Plasticity of the Burst-Pause Response in the Tonically Active Cholinergic Interneurons of the Striatum in Normal and Parkinsonian Mice

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Plasticity of the Burst-Pause Response in the Tonically Active Cholinergic Interneurons of the Striatum in Normal and Parkinsonian Mice

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Parkinson's disease & PD-related disorders

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Research Abstract
Our ability to attend to novel stimuli requires an intact projection from the parafascicular (PF) nucleus of the thalamus to the cholinergic interneurons (ChIs) of the striatum. ChIs respond to novel stimuli with a burst-pause (B-P) in their tonic firing. The B-P response is a neural correlate of classical conditioning, and as such shows a large degree of plasticity in response to behavioral contingencies. The B-P response (and its plasticity) are severely compromised in animal models of Parkinson’s disease (PD), which may be related to the akinetic nature of the disorder.
The biophysical mechanism of the B-P response is still debated, but to date none of the candidate mechanisms has accounted for its plasticity. In the current proposal, we will identify and characterize the mechanism that gives rise to the plasticity using acute brain slices from mice. The study will combine optogenetics (to selectively activate afferent inputs to ChIs), wide-field calcium imaging of ChIs, molecular biology, numerical and analytical tools.
Preliminary results show that the current underlying the prominent slow afterhyperpolarization (IsAHP) in ChIs, is up-regulated merely by stimulating the afferent glutamatergic PF (but not the cortical) projection. This is the first-ever description of an up-regulation of IsAHP in any brain region. Because the up-regulation is synaptically generated, it suggests the involvement of group I metabotropic glutamate receptors. This possibility will be tested, as well as the role of intracellular calcium stores.
Because the B-P response is known to be dopamine dependent, we will also study the impact of dopamine depletion on the mechanism of the B-P response and on its plasticity. We believe that this study can potentially point to therapeutic targets aimed at normalizing the B-P response in order to alleviate akinesia and other symptoms of PD.

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