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The Role of Calcium Signaling Genes in Schizophrenia Development

Background. Schizophrenia development involves the interplay of several different complex signaling pathways. Genetic studies of schizophrenia have repeatedly implicated calcium signaling genes. (Mizoguchi, Kato, Horikawa, & Monji, 2014). Specifically, calcium/calmodulin (CAM)-dependent protein kinase 2 (CAMKK2) seems to play a strong role in the faulty calcium regulation schizophrenics exhibit (Luo et. al, 2013). Genetic markers that involve L-type voltage-gated calcium channels seem to also be a commonality among schizophrenic individuals.

Methods. We carried out a selected literature review and integration, considering recent articles about calcium signaling genes and the ways in which they might affect schizophrenia development.

Results. Schizophrenics exhibit lower expression of the CAMKK2 gene, which is primarily associated with maintaining cognitive functions such as learning, memory, and dopamine regulation as well as regulating neuronal calcium sensor-1 (NCS-1) in the cells (Robison, 2014). Indirectly, CAMKK2 may be associated with the high levels of intracellular calcium found in the cells of schizophrenics, which can disrupt normal gamma rhythms in the brain for memory formation as well as making the neurons vulnerable to premature aging (Berridge, 2013; Heidarsson et. al, 2014). The release of too much calcium also activates the microglia immune cells in the brain, which in turn releases many proinflammatory cytokines. Additionally, if the voltage-gated calcium channels in the brain are dysfunctional, the calcium levels will remain increased in the cells creating a toxic intracellular environment (Mizoguchi, Kato, Horikawa, & Monji, 2014). NCS-1 is normally responsible for responding to these calcium changes within the cell. However, too much calcium in the cell can cause the NCS-1 sensors to misfold, making them unable to respond as effectively. Schizophrenics have upregulated levels of NCS-1, possibly to compensate for the defective misfolded sensors (Heidarsson et. al, 2014).

Conclusions. The widespread effects of calcium signaling deficits include high level of intracellular calcium, inflammation and downstream problems with cognitive function. These are worth investigating further, as there seems to be many overlaps between what is currently known about schizophrenic development and how calcium signaling contributes to those factors.

Keywords: schizophrenia, calcium signaling, CAMKK2, microglia, dopamine, calcium channels