Synaptic Imbalance in Mental Disorder

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Synaptic Imbalances in so called Mental Disorders

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In this short communication I will attempt to outline imbalances of information processing in tripartite synapses that could explain the basic pathophysiology of depression, mania and schizophrenia.

First, let me start out with the model of an undisturbed tripartite synapse according to Araque et al. (1999). The signalling pathway at a tripartite synapse can be schematically described as follows: during synaptic neurotransmission neurons release neurotransmitters from synaptic nerve terminals into the synaptic cleft to communicate with other neurons or effector cells such as muscle fibers. The neurotransmitter released from the synapse (or other co-released neurotransmitters) can, under certain circumstances, spill over from the synaptic cleft and reach neurotransmitter receptors in adjacent glial cells (astrocytes or perisynaptic Schwann cells), eliciting intracellular increases in Ca2+ concentrations in the glial cells. The increase in the glial-cell Ca2+ concentration causes it to release a chemical neurotransmitter from the glial cell that feeds back to the presynaptic nerve terminal to modulate synaptic neurotransmission.

Admittedly, this description of synaptic information processing is schematic and not referring to the other important substances as ions, transporters etc. (see Auld and Robitaille, 2003). However, it represents an elementary synapse-glial-synapse regulatory loop that can be formally interpreted.

The formalism applied is "logical balance" which has been introduced to logic by the German-American philosopher G. Guenther (1963). Logical balance means that if a system consists of values and variables, the numbers of values and the numbers of variables must be equal. In the case where the variables outnumber the values, the system is underbalanced. By contrast, if the values outnumber the variables, the system is overbalanced. If there are no variables available at all, the system is thoroughly unbalanced.

As I have already proposed (Mitterauer, 2004; 2005), in synaptic information processing one can interpret the components (substances) of the neuronal system as values and the components of the glial system as variables. Let me give some arguments why it is legitimate to speak of (very) variable glial functions. First of all, the active and modulatory ("boundary-setting", Mitterauer, 1998; 2007) role of glia in glial-neuronal interactions is experimentally well established (for review see Auld and Robitaille, 2003). Glial cells (astrocytes) are capable to exert a negative feedback by occupying presynaptic receptors with neurotransmitters that are produced within the glial cells. One can also say that astrocytes serve as feedback

elements at tripartite synapses (Araque et al., 1999; Smit et al., 2001). In addition, astroglial process endings display a high degree of dynamic morphological changes in tripartite synapses (Hirrlinger et al., 2004).

Now, based on the formalism proposed, it is possible to differentiate between all the substances (and receptors) produced by the neuronal system as values and those produced by the glial system as variables. Here, I will focus on the glial receptors or proteins and their possible role in balancing of information processing in tripartite synapses.

According to the logic of balance four system states can occur:

First, the interplay between neurotransmitters (values) and glial receptors (variables) is balanced in the sense of an undisturbed function of the brain.

Second, the receptors for neurotransmitters on astrocytes (variables) are increased so that a lack of neurotransmitters (values) arises. This may lead to prolonged cycles of information processing, since the system is underbalanced. This mechanism may cause depression (Mitterauer, 2004).

Third, the number of glial receptors (variables) is decreased and hence "overloaded" with neurotransmitters (values), so that information processing is overbalanced. This may lead to shortened cycles of information processing in tripartite synapses, which may be the cause in mania (Mitterauer, 2004).

Fourth, the glial receptors (variables) are totally non-functional and cannot be occupied by neurotransmitters (values). These tripartite synapses are unbalanced, since glia (variables) are unable to actively influence or modulate the information processing in the neuronal system (values). This system state is unbalanced and may cause an unconstrained neuronal information flux, basically responsible for the pathophysiology of schizophrenia (MItterauer, 2003; 2005).

My bio-logical model proposed is testable and focuses on a proteomic approach. Admittedly, great work has been accomplished in psychopharmacology to identify and treat the various receptor types that could play a role in bipolar disorders and schizophrenia. However, this research focuses mainly on bipartite synapses. Although biological psychiatry is becoming aware of the important role of glia in the pathophysiology of so-called mental disorders, it is presently poor of comprehensive hypotheses, and experimental results are more or less a gathering of data without good questions. My model outlined here represents a further modest attempt to improve this situation.

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