schizophrenia (Kubicki et al, 2005). Hof and colleagues (2003) found a decreased density of oligodendrocytes as well as a less clustered arrangement of oligodendrocytes in white matter of brains with schizophrenia. Based on the identification of NMDA receptors in the processes of oligodendrocytes, my model of schizophrenia could explain why oligodendroglia are affected in schizophrenia.

Recently, Káradóttir and colleagues (2005) showed that precursor, immature and mature oligodendrocytes in the white matter of the cerebellum and corpus callosum exhibit NMDA-evoked currents. NMDA receptors are present in the myelinating processes of oligodendrocytes, where the small intracellular space could lead to a large rise in intracellular ion concentration in response to NMDA receptor activation. These oligodendrocyte NMDA currents may represent a general property of white matter oligodendrocytes. Most importantly, oligodendrocyte NMDA receptors may contribute to causing white matter damage in various disorders like stroke, multiple sclerosis etc., and, as I am trying to show, also in schizophrenia. In general, this may occur when the extracellular glutamate concentration is increased.

The mechanism that may be responsible for an increase of glutamate in the oligodendrocyte-axonic pathway can be deduced from my synaptic model of schizophrenia. In brain injury, oligodendrocyte NMDA receptors could contribute in causing white matter damage that occurs when the extracellular glutamate concentration is increased. However, in schizophrenia the damage or disorganization of the oligodendroglia may be caused by another distinct mechanism.

Supposing that an unconstrained synaptic flux of glutamate is transmitted along the axons where glutamate is flooding the NMDA receptors of the oligodendroglia, then the oligodendrocyte-myelin system is affected so to say from within. Káradóttir and coworkers describe two different locations of NMDA receptors in the membranes of oligodendrocyte processes: NMDA receptors in the outer membrane of myelin, where the receptors may sense glutamate released from surrounding cells, and NMDA receptors in the innermost membrane, where the receptors may sense glutamate from the axon. This means that abnormalities of oligodendroglia in schizophrenia may not be primarily determined by the glial syncytium, but may rather be directly caused by the flooding of axons with glutamate.

According to my theory of glial-neuronal interactions, especially what information processing concerns, the glial system is composed of the "horizontal" astrocyte-synaptic loop and the "orthogonal" oligodendrocyte-axonic system, mediated by the panglial syncytium. The putting together of axons into groups via a specific number of oligodendrocyte processes can be interpreted as an "orthogonal" glial-neuronal compartmentalization.

Therefore, if a decay of oligodendroglia occurs in schizophrenia, the orthogonal pathway of glial-neuronal information processing becomes compartmentless. However, the loss of compartmentalization in brains with schizophrenia may be essentially based on a disorder in the horizontal astrocyte-synaptic loops, as already described (Mitterauer, 2003; 2005).

Let me give as an example the schizophrenic behavior of catatonia, where the motoric system is severely disturbed. According to my model, the loss of oligodendroglia may lead to spontaneous, uncontrolled and disturbed movements (stereotypes) comparable to movement disorders in multiple sclerosis, but caused by a different pathophysiological mechanism.

Finally, the identification of NMDA receptors in the processes of oligodendrocytes allows for speculations that the identification of receptors of other neurotransmitters will also be possible in the near future, as is already the case in astrocytes. Then we must realize that oligodendrocytes are also actively involved in information processing. However, astrocytes may exert the key functions in glial-neuronal interaction because of their "omni-relational" structure.

References cited:

Auld D.S. and Robitaille R. 2003. Glial cells and neurotransmission: an inclusive view of synaptic function. Neuron 40, 389-400.
Hof P.R. et al. 2003. Loss and altered spatial distribution of oligodendrocytes in the superior frontal gyrus in schizophrenia. Biol. Psychiatry 53, 1075-1085.
Káradóttir R. et al. 2005. NMDA receptors are expressed in oligodendrocytes and activated in ischaemia. Nature 438, 1162-1166.
Kubicki M. et al. 2005. Evidence for white matter abnormalities in schizophrenia. Curr. Opin. Psychiatry 18, 121-134.
Mitterauer B. 2003. The loss of self-boundaries: towards a neuromolecular theory of schizophrenia. BioSystems 72, 209-215.
Mitterauer B. 2005. Non-functional glial proteins in tripartite synapses: a pathophysiological model of schizophrenia. Neuroscientist 11, 192-198.