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DRD1 signaling modulates TrkB turnover and BDNF sensitivity in direct pathway striatal medium spiny neurons.

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Disturbed motor control is a hallmark of Parkinson's disease. Despite significant progress in understanding alterations in network activity and the effects of electrical stimulation of network regions within the motor circuit, not much is known about the molecular and cellular mechanisms that cause long-term changes at individual synapses within this network. Corticostriatal synapses play a central role in motor learning, and long-term potentiation (LTP) at synapses between cortical afferents and striatal D1 direct pathway projection neurons appears central for motor learning and execution of learned motor tasks. In Parkinson's disease, LTP switches to LTD at corticostriatal synapses when activation of dopamine D1 receptors is absent. However, the mechanisms underlying this altered plasticity remained unknown so far.

Brain-derived neurotrophic factor (BDNF) plays a central role in LTP induction through activation of its receptor TrkB in multiple regions of the CNS. Corticostriatal synapses differ from hippocampal synapses in that LTP depends on simultaneous activation of both NMDA receptors and dopaminergic D1 receptors, and this appears as a prerequisite for the activation of TrkB. In order to study the mechanisms that modulate Trk-B sensitivity in D1-expressing striatal spiny projection neurons, we developed methods for isolation and enrichment of these neurons in cell culture and measured TrkB cell surface expression. TrkB cell surface levels increase dramatically when D1 receptors are activated in direct pathway striatal projection neurons. TrkB moved from intracellular stores to the cell surface after initiation of DRD1-Gαs mediated signaling. This enhanced BDNF sensitivity as a prerequisite for LTP induction. In the 6-OHDA rat model of severe dopamine depletion, TrkB remained within intracellular stores and formed cluster-like structures that became insoluble after prolonged times of dopamine depletion. TrkB clusters appeared closely associated with structures of the lysosomal degradational pathway. Correlative high-resolution SIM microscopy and electron microscopy revealed that TrkB was surrounded by cathepsin-D-immunoreactive lysosomal structures, but fusion of the TrkB-containing clusters with lysosomes did apparently not take place. Similar TrkB clusters are also found in post-mortem brain within striatal SPNs of patients with PD.

This work highlights the importance of D1 signaling for TrkB turnover in the context of proper synaptic function between corticostriatal afferents and striatal direct pathway spiny projection neurons. Restoring TrkB cell surface expression appears essential for corticostriatal circuit activity. The effects of STN-DBS on TrkB subcellular distribution are currently studied, and TrkB distribution in direct pathway striatal projection neurons could be used for optimizing DBS-based therapies for Parkinson's disease and dystonia.

Dr. Thomas Andreska

Thomas Andreska has been a postdoctoral researcher at the Department of Clinical Neurobiology at the University Hospital of Würzburg. He has developed techniques for highly enriched cell cultures of D1- and D2-expressing spiny projection neurons from mouse brain. This allows new approaches to study molecular mechanisms for plasticity and adaption in specific types of neurons with central function in the motor circuit.

Prof. Dr. Michael Sendtner

Michael Sendtner is Chair of the Institute of Clinical Neurobiology. His research focuses on understanding of molecular and cellular mechanisms underlying diseases of the motor system, and the development of new molecular therapies for motoneuron diseases and other neurodegenerative disorders.

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