In This Issue

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A brief summary of the articles appearing in this issue of *Biological Psychiatry*.

Mechanisms of L-DOPA–Induced Dyskinesia

A systematic search for nuclei involved in L-DOPA–induced dyskinesia (LID), a side effect of treatment for Parkinson's disease commonly associated with the striatum, suggested that the lateral habenula may also play a role. **Bastide *et al.*** (345–353) tested this hypothesis using both rat and macaque models of Parkinson's and LID and report that the lateral habenula displays dyskinesia-related abnormal activity. Inhibition of lateral habenula activity improved dyskinesia severity, indicating that this region may serve as a novel target for the treatment of LID.

L-DOPA–induced dyskinesia is associated with overexpression of the transcription factors FosB and ΔFosB in the striatum. Using a cell-specific inactivation method in rat and monkey models of LID, **Engeln *et al.*** (354–361) demonstrate that the electrical activity of neurons expressing FosB/ΔFosB not only is directly responsible for these abnormal movements but also blunts the symptomatic effect of the antiparkinsonian treatment. Selective inactivation of these striatal neurons decreased LID severity and improved L-DOPA's therapeutic effect, suggesting a potentially promising strategy for the prevention of LID.

In a mouse model of Parkinson's disease, **Feyder *et al.*** (362–371) report that genetic inactivation of mitogen- and stress-activated kinase 1 (MSK1) reduced LID and the expression of the ΔFosB transcription factor. Overexpression of ΔFosB in the medium spiny neurons of the striatum exacerbated dyskinesia, whereas overexpression of ΔcJun, which reduces ΔFosB-dependent transcriptional activation, counteracted dyskinesia. These results indicate the involvement of MSK1-mediated gene expression in the motor complications caused by prolonged administration of L-DOPA.

Genetic Investigations of Tourette Syndrome

Identifying risk genes for Tourette syndrome (TS) is an important research focus. Using RNA sequencing in postmortem brain tissue, **Lennington *et al.*** (372–382) analyzed global changes in gene expression in the basal ganglia of individuals with Tourette syndrome. Their data implicate gamma-aminobutyric acid and cholinergic interneurons in the pathophysiology of TS and suggest that dysfunction or death of these interneurons may be linked to metabolic alterations. Unrelated to the neuronal alterations, they also found an increase in immune transcripts.

Few candidate susceptibility genes have been identified for Tourette syndrome. **Bertelsen *et al.*** (383–391) report an association between deletion of the arylacetamide deacetylase (*AADAC*) gene and TS in a discovery cohort, which was replicated in a meta-analysis using data from a larger European cohort. In addition, they detected *AADAC* expression in mouse and normal human brain in several regions implicated in TS pathogenesis, including hippocampus, corpus callosum, and caudate nucleus, suggesting that *AADAC* may be a genetic susceptibility factor for TS.

Thalamic Deep Brain Stimulation for Tourette Syndrome

Deep brain stimulation (DBS) has shown promise for the treatment of Tourette syndrome, characterized by chronic motor and phonic tics, but the ideal neural targets remain undetermined. In this open-label trial, **Huys *et al.*** (392–401) report that DBS delivered at the thalamus improved patients' Tourette-related symptoms, quality of life, and overall functioning over a 1-year period and was generally well tolerated. Personality traits and emotional state at baseline predicted outcome following DBS surgery. These data suggest that thalamic DBS may be beneficial for some patients with TS.

Alpha-synuclein and Striatal Synaptic Dysfunction

Loss of striatal synaptic plasticity in advanced Parkinson's disease may be related to aggregation of α-synuclein. Using transgenic rodent models of early Parkinson's disease, **Tozzi *et al.*** (402–414) report that overexpression of α-synuclein induces impairment of long-term synaptic potentiation of cholinergic interneurons and alterations in cognition and motor activity. Alpha-synuclein modulation of GluN2D-expressing *N*-methyl-D-aspartate receptors was critical for these effects, suggesting that early striatal cholinergic dysfunction may represent a biological marker of early Parkinson's.

Using Molecular Histochemistry to Identify Peptides

The functions of neuropeptides in the brain are still poorly understood due to a lack of technical means to comprehensively and quantitatively characterize regulation of peptides along anatomic units in the brain. In this Methods article, the exploratory analyses of **Hishimoto *et al.*** (415–420) demonstrate the technical capacity of matrix-assisted laser desorption ionization imaging mass spectrometry for identification of peptidomic regulation patterns along histochemically distinguishable striatal projection pathways.

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