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The physiology and pathophysiology of basal ganglia: From signal transduction to circuits

Since finding of their role in motor coordination in early 20th century, understanding of functions of the basal ganglia have extended to include cognition, habit formation, reward-related learning and motivation control. The list of the functions mediated by the basal ganglia appears to continue expanding, and it now covers most of the crucial behaviors for animal survival. The basal ganglia were originally recognized as a large structure located under the cortex in human brain, comprised of the striatum and globus pallidus. Nowadays, because of their connectivity and functional relevance, the subthalamic nucleus and substantia nigra are usually included as well. The basal ganglia receive input from the cortex and sends output back to the cortex through the thalamus, and this circuit is under control of monoaminergic projections from the midbrain. This interesting circuitry places the basal ganglia as a crucial center for controlling executive functions. Indeed, many clinical findings have pointed that perturbation of basal ganglia circuitry and its chemical modulators underlies symptoms of neuropsychiatric disorders, such as Parkinson's disease, Huntington's disease, schizophrenia, obsessive-compulsive disorder, and substance-abuse.

Since recognized as key structures for motor control, the basal ganglia have attracted many neuroscientists, and they still remain as one of the hottest areas in current research. Recent studies have revealed that the basal ganglia are functionally more complex with finer regional heterogeneity than formerly thought. Development of new techniques, such as more sophisticated viral tracers, designer receptors exclusively activated by designer drugs (DREADDs), and optogenetics, clearly have contributed to these new findings.

We organized this special issue to overview current status of basal ganglia research, when the newly developed techniques are fairly mature and widely used.

Most of articles in this issue are about a single structure, the striatum including the nucleus accumbens. Nevertheless, topics in this special issue covers in quite a range: cellular level to whole animal with variety of techniques, focusing on different aspects of functions in normal and/or pathological states. The striatum receives major excitatory inputs from the cortex and the thalamus, and dense dopaminergic inputs from the substantia nigra and ventral tegmental area. In spite of functionally heterogeneous subregions, the cytoarchitecture of the striatum is fairly uniform: more than 95% GABAergic projection neurons and less than 5% interneurons, comprised of cholinergic interneurons and several types of GABAergic interneurons. All through the striatum, there are two compartments with different protein expression patterns, called striosome and matrix. Fujiyama et al. focus on striosome and matrix, and discusses about differential connectivity in these two compartments based on studies with single cell axon tracing. The topic of Abe et al. is also cellular morphology of medium spiny projection neurons (MSNs). They studied interesting relationship between neuronal activity and resultant morphological change of MSNs using MRI.

Reflecting dense dopamine projection from the ventral midbrain, the striatum highly expresses dopamine receptors. Gallo focuses on dopamine D2 receptors in the striatum and discusses their functions. Zhang et al. studied downstream cell signaling cascade of dopamine D1 and D2 receptors in the MSNs and cooperative action with dopamine and adenosine. Another highly expressed receptor type in the striatum is adenosine A2A receptors. Zhou et al. showed that ablation of A2A receptor-expressing cells affected sleep homeostasis.

Recent studies have shown that the striatum is comprised of finer functional subregions, beyond simple ventral-dorsal or medial-lateral division. Mingote et al. focus on one of these fine functional subregions, the medial shell of the nucleus accumbens, and discuss functional roles of unique dopamine neuron projection to this particular location. Sugiyama et al. also focused the medial shell of the nucleus accumbens and studied dopamine levels with imaging mass spectrometry in an animal model of mechanical allodynia.

Parkinson's disease is one of the most recognized striatal disorders, which shed a light to striatal function as a motor control center. In this special issue, three articles discuss this disease. Ztaou and Amalric focus on dopamine and acetylcholine balance in the striatum and discuss the roles of cholinergic interneurons. Kurosaki et al. studied relationship between oxidative stress and Parkinsonism. Sano and Nambu studied mechanisms of anti-epileptic drug zonisamide effects on L-DOPA-induced dyskinesia. Although Parkisonism itself is not the major focus of Bonnavion et al., their topic is highly related functions of the striatum: motor learning and behavioral flexibility. Their article discusses finer functional subdivisions of the striatum as well.

Parkison's disease is not the only disorder caused by malfunction of striatal circuits. Simmler and Osawa discuss goal-directed and habitual

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behaviors in the context of obsessive-compulsive disorder. Hamaguchi et al. studied relationship between amyloid plaque in the striatum and motivation in mouse model of Alzheimer's disease.

The following two articles focus on non-striatal components of the basal ganglia and both addressed aversive learning. Margolis and Karkhanis discuss control of dopamine neuron activity through opioid receptors in the ventral midbrain in relation to aversive learning. Macpherson et al. showed that activation of preproenkephalin positive neurons in the ventral pallidum suppressed aversive learning.

This special issue includes both review articles and original research papers. We hope readers will enjoy this interesting selection of papers. We also hope this special issue provides some insights into future research of the basal ganglia and serve to develop this field of research.

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