M555 – Medical Neuroscience

Basal Ganglia and Associated Pathways

Overview

The basal ganglia are a set of subcortical nuclei, of varied origin, buried within each cerebral hemisphere and situated at the base of the forebrain and lateral to the thalamus. They consist of three major components: the caudate nucleus and putamen (collectively known as the striatum), and the globus pallidus. The nuclei are strongly interconnected with the cerebral cortex, thalamus, and brainstem and are involved in a variety of functions including: general motor control, eye movements, cognitive functions, and emotional functions.

The basal ganglia lack direct connections to the spinal cord, so their primary influence, especially on motor control, is through modulation of the cerebral cortex via the thalamus. Therefore, as the cerebral cortex is the major source of input to the basal ganglia, as well as the final target of basal ganglia efferents via the motor thalamus, the basal ganglia can be considered “pathways” through which the motor cortex modulates itself, either in an excitatory or inhibitory manner, by either decreasing or increasing basal ganglia output.

Key Points

- **Thalamus** is the entry way into the cerebral cortex and primarily has excitatory effects, but the thalamus itself is primarily regulated via inhibitory mechanisms, such as those of the basal ganglia.

- **Basal ganglia** are part of a network of complex loops that modulate descending motor pathways through projections, via the thalamus, to the motor and premotor cortex; the substantia nigra, in turn, modulates the basal ganglia; this combination of modulators can facilitate rapid simultaneous excitation and inhibition of agonist and antagonist muscles, respectively, or may serve to coordinate smooth execution of a sequence of motor movements.

- **Movement disorders** (dyskinesia) may be caused by dysfunction anywhere within the motor network from upper motor neurons, lower motor neurons, cerebellar pathways, basal ganglia pathways, and motor areas of the cortex, but the term generally is applied to disorders of the basal ganglia.
  - **Hyperkinetic movement disorders** are the result of decreased basal ganglia output, resulting in increased thalamus activity which excites motor areas of the cerebral cortex.
  - **Hypokinetic movement disorders** are the result of increased basal ganglia output, resulting in decreased thalamus activity which suppresses motor areas of the cerebral cortex.

- **Direct** and **Indirect Pathways** are models developed to attempt to explain the hyperkinetic and hypokinetic movement disorders associated with damage to the basal ganglia; while the models are useful, they are incomplete and do not explain all the signs associated with disorders of the basal ganglia; ultimately, it may be more accurate to think of patterns of activity instead of pathways.
  - **Direct pathway** results in excitation of thalamus and facilitates movement via connections with the motor cortex; the pathway travels directly from the striatum to the internal segment of globus pallidus or substantia nigra pars reticulata.
  - **Indirect pathway** results in inhibition of thalamus and therefore suppresses movement via connections with the motor cortex; the pathway travels indirectly (takes a detour through the external segment of globus pallidus and the subthalamic nucleus), from the striatum to the internal segment of globus pallidus or substantia nigra pars reticulata.
Connections

**Input:** input to the basal ganglia is principally through the striatum which has inhibitory spiny neurons

Sources of incoming connections:

- Cerebral cortex supplies the majority of input to the basal ganglia; it provides excitatory input using glutamate as the neurotransmitter

- Substantia nigra par compacta supplies both excitatory and inhibitory input to the basal ganglia using dopamine as the neurotransmitter, but the overall effect is increased motor activity
  - D1 receptors on cells in the striatum receive excitatory effects from dopamine; these cells are part of the direct pathway (so net result = increased motor activity)
  - D2 receptors on cells in the striatum receive inhibitory effects from dopamine; these cells are part of the indirect pathway (so net result = increased motor activity)

- Intralaminar nuclei of the thalamus (centromedian and parafascicular nuclei) provide excitatory input to the basal ganglia using glutamate as the neurotransmitter

- Raphe nuclei of the brainstem provide input to the basal ganglia using serotonin as the neurotransmitter; however, the overall effects of this input remain unclear

Targets of incoming connections:

- Putamen is involved primarily in the motor functions of the basal ganglia and receives connections from the cerebral cortex, substantia nigra (pars compacta), and the thalamus

- Caudate nucleus is involved more in the cognitive functions (and to a lesser extent the motor functions) of the basal ganglia and receives connections from the prefrontal and other association areas of the cortex

**Output:** output from the basal ganglia is through the globus pallidus or substantia nigra and is inhibitory

Sources of outgoing connections:

- Internal segment of globus pallidus conveys information for modulation of motor control of muscles of the limbs and trunk and uses GABA as the neurotransmitter

- Substantia nigra pars reticulata conveys information for modulation of motor control of muscles of the head and neck and uses GABA as the neurotransmitter

Targets of outgoing connections:

- Ventral lateral (VL) and ventral anterior (VA) nuclei of the thalamus are the major targets of output from the basal ganglia; the thalamic nuclei project to the cerebral cortex via the thalamocortical radiations and have an excitatory effect via glutamate as the neurotransmitter

- Outputs also exist to other thalamic nuclei, reticular nuclei of the brainstem, and superior colliculi, allowing for modulation of additional motor pathways (e.g., reticulospinal and tectospinal) beyond just the lateral motor pathways (e.g., lateral corticospinal)
**Direct and Indirect Pathways**

Cortex → Striatum (“entry” into BG) → Globus pallidus (“exit” from BG) → Thalamus → Cortex → ...

**Direct Pathway**: has the net effect of disinhibiting (“freeing”) the thalamus, which then excites cortical neurons, and results in **increased motor activity**

\[
\begin{align*}
\text{Cortex} & \rightarrow \text{Striatum} \rightarrow \text{Globus pallidus} \rightarrow \text{Thalamus} \\
+1 & \times -1 & \times -1 \\
= & +1
\end{align*}
\]

The direct pathway provides a mechanism for the cortex to excite its motor nuclei by inhibiting the basal ganglia’s inhibition of the thalamus (i.e., dis-inhibition). This occurs by the cortex exciting the striatum, via glutamate, which then inhibits the internal segment of globus pallidus via GABA/Substance P. The internal segment is then stopped from tonically inhibiting the thalamus via GABA. This “frees” the thalamus to excite the motor areas of the cerebral cortex via glutamate.

**Indirect Pathway**: has the net effect of inhibiting the thalamus, preventing it from exciting cortical neurons; the pathway travels indirectly to the internal segment of globus pallidus by detouring through the external segment of globus pallidus and the subthalamic nucleus; the result is **decreased motor activity**

\[
\begin{align*}
\text{Cortex} & \rightarrow \text{Striatum} \rightarrow \text{Globus pallidus} \rightarrow \text{Thalamus} \\
+1 & \times -1 & \times +1 & \times -1 \\
= & -1
\end{align*}
\]

The indirect pathway provides a mechanism for the cortex to decrease the activity of its motor nuclei by inhibiting the thalamus. This occurs by the cortex exciting the striatum, via glutamate, which then inhibits the external segment of globus pallidus via GABA/Enkephalin. The external segment is then stopped from inhibiting the subthalamic nucleus via GABA. This “frees” the subthalamic nucleus to excite the internal segment of globus pallidus via glutamate which then inhibits the thalamus via GABA. The thalamus is thus unable to excite the motor areas of the cortex (they are effectually inhibited).
Modulating the Pathways: Dopaminergic and Cholinergic Modulation of the Striatum

Dopamine and acetylcholine both act upon the projection neurons of the striatum to modulate the direct and indirect pathways. These two neuromodulatory systems have opposite effects of each other and work together to modulate the amount of motor activity that is produced:

- **Dopamine** leads to increased motor activity, via selective excitation of the direct pathway and inhibition of the indirect pathway
- **Acetylcholine** leads to decreased motor activity, via selective excitation of the indirect pathway and inhibition of the direct pathway

**Dopamine**

The **nigrostriatal pathway** is a connection between the **substantia nigra pars compacta** and the **striatum**. It is a source of input into the basal ganglia (striatum) and serves as a modulatory pathway of the direct and indirect basal ganglia pathways. **Inputs into the pars compacta itself remain unclear**, but at least some are from the striatum (**striosome**). Clinically, this pathway is most important for its role in **Parkinson’s disease**.

*Note: it is important to keep in mind the distinction between the **substantia nigra pars compacta** which produces dopamine and is a source of input information to the basal ganglia, and the **substantia nigra pars reticulata** which, along with the internal segment of globus pallidus, is a source of inhibitory output (GABA) from the basal ganglia.*

**Dopamine** produced by cells of the **substantia nigra pars compacta** has both excitatory and inhibitory effects upon the cells of the striatum due to the presence of different dopamine receptors; however, as these cells are part of the direct and indirect pathways, respectively, the overall effect is **increased motor activity**.

**D1 dopamine receptors** are present on cells in the striatum which are part of the **direct pathway** (increases motor activity); the receptors produce excitatory effects, thus activating the pathway and leading to increased motor activity. **D2 dopamine receptors**, on the other hand, are present on cells which are part of the **indirect pathway** (decreases motor activity): they produce inhibitory effects, thus inhibiting the pathway (which is itself inhibitory) and freeing the thalamus to increase motor activity. The combined effect of dopamine acting upon both classes of receptors is increased activity of the motor thalamus and increased motor activity.

**Acetylcholine**

In addition to the projection neurons (spiny neurons), the striatum also contains large interneurons called **aspy neurons**. These neurons are excitatory and use **acetylcholine** as the neurotransmitter. They seem to preferentially excite projection neurons in the striatum which are part of the **indirect pathway**, but they likely also inhibit striatal cells that are part of the direct pathway. The combined effect of their activity is inhibition of the motor thalamus and **decreased motor activity**.

**Movement Disorders**

Disorders of the basal ganglia that affect motor function are referred to as **movement disorders** or **dyskinetic disorders**. As output from the basal ganglia goes to the **ipsilateral cerebral cortex**, movement disorders occur on the **contralateral side of the body** to the side of basal ganglia damage.

Such disorders can usually be differentiated from other motor disorders, such as the irregular uncoordinated movements (ataxia) resulting from cerebellar lesions. However, the extensive network of reciprocal connections between the various components of the motor system make simplistic classifications and explanations of disorders difficult and usually incomplete in accounting for all the problems associated with a given disease.
Movement disorders of the basal ganglia are generally classified as either hyperkinetic or hypokinetic disorders, but in reality, most patients will, at least eventually, exhibit a mixture of both kinds of disorders:

- **Hyperkinetic movement disorders** are the result of decreased basal ganglia output, resulting in increased thalamus activity which excites motor areas of the cerebral cortex
  - Uncontrolled, involuntary movements produce a random pattern of jerks and twists
  - Can result from decreased indirect pathway activity or increased direct pathway activity
  - Often involve lesions to the subthalamic nucleus causing disruption of the indirect pathway and resulting in a reduction of inhibitory output to the thalamus
  - Huntington’s disease is a congenital disease resulting from the loss of neurons of the striatum (putamen and caudate) with abnormalities in all domains of basal ganglia function
    - Enkephalin-expressing neurons of the indirect pathway appear to be more affected, resulting in a reduction of inhibitory output to the thalamus
    - Advanced Huntington’s leads to degeneration of both the direct and indirect pathways resulting in an eventual rigid, hypokinetic Parkinsonian state

- **Hypokinetic movement disorders** are the result of increased basal ganglia output, resulting in decreased thalamus activity which suppresses motor areas of the cerebral cortex
  - Rigidity, slowness, and marked difficulty in initiating movements
  - Can result from decreased direct pathway activity or increased indirect pathway activity
  - Possible causes include: loss of function of the nigrostriatal system, loss of inhibitory pathways from the striatum to the substantia nigra and internal segment of globus pallidus, or loss of inhibitory neurons from the external segment of globus pallidus to the subthalamic nucleus
  - Parkinson’s disease results from the loss of dopamine-producing neurons in the substantia nigra pars compacta (e.g., loss of nigrostriatal modulating system)
    - Dopamine has a net excitatory effect on the thalamus via its excitatory effects on the striatal projection neurons of the direct pathway (D1 receptors) and inhibitory effects on the neurons of the indirect pathway (D2 receptors)
    - Loss of dopamine leads to a net inhibitory effect on the thalamus via a loss of activation of the direct pathway and a loss of inhibition of the indirect pathway; additionally, the net inhibitory modulating effect of acetylcholine in the striatum remains unaffected (further suppressing the thalamus)
    - The classic triad of Parkinson’s includes bradykinesia, rigidity, and resting tremor (in 70% of patients); the signs usually begin unilaterally, eventually becoming bilateral, but severity remains asymmetric
    - Almost always improves with Levodopa (L-DOPA), at least for a time
    - While the pathways model of the basal ganglia can explain the bradykinesia and rigidity, the model does not account for the resting tremor; impairment of olfaction (anosmia) may be one of the earliest signs of Parkinson’s disease but is also not accounted for (especially as olfaction is the only sense that bypasses the thalamus)
Possible therapies for basal ganglia disorders include medications, surgical lesioning, deep-brain stimulation, and transplantation of neurotransmitter-producing cells.

- **Medications**:
  - **L-DOPA** (Levodopa) is the most effective treatment for Parkinson’s disease: upon crossing the blood-brain barrier it is converted to dopamine; it is normally administered with another drug, such as Carbidopa which cannot cross the blood-brain barrier and prevents conversion of levodopa into dopamine in the peripheral tissues
  - **Anticholinergic agents** may provide some benefit in Parkinson’s disease by reducing the cholinergic modulation in the striatum which normally serves to decrease motor activity
  - **Dopaminergic agonists**

- **Surgical Lesions**: early Parkinsonian researchers noticed that certain Parkinson’s patients who had strokes experienced amelioration of their conditions, leading to speculation that selective lesioning of basal ganglia nuclei or the thalamus could serve as a treatments
  - **Pallidotomy** is the most common lesioning procedure and involves lesioning the internal segment of globus pallidus reducing inhibitory basal ganglia output to the thalamus
  - **Subthalamotomy** involves lesioning of the subthalamic nucleus reducing inhibitory basal ganglia output to the thalamus by disruption of the indirect pathway
  - **Thalamotomy** involves lesioning the VL nucleus of the thalamus to reduce tremors

- **Deep-Brain Stimulation (DBS)**: placement of stimulating electrodes into basal ganglia nuclei or the thalamus; the mechanism of action remains unclear but it is thought to cause reversible dysfunction of neurons at the electrode tip; targeted locations are generally the same as those for surgical lesions and investigations are underway to compare the effectiveness of the two procedures, but DBS is currently much more widely used

- **Cell Transplants**: cell transplantation has generally focused on attempting to increase dopamine in the striatum in Parkinson’s patients; trials have involved transplanting cells either from the adrenal medulla or fetal dopamine-producing cells from the substantia nigra directly into the striatum; the overall effectiveness and benefit of these transplants remains unclear
Clinical Considerations

1. In 1947, Dr. Albert Ziering, working at Hoffman-LaRoache Laboratories, synthesized a new opioid analgesic drug (desmethylprodine or MPPP). The drug was a slight variation of the opioid drug pethidine, but was no more effective and so was never marketed. The findings were, however, published. In 1976, Barry Kidston, a 23-year-old chemistry student in Maryland discovered the paper when trying to synthesize new recreational drugs, perhaps in the hopes of creating recreational drugs which were not yet legally restricted. He managed to successfully synthesize the drug and administered it to himself intravenously for several months before synthesizing a new batch. He took “synthetic shortcuts” with the new batch and after several days of injections, he was hospitalized in a “frozen” state, with muscle rigidity and unable to move or speak.

   What might explain his condition?

   What pathways in the basal ganglia could be involved?

   Treatment with L-DOPA improved his condition; what does this suggest?

In 1978, Barry Kidston died of a cocaine overdose and an autopsy was performed. It showed a destruction of cells in the substantia nigra. Researchers attempted to recreate his drug synthesis reaction conditions and compared their findings against residues found in his laboratory glassware. The findings showed several synthetic impurities including MPTP. These findings were published in 1979. In 1982, six recreational drug-users were hospitalized in California, all appearing to have the same rapid-onset, advanced Parkinson’s disease. Remembering the Kidston article, researchers wondered if there might be a connection. It was discovered that all six new patients had all recently injected heroin. Testing of a sample of the heroin showed MPTP contamination. Further studies eventually showed that MPTP itself was not toxic but was metabolized to MPP+ which was highly toxic to dopamine-producing neurons.

   What role does dopamine play in basal ganglia motor pathways?

   What treatments might have been considered for the patients?

   What “good” might have come from the discovery of MPP+?
2. A 65-year-old HIV-Positive man began having involuntary flinging movements of the right arm and leg, becoming progressively worse over the course of one month. On exam, he had continuous wild, uncontrollable flapping and circular movements of the right arm and occasional jerky movements of the right leg, with an unsteady gait. The remainder of the exam was unremarkable.

On the basis of the given signs and symptoms, where are likely locations for a lesion?

What is a likely diagnosis? Why?

3. Prior to the onset of illness, a 25-year-old woman had been a high school honor student, was employed full-time, lived independently, and was engaged to be married. For the period of a month she suffered daily headaches with occasional nausea and vomiting. She then disappeared for three days. When found, she had undergone a dramatic personality change. Her abnormal behaviors included vulgarity, impulsiveness, easy frustration, violent outbursts, hypersomnia, enuresis, indifference, wandering, increased appetite, polydipsia, hypersexuality, criminal behavior, and poor hygiene. A year later, she had been married and divorced, was unemployed, and had little improvement in behavior. Psychiatric hospitalizations and tranquilizers were not beneficial.

What area of the cortex does this suggest a problem with?

How is this associated with the basal ganglia?

Imaging later showed profound degeneration of the heads of the caudate nuclei. Where would this be the most visible in the imaging? What other conditions have damage to this area?
The Flu Pandemic of 1918 is estimated to have infected 500 million people around the world and killed at least 50 million. Up to five percent of the human population was killed. In the wake of the outbreak, between 1917 and 1928, nearly five million people succumbed to a mysterious illness known as encephalitis lethargica. A third of the patients died acutely from the disease, while the majority of the survivors never fully recovered: “sitting motionless and speechless all day… they registered what went on about them without active attention, and with profound indifference.” After the outbreak, no confirmed recurrence of the disease has since been reported.

What are possible explanations for the observed signs of those suffering from the disease?

What are possible ways the disease could have been caused by the Flu Pandemic?

In 1969, Dr. Oliver Sacks worked with hospitalized patients in the Bronx suffering from encephalitis lethargica from the 1917-1928 outbreak. He discovered that many of the patients had initially recovered from the disease before subsequently developing progressive movement disorder symptoms. Dr. Sacks began experimenting with administration of L-DOPA to the patients. Many patients experienced remarkable “awakenings” of physical and cognitive ability after decades of being in their catatonic states. Sadly, these improvements did not last and the patients returned to their previous conditions.

What does the initially-successful treatment of L-DOPA suggest?

What are possible reasons the treatments did not continue to work?

Despite nearly a century of investigation, the etiology of encephalitis lethargica remains mysterious. Debate continues as to the possible roles of influenza, other viral or bacterial infectious agents, or inflammatory conditions in the causation of the disease.