NEUROPHARMACOLOGY OF PARKINSON'S DISEASE

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Introduction
Movement disorders are neurologic syndromes in which there is either an excess of movement or a paucity of voluntary and automatic movements unrelated to weakness or spasticity. They can be characterized as **hypokinetic** (not enough movement), **hyperkinetic** (too much movement), or **other/mixed**. Parkinson's disease is the prototypic hypokinetic movement disorder, and the atypical parkinsonisms are also included in this category. This discussion will focus on Parkinson's disease.

Anatomic circuitry of the basal ganglia
The basal ganglia are a group of nuclei that act as a cohesive functional unit. It is comprised of the **striatum** (caudate and putamen), **globus pallidus** (pars externa and pars interna), **subthalamic nucleus (STN)**, and **substantia nigra** (pars reticulata and pars compacta). The major input nuclei of the basal ganglia are the caudate and putamen, which receive information from corticostriatal, thalamostriatal, and nigrostriatal pathways, as well as additional information from the raphe nuclei and locus ceruleus. The major output nuclei are the globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr), which both send projections to the ventrolateral and ventral anterior nuclei of the thalamus. In turn, thalamocortical projections comprise the final component of the **cortico-striatal-thalamo-cortical circuit** that underlies movement control.

Internally, the basal ganglia are organized into **hyperdirect**, **direct**, and **indirect pathways**. The functional significance of this segregation is to help "scale" and "focus" voluntary movements so that only the selected movement is initiated, executed and terminated appropriately, with precision. Dopamine (via nigrostriatal projections) excites the direct pathway (via D1 receptors) and inhibits the indirect pathway (via D2 receptors).

Within the striatum, the neuronal population consists of GABA-ergic medium spiny neurons (MSNs), numerous large axon collaterals, a few large cholinergic interneurons, and other interneurons. Functionally the MSNs give rise to the direct and indirect pathways according to their dopamine receptor subtype.

Pharmacology
- Endogenous Dopamine

A comprehensive knowledge of dopamine synthesis and transmission in the **nigrostriatal system** is essential to the understanding of the pathogenesis and pharmacology of Parkinson's disease. In the pre-synaptic dopaminergic neuron, tyrosine is metabolized to L-DOPA by the enzyme **tyrosine hydroxylase** (rate limiting step), and L-DOPA is further metabolized to dopamine by DOPA decarboxylase. Dopamine is then incorporated into a pre-synaptic vesicle by **vesicular monoamine transporter type 2** (VMAT2). Cytosolic dopamine that is not incorporated in to vesicles is degraded by the enzyme **monoamine oxidase** type A (MAO-A). An action potential triggers fusion of the vesicle to the pre-synaptic membrane and release of dopamine into the synaptic cleft. Dopamine can then act post-synaptically at either D1 or D2 receptors in the striatum to exert downstream effects (direct and indirect pathways discussed above). It can also diffuse to nearby glial cells, where it can be metabolized by monoamine oxidase (type A or B). Any free dopamine remaining in the synaptic cleft can be re-uptaken by the pre-synaptic neuron via the **dopamine transporter** (DaT) which is localized to the nerve terminal. Thus, dopamine is "recycled" by the pre-synaptic neuron.

Dopamine receptors are also present in other areas of the central nervous system, and hence are important to consider especially in view of potential medication side effects.
- **Mesolimbic circuit:** dopamine-containing neurons originate in the ventral tegmental area (VTA) and innervate the nucleus accumbens (NAc) (ventral striatum), amygdala, hippocampus and the prefrontal cortex. This circuit has implications for dopaminergic medication side effects including impulse control disorders.

- **Mesocortical circuit:** originates in the ventral tegmental area (TVA) and innervates only the prefrontal and orbitofrontal cortex. This circuit has implications for dopaminergic medication side effects including hallucinations.
- **Tuberoinfundibular circuit:** originates in the hypothalamus and innervates the pituitary. This circuitry is relevant to anti-dopaminergic medication side effects.
- **Diencephalic-spinal dopaminergic tracts** are lesser known, but have relevance to the pathophysiology and treatment of restless legs syndrome. The **A11 dopaminergic cell cluster** located in the hypothalamus is the primary source of descending dopaminergic input into the spinal cord. This cell cluster connects locally to the hypothalamus (with implications for circadian rhythm control), to the neocortex, and to the dorsal raphe nucleus (with implications for the effect of serotonergic medications), as well as descend into the spinal tracts where they are especially concentrated in the dorsal horn and intermediolateral nucleus (with implications for autonomic effects).

- Exogenous dopamine

Dopamine cannot be administered directly for the treatment of movement disorders because it is hydrophilic and lacks a transporter in the periphery, both of which contribute to its inability to cross the blood brain barrier. L-DOPA (levodopa) is a precursor to dopamine that competes with other amino acids for transport across the gut wall into the bloodstream. Once there, it is lipophilic and can cross the blood brain barrier via the large neutral amino acid transporter system. However, **dopa decarboxylase** (DD) and a soluble form of **catechol-0-methyl transferase** (COMT) activity in the bloodstream limit the availability of orally ingested l-DOPA to actually penetrate the central nervous system by metabolizing l-DOPA. DD uses pyridoxal phosphate as a cofactor and rapidly converts l-DOPA to dopamine in the bloodstream, where it can cause nausea and orthostasis by stimulating peripherally located receptors. COMT converts l-DOPA to 3-O-methyldopa (3-OMD), further diminishing l-DOPA availability to the brain. Any l-DOPA that does cross into the brain is then beneficially decarboxylated by DD to dopamine, where it can exert its effects on dopamine receptors. Once again, however, l-DOPA is subject to degradation by a membrane-bound COMT to 3-OMD, and dopamine is subject to breakdown by COMT or **monoamine oxidase** (MAO) to 3-MT and DOPAC, respectively. MAO is present in two forms - type A and type B. MAO-A is present in the presynaptic dopaminergic neuron while both MAO-A and MAO-B are present in microglial cells, as discussed previously. Under normal circumstances, MAO-A activity is the predominant mechanism of dopamine regulation after re-uptake. However, with aging and neurodegeneration, MAO-B metabolism becomes more relevant.

- Acetylcholine (as pertains to striatum)

Cholinergic interneurons (ChIs) within the striatum have autonomous activity with various spontaneous tonic firing patterns. They are influenced by glutamatergic input from the cortex and dopaminergic input form the SNc. D2 receptors inhibit acetylcholine release (indirect pathway) but other neurotransmitters also exert effects. These ChIs have direct effects on the firing of medium spiny neurons in the striatum. Loss of dopaminergic input as in Parkinson's disease leads to excessive excitability of ChIs, thereby contributing to imbalanced striatal outflow.

Pharmacologic Management of Parkinson's disease

Treatment options in Parkinson's disease may involve manipulating dopamine, or using non-dopamine, symptom-related strategies. In order to improve motor symptoms, dopamine can either be "replaced", dopamine receptors can be stimulated, or the metabolism of dopamine can be prevented. Alternately medications that may specifically address tremor, dyskinesia, dystonia or rigidity may be sued. Parkinson's disease treatment is associated with the development of motor complications, including fluctuations and dyskinesias, in which the duration of benefit from a dose of medication is offset by involuntary hyperkinetic movements. Combinations of multiple medications are often required to optimize symptom control. The unpredictability of response to medications can be quite disabling, and is attributed to the pulsatile stimulation of dopamine receptors. By contrast, the strategy of continuous dopaminergic stimulation emphasizes the maintenance of regular concentrations of dopamine in the striatum and has gained acceptance as a potential mechanism by which to avoid or delay the development of motor complications.

- Medications used to treat Parkinson's disease
  - **Levodopa** – converted centrally to dopamine were it can stimulate receptors
  - **Carbidopa** – inhibits DD in the periphery to increase the amount of levodopa available to cross into the CNS, and prevent nausea from dopamine

- **Dopamine agonists** – stimulate dopamine receptors but with greater affinity for D3 receptors, which may underlie their particular side effect profile including greater risk for impulse control disorders and hallucinations
- **MAO-inhibitors** – prevent breakdown of dopamine, increasing its availability to act at receptors; mild symptom benefit in monotherapy, decrease motor fluctuations when added to levodopa.
- **COMT-inhibitors** – prevent breakdown of levodopa and dopamine, increasing dopamine availability to act at receptors; decrease motor fluctuations.
- **Amantadine** – mild dopaminergic, weak non-competitive NMDA receptor antagonist, and mild anticholinergic mechanisms; mild symptom benefit in early disease, reduce dyskinesias in advanced disease
- **Trihexyphenidyl** – anticholinergic (muscarinic receptor antagonist); only beneficial effect is on tremor.

- Strategies to mitigate motor complications in Parkinson's disease:
  - Early or adjunctive use of MAO-Inhibitor
  - Early or adjunctive use of dopamine agonists
  - Amantadine for dyskinesia
  - COMT-inhibitor or MAO-Inhibitor for wearing off
  - Smaller doses of levodopa more frequently
  - Extended release formulations of levodopa

References

- Bonsi P, Cuomo Dario, Martella Giuseppina M, et al. Centrality of striatal cholinergic transmission in basal ganglia function. Front. Neuroanat, 2011. doi: 10.3389/fnana.2011.00006. Accessed 2/23/16.
- Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. JAMA. 2014;311:1670-83.
- Crittenden JR, Graybiel AM. Basal Ganglia disorders associated with imbalances in the striatal striosome and matrix compartments. Front Neuroanat. 2011;5:59. doi: 10.3389/fnana.2011.00059. Accessed 2/23/16.
- DeLong M, Wichmann T. Changing views of basal ganglia circuits and circuit disorders. Clin EEG Neurosci. 2010;41:61-7.
- DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 1990;13:281-5.
- Jimenez-Shahed J. A review of current and novel levodopa formulations for the treatment of Parkinson's disease. Ther Deliv. 2016;7:179-91.
- Mink JW. The Basal Ganglia and involuntary movements: impaired inhibition of competing motor patterns. Arch Neurol. 2003;60:1365-8.
- Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. Lancet Neurol. 2006;5:677-687.
- Salat D, Tolosa E. Levodopa in the treatment of Parkinson's disease: current status and new developments. Journal of Parkinson's disease. *2013;*3:255-269.