UKE Paper of the Month Juli 2022

Presynaptic cGMP sets synaptic strength in the striatum and is important for motor learning

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ABSTRACT:

The striatum is a subcortical brain region responsible for the initiation and termination of voluntary movements. Striatal spiny projection neurons receive major excitatory synaptic input from neocortex and thalamus, and cyclic nucleotides have long been known to play important roles in striatal function. Yet, the precise mechanism of action is unclear. Here we combine optogenetic stimulation, 2-photon imaging and genetically encoded scavengers to dissect the regulation of striatal synapses in mice. Our data show that excitatory striatal inputs are tonically depressed by phosphodiesterases (PDEs), in particular PDE1. Blocking PDE activity boosts presynaptic calcium entry and glutamate release, leading to strongly increased synaptic transmission. Although PDE1 degrades both cAMP and cGMP, we uncover that the concentration of cGMP, not cAMP, controls the gain of striatal inputs. Disturbing this gain control mechanism in vivo impairs motor skill learning in mice. The tight dependence of striatal excitatory synapses on PDE1 and cGMP offers a new perspective on the molecular mechanisms regulating striatal activity.

STATEMENT:

Our work opens a new view of striatal regulation that may be relevant for the treatment of movement disorders, e.g. Huntington's or Parkinson's disease. While cAMP signalling was known to be important for presynaptic function, cGMP was not previously recognized as presynaptic regulator, a mechanism that may be specific to striatal input synapses. Remarkably, due to the high activity of endogenous PDE1, these synapses seem to be in a tonically depressed state under physiological conditions. How diseased brains react to the release of this "striatal brake" remains to be seen.

BACKGROUND:

This work was performed at the Institute for Synaptic Physiology in the group of Thomas Oertner who holds a professorship at UKE since 2011. It was conducted by Tim Fieblinger, who has a long-standing research interest into the mechanisms of Parkinson's disease and joined Thomas Oertner's group in 2018 as a postdoctoral researcher. Genetically encoded nucleotide scavengers allowed him to control cGMP levels in specific neuronal populations, an important technical advance that led to the discovery of presynaptic gain-control at striatal inputs. The work was supported by a Marie Sklodowska-Curie grant (to T.F.) and by the DFG (SFB936, SFB1328, FOR2419).