Preview

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The syncytiopathy hypothesis of depression:
downregulation of glial connexins may protract synaptic information processing and cause memory impairment

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Let me shortly report on a novel hypothesis of the possible pathophysiology of depression recently published in Medical Hypotheses (Mitterauer, 2009). First of all, I am very indebted to James Robertson for the concept of syncytiopathy.

Astrocytes interconnected via gap junctions build an astrocytic syncytium. Gap junctions are composed of connexin proteins that are activated by substances of the neuronal system. It is hypothesized that disorders in the astrocytic syncytium may represent a main component of the pathophysiology of depression, called syncytiopathy. If the expression of connexin proteins is downregulated, a compensatory upregulation of astrocytic receptors may occur leading to an overproduction of these. Such an excess of astrocytic receptors exerts an imbalance of synaptic neurotransmission, because of a relative lack of neurotransmitters for the occupancy of astrocytic receptors so that neurotransmission is protracted. This delay of information processing may be responsible for the main symptoms of depression. In addition, the downregulation of connexin expression may also lead to an incomplete syncytium formation, responsible for memory impairment in severe depression.

Recently, there has been a significant increase in studies involving astrocytic gap junctions. These have demonstrated astrocytic networks (syncytia) in the juvenile brain and a gap junction mediated astrocytic network in the mouse barrel cortex. These studies are reminiscent of the study of neuronal tracts and pathways almost a century ago. Although it is presently not possible to visualize all of the plaques and constituent connexins of gap junctions in the entire brain simultaneously in vivo, the only way currently is to visualize individual plaques that are infinitely small representations of the total number of plaques.

However, the investigation of the expression of connexins in tissue of post-mortem brains with depression should be possible using freeze etched ultrastructure of plaques that immuno-label various connexins. Moreover, the expression of connexin proteins must be analyzed with the common methods (Northern blot analyses, etc.). If downregulation of astrocytic connexins can be identified in brains with depression, one can speak of syncytiopathy. In addition, the various receptor types for neurotransmitters on astrocytes should be counted and quantitatively compared with the astrocytic receptors in normal brains, for instance with atomic force microscopy.

What the genetic mechanism responsible for a downregulation of astrocytic connexin concerns, one should be cautious to look for specific "depression genes". A highly complex transcriptomic network may regulate genes encoding connexin proteins with synergistic or antagonistic functions. Importantly, variability in the human genome has far exceeded expectations. Recent studies reveal that structural variants including copy-number variants are an important contributor to disease risk. Hence, new approaches are needed to understand the contribution of structural variants to disease. In sum, despite these genetic complexities the identification of syncytiopathy proposed in depression accompanied with a synaptic imbalance caused by an excess of astrocytic receptors may represent a new approach to depression research and treatment.

Reference:

Mitterauer B.J. (2009). The syncytiopathy hypothesis of depression: downregulation of glial connexins may protract synaptic information processing and cause memory impairment. Medical Hypotheses, doi:10.1016/j.mehy.2009.09.058