LECTURE 31: MOTOR SYSTEMS IV - BASAL GANGLIA

TIMOTHY J. EBNER

READING:  p. 324-331

I. Clinical correlation

A. Twenty-six year old white male develops uncontrolled (involuntary) movements of the limbs, body and trunk are progressively getting worse.

B. Loss of cognitive functions.

C. Father died of a similar disease but onset was later in life with slower progression of the disease.

II. Anatomy and circuitry

A. Neostriatum: Receives major inputs

1. Made up of caudate and putamen

   a. Cytoarchitecturally similar nuclei

   b. Spiny neurons: Receive input and are primary output neurons of neostriatum

      i. Most have GABA as their transmitter (90-95%) – two groups

         a) GABA/substance P (SP) group

         b) GABA/enkephalin (ENK) group

   c. Aspiny neurons and interneurons:

      i. Use ACH or somatostatin

      ii. Important in movement disorders

2. Afferent input to striatum from outside basal ganglia

   a. Cerebral cortex to striatum (corticostriate pathway)

      i. Originates from many cortical areas, especially premotor and primary motor cortex

      ii. Terminates on spiny neurons in neostriatum

iii. Transmitter: Glutamate
iv. Excitatory projection
v. Information reflects "specific" cortical activity

b. Principal path through basal ganglia
i. Cortex to basal ganglia
ii. Basal ganglia to motor thalamus
iii. Motor thalamus to cortex

B. Globus Pallidus (GP): Major output system

1. Internal segment (GP_I)
   a. Projects to VA and VL nuclei of thalamus (via ansa lenticularis/lenticular fasciculus). These areas project back to cortical areas that are source of corticostriate pathways.
   b. Inhibitory (GABA)

2. External segment (GP_E)
   a. Projects to subthalamic nuclei (STN)
   b. Primarily inhibitory and uses GABA

C. Substantia nigra (SN)

1. Located in midbrain

2. Composed of two parts: Pars compacta (SN$_c$) and pars reticulata (SN$_r$)

3. Receives input from striatum (striatonigral projection)
   
   a. To pars reticulata and compacta of substantia nigra
   
   b. From GABA/SP spiny neurons
   
   c. Inhibitory

4. Substantia nigra pars compacta projects to striatum (nigrostriatal projection)
   
   a. Terminates on spiny neurons
   
   b. Uses dopamine: Has two actions
      
      i. Inhibitory effects on GABA/ENK neurons via D$_2$ receptors
      
      ii. Excitatory effects on GABA/SP neurons via D$_1$ receptors
      
      iii. "Closed Circuit" Major input to substantia nigra is from striatum. Same area of striatum projecting to substantia nigra receives projection from substantia nigra.

5. Substantia nigra pars reticulata: Part of the output projection of the basal ganglia used to control eye movements
   
   a. To thalamus (VA and VL) and brainstem
   
   b. Similar to internal globus pallidus (GP$_I$)

D. Subthalamic Nucleus (STN): Also located in the midbrain

1. Input
   a. Receives projections from external segment of globus pallidus (GP_E)
   b. Primarily inhibitory (GABA)

2. Output
   a. Projects to internal segment of globus pallidus (GP_I)
   b. Primarily excitatory (glutamate)

3. Ideally suited to modulate output of the basal ganglia

E. Projection from striatum to globus pallidus (striatopallidal projection)

1. To both GP_I and GP_E
2. GABA/SP group to GP_I
3. GABA/ENK group to GP_E

III. How does this circuit function?

A. Two key points:

1. GP_I is mainly inhibitory to thalamus!
2. Therefore, two pathways from striatum to GP_I
   a. Direct pathway: Striatum → GP_I
   b. Indirect pathway: Striatum → GP_E → STN → GP_I
B. Most accepted scheme

1. GPᵢ activity normally high - tonically inhibiting thalamus and motor activity

2. To produce motor activity must decrease GPᵢ activity

3. Consider how dopamine effects striatum
   a. Inhibits part of striatum that would increase GPₑ output that would in turn decrease STN excitatory action on GPᵢ. This is the GABA/ENK neurons.
   b. Also, excites part of striatum that inhibits GPᵢ. This is the GABA/SP neurons.
   c. Normal state of balance is tonic GPᵢ activity that inhibits VL
   d. Increase in dopamine release would result in:
      i. Less excitation of STN on GPᵢ
      ii. Increase of inhibition on GPᵢ via putamen
      iii. Net effect is less GPᵢ inhibitory output to VL: Therefore motor activity!

IV. Lesion studies and human movement disorders

A. Subthalamic lesions - hyperkinetic dyskinesia

1. Results in ballismus – wild exaggerated movements of limbs

2. Due to loss of excitatory drive to GPᵢ
B. Substantia nigra pars compacta

1. Bilateral lesions in animals produce akinesia

2. MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine)
   a. Produces selective dopamine cell death in primates
   b. Mimics human Parkinson’s disease

3. Parkinson’s Disease
   a. Four major clinical findings
      i. Bradykinesia
      ii. Rigidity
      iii. Rest tremor of 4 to 7 Hz
      iv. Postural instability
   b. Main pathology is loss of pigmented cells in substantia nigra pars compacta
   c. Etiology
      i. Not known for vast majority of cases
         a) Current hypothesis is oxidative stress
      ii. Encephalitis lethargica - viral encephalitis
      iii. Toxins - carbon monoxide, manganese
      iv. Head trauma - boxers
   d. Treatment: Restore dopamine using L-DOPA, but can produce hyperkinetic movements
   e. How might one treat parkinsonism surgically?
C. Globus Pallidus

1. Bilateral lesions
   a. Flexion dystonia/flexion posturing
   b. Performance of extension-flexion movements severely hampered
   c. Co-contraction of biceps and triceps activity
   d. Dystonia/rigidity represents an increase in motoractivity
   e. Interpretation: Loss of normal tonic inhibitory activity of GP₁ on VA/VL

D. Striatal lesions – complex movement disorders

1. Putamen
   a. Obstinate progression
   b. Stereotypic behavior

2. Caudate
   a. Changes in more "complex behavior" with bilateral lesions
      i. Compulsory approaching syndrome
      ii. Perseverative behavior

3. Consider loss of GABA/ENK neurons

4. What would happen with loss of GABA/SP neurons?

5. Stimulation of putamen and caudate
   
a. Produces increases and decreases in motor activity
   
b. Can activate (desynchronize) or deactivate (synchronize) cerebral cortical activity
   
c. Neostratium may be turning movements "on" or "off", controlling activation of cerebral cortex

6. Huntington's Chorea
   
a. Hereditary: Autosomal dominant
      
i. Abnormal gene on the short arm of chromosome 4
      
ii. CGA repeat, gain of function
      
iii. Onset 25-40 years old
   
b. Pathology
      
i. Death of spiny neurons in neostriatum/particularly GABA/ENK group
      
ii. Also loss of cerebral cortical neurons
   
c. Symptomatology
      
i. Involuntary movements: Chorea and athetosis
      
ii. Dementia/personality changes
   
d. Biochemical profile in striatum
      
i. GABA and ENK decreased
      
ii. Somatostatin increased and somatostatin potentiates dopamine!!
   
e. Interpretation of chorea/athetosis
      
i. Involuntary movements a form of hyperkinetic/dyskinesia
      
ii. Suggests GP₁ inhibition of thalamus decreased/abnormal
   
f. How would one treat Huntington's patients?