The Thalamic Regulation of Striatal Function in Normal and Parkinsonian States

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The classical view of the cortico-basal ganglia-thalamocortical circuitry

The thalamostriatal system: How does it functionally integrate the basal ganglia circuitry?
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Two sources of extrinsic glutamatergic drive
to the striatum

Talk outline

• Functional anatomy and synaptic connectivity
  of the thalamostriatal system
• Potential role of the thalamostriatal system
  from CM/Pf in attention
• Potential impact of CM/Pf degeneration
  on cognitive processes in Parkinson’s disease
• Conclusions

Functional anatomy and synaptic connectivity
of the thalamostriatal system
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The existence of the thalamostriatal system has long been established


The thalamostriatal projection has a widespread origin in the primate and non-primate thalamus

(Smith and Parent, 1986, Neuroscience 18: 347)

- WGA-HRP injection in ventral motor thalamic nuclei
- Rostral ILN, midline and mediodorsal thalamic nuclei

In primates, thalamostriatal projections from intralaminar and non-intralaminar nuclei to the caudate nucleus and putamen arise from functionally segregated neuronal sub-populations.

Thalamostriatal projections are highly topographic in rats and monkeys

Smith Y et al. (2004) TINS 27: 520-527
Berendse and Groenewegen (1990) JCN 299: T17

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Functionally segregated basal ganglia-thalamostriatal loops

Nerurosci 7: 131.

Synaptic connectivity of CM/Pf vs. cortical afferents to the striatum
(Sadikot et al., 1992, JCN 320: 228)

More than 70% CM/Pf terminals form axo-dendritic synapses in the monkey striatum

Both vGluT1- and vGluT2-immunoreactive terminals form axospinous synapses in rat and monkey striatum

Fremeau et al., TINS 2004 27: 108-103
Rajo and Fremeau, 2008 TINS 31: 231

• vGluT1 = Specific marker of glutamatergic cortical terminals
• vGluT2 = Exclusively labels thalamic afferents
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Glutamatergic inputs from most thalamic nuclei, except PF, form axo-spinous synapses in the rat striatum
(Raju and Smith, 2006, JCN 499: 231)

1. Degree of cortical innervation
- CM/Pf: Projects preferentially to the striatum with collaterals to the cortex
- Non CM/Pf: Projects preferentially to the cortex with collaterals to the striatum

2. Matrix/Patch preference
- CM/Pf: Innervates preferentially matrix
- Non CM/Pf: Shows no clear preference for matrix or patches

3. Pattern of innervation
- CM/Pf: Focal, convergent sites of termination in the striatum
- Non CM/Pf: Diffuse pattern of termination in the striatum

Potential role of the thalamostriatal system from CM/Pf in attention
The CM/Pf nuclear complex is activated in humans during high vigilance and general attention
(Kinomura et al., 1996, Science 271: 512)

PET for Cerebral blood flow in humans under three conditions:
1. Rest: Quiet, eyes closed, hold a response key
2. Visual RT: eyes opened, responded when change luminescence of yellow light on screen
3. Somatosensory RT: eyes opened, looked at yellow light, responded when felt sensation on right index finger

The CM/Pf and the midbrain reticular formation are activated irrespective of the sensory modality (visual or somatosensory) that provides the alerting signal.

CM and Pf neurons respond differently to attention-related sensory stimuli
(Matsumoto et al., J. Neurophysiol. 85: 960-976)

- CM and Pf neurons respond to salient sensory stimuli in attention-related cognitive tasks but, in a very different manner:
  - LLF neurons (long-latency facilitation)
    - 200-250 msec response latency after stimuli
    - Almost exclusively in CM
  - SLF neurons (short-latency facilitation)
    - 30-90 msec response latency after stimuli
    - Almost exclusively in Pf

- The responses of both LLF and SLF neurons to sensory stimuli are independent of reward.

One of the main targets of CM/Pf terminals in the striatum are the cholinergic interneurons

- About 1-2% of total striatal neuronal populations
- Provide widespread innervation to striatal projection neurons
- Receive direct synaptic inputs from CM/Pf, but very light innervation from the cerebral cortex

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Inactivation of neuronal activity in CM/Pf affects the responses of striatal cholinergic interneurons (or TANs) to reward-related sensory stimuli
(Matsumoto et al., J. Neurophysiol. 85: 960-976)

Neurons in the Thalamic CM-Pf Complex Supply Striatal Neurons With Information About Behaviorally Significant Sensory Events
Sakurai, T., Matsumoto, M., Niki, T., Inomata, Y., Kawamura, M., and Kita, H.

• Cholinergic responses consists of 3 main events:
  - initial facilitation (IF), pause (P) and rebound facilitation (RF)

• Chemical inactivation of CM/Pf reduces the pause and rebound facilitation, but not the initial facilitation, components of TANs response to reward-related sensory stimuli.
(Matsumoto et al., J. Neurophysiol. 85: 960-976)

How does lesion of the thalamostriatal system from CM/Pf affect motor and cognitive behaviors?
(Kato et al., 2011, JNS 31: 17169-17179)

Selective Neural Pathway Targeting Reveals Key Roles of Thalamostriatal Projection in the Control of Visual Discrimination
Kato, T., Ikezawa, H., Nakashima, T., and Sasaki, H.

• Retrograde gene transfer vector method and immunotoxin delivery to destroy the Pf-striatal system in mice
• Massive loss of Pf-striatal neurons
• Selective lesion of the Pf-striatal system has no effect on locomotion and motor skill learning
(Kato et al., 2011, JNS 31: 17169-17179)

Mice with selective lesion of the Pf-striatal system display deficits in discrimination learning
(Kato et al., 2011, JNS 41: 17169-17179)

• Acquisition (Lesion before learning session):
  Pf-striatal lesion disturbs the acquisition of the two-choice visual discrimination task

• Performance (Lesion after learning session):
  Pf-striatal lesion disturbs the performance of the two-choice visual discrimination task

• Motor response and motivation (Lesion before learning session):
  Pf-striatal lesion has no effect on the motor response and motivation to perform simple reaction time task without visual discrimination

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Behavioral role of CM/Pf-striatal network

- The CM/Pf-striatal system plays an essential role in the process of attentional orienting to external events, most likely through a tight regulation of striatal cholinergic interneurons and projection neurons.
- Lesion of the CM/Pf complex does not induce significant motor disturbances.

Potential impact of CM/Pf degeneration on cognitive processes in Parkinson’s disease?

CM/Pf neurons degenerate in Parkinson’s disease

Cell loss in CM of Parkinsonians

Significant cell loss in CM and Pf of PD patients

The extent of cell loss in CM and Pf partly correlates with the degree of severity of PD.
CM/Pf neuronal loss in PD can be mimicked in motor "symptomatic" and "asymptomatic" MPTP-treated monkeys

CM/Pf neuronal counts

Motor-symptomatic

Motor-asymptomatic

Unbiased stereology of synaptic counts

"The Brick Method" (Howard et al., 1985)

The total number of asymmetric synapses is reduced by more than 40% in the striatum of MPTP-treated Parkinsonian monkeys.

Does the synaptic loss in the Parkinsonian striatum affect preferentially thalamic or cortical glutamatergic synapses?

The glutamatergic synaptic denervation of the striatum in the MPTP-treated monkey model of Parkinson's disease is due predominantly to the degeneration of the thalamostriatal system from CM/Pf.
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**Conclusions**

- The thalamostriatal system has a dual (or more) thalamic origin: CM/Pf vs. non-CM/Pf nuclei.
- The CM/Pf vs. non-CM/Pf striatal systems differ in their anatomical origin, synaptic connectivity, relationships with the nigrostriatal DA system, synaptic receptors localization and extent of degeneration in Parkinson's disease.
- The CM/Pf is part of functional basal ganglia-thalamostriatal loops.
- The CM/Pf-striatal system (via regulation of striatal cholinergic interneurons) plays an important role in mediating selective attention to external events.
- The CM/Pf, but not other thalamic nuclei, undergo severe "early" degeneration in Parkinson's disease.

**Future studies**

- Could the degeneration of the CM/Pf-striatal system account for early cognitive deficits in attentional set-shifting seen in Parkinson's disease?
- When does CM/Pf degeneration occur during the course of PD? Does it correlate with early attention deficits?
- What are the specific roles of the "sensorimotor" CM-putamen vs. the "associative" Pf-caudate subsystems in basal ganglia-mediated regulation of selective attention? Do they specifically regulate habitual (CM-putamen) vs. goal-directed (Pf-Caudate) behaviors?
- What are the main functions of the non-CM/Pf-striatal system? How do these thalamic afferents functionally interact with corticostriatal afferents? How are these interactions altered in diseased states?

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