

The Nogo-A^{-/-} mouse, an animal model for schizophrenia, exhibits disrupted hippocampal CA3 function through down-regulation of mGlu3 metabotropic glutamate receptors

Berry S, Weinmann O, Fritz AK, Wolfer DP, Schwab ME, Gerber U, Ster J

Nogo-A is a membrane protein well established as an inhibitor of neurite outgrowth in the CNS that regulates circuit formation during development, but curtails regeneration after injury. Recent evidence implicates Nogo-A dysfunction in neuropsychiatric disorders such as schizophrenia. Here we characterized functional roles of Nogo-A in the hippocampal CA3 network. Patch clamp recordings from pyramidal cells revealed that loss of Nogo-A significantly increased spontaneous excitatory activity. In addition, mGlu3 receptors, which exhibit mutations in certain forms of schizophrenia, were down-regulated specifically in the CA3 region of Nogo-A^{-/-} mice. This reduction in mGlu3 was accompanied by a disruption of theta oscillations manifesting as a decrease in incidence and frequency as well as a shift in polarity from inhibitory to predominantly excitatory. As altered hippocampal rhythmicity is associated with impaired spatial navigation, we tested mice in a Morris water maze task. Search strategies were modified in Nogo-A^{-/-} mice in that they exhibited a greater dependence on global versus local reference frames. These results suggest that the absence of Nogo-A disrupts hippocampal activity by reducing the expression of mGlu3. Our evidence for a link between these two proteins provides a new perspective in the search for cellular mechanisms underlying psychiatric disease.