Mechanisms of Action of Deep Brain Stimulation (DBS) for Movement Disorders

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Outline of talk

A. What/where are the basal ganglia?
B. Models of basal ganglia function/dysfunction in PD
C. Other movement disorders currently treated with DBS
D. Brief review of literature on DBS mechanisms
E. New data in human GPi on DBS mechanisms
A. The Basal Ganglia

- Regulates flow of ‘volitional’ drive to premotor centers
- 2 tiers of nuclei, collectively known as ‘striatum’ and ‘pallidum’ (internal/external)
  - **striatum**: topographic input from cerebral cortex and thalamus (centromedian nucleus)
  - **Internal pallidum**: projects to premotor centers
B. Basal Ganglia Rate Model

STN - subthalamic nucleus; GPe - globus pallidus externus; GPI - . . internus; SNr - substantia nigra pars reticulata; Thal - motor thalamus; glu - glutamate
B. Parkinson’s Disease

- Diagnosis requires two out of three signs: Brady-, akinesia; rigidity; resting tremor, (postural instability)
- Marked striatal dopamine depletion - “Striatal DA deficiency syndrome”, ~70% DA loss for symptom manifestations
B. Parkinson’s disease

DBS therapy inhibits STN

STN → GPe → GPi/SNr → Thal

GABA → Striatum → GABA

Stages of the disease:
- Cortex
- Striatum
- GABA
- Glu

Dotted line indicates inhibitory connections.
B. Oscillation Model - Normal

Cortical Motor Areas

- Alpha rhythm - quiet rest, also increased with salient sensory stimuli
- Mu rhythm - motor or beta rhythm activate with movements
- Gamma rhythm - role in attention, working memory

Basal Ganglia
- STN
- GPi/SNr

11-30 Hz

<10 Hz

> 70 Hz

modified from Brown. Mov Disord. 2003
B. Oscillation Model – Parkinson’s disease

modified from Brown. Mov Disord. 03
c. Other movement disorders - Dystonia

• A syndrome of sustained muscle contraction, frequently causing twisting and repetitive movements, or abnormal postures (co-contraction of agonist and antagonist)

• Globus Pallidus internus DBS is the “gold standard” for primary dystonia, also secondary dystonia, cervical dystonia
Essential Tremor

- Rhythmic, oscillatory movement of a body part during action or movement intention

- DBS in ventral intermediate nucleus (VIM) and of thalamus for essential tremor
Deep Brain Stimulation (DBS)

1. Frame mounting
2. MRI scan
3. Preop targeting
4. Insert electrodes
5. Listen to the Neurons
6. Implant system

(Courtesy of Dr. Stone)
Methods

• **A**, The electrodes used were independently driven with hydraulic microdrives (rectangles) and separate amplifiers (triangles) recorded the signals. **B**, The electrode tips were spaced 600 µm apart. One electrode stimulated and the other recorded. **C**, Each electrode was extruded from its own guide tube.
D.

Hypotheses of DBS mechanisms

1. Trans-synaptic silencing of neuronal activity (GABA release hypothesis)
2. Orthodromic effects on downstream target structures (i.e. Motor thalamus)
3. Antidromic activation effects on upstream targets (i.e. Motor cortex)
4. Activation of axons of passage
5. Suppression of beta network oscillations
Different types of recordings have been used to study DBS mechanisms from patients and in vivo models to in vitro slices. Each has its advantages and pitfalls, but the combination allows understanding of DBS mechanisms.
D1. Synaptic Inhibition of neurons

Inhibition of STN and GPi neurons during stimulation with a nearby microelectrode

Filali et al. J Neurophysiol. 2004
D2. Orthodromic activation of target structures

2Hz

136Hz

157Hz

pre-stimulation
during 136 Hz stimulation
post-stimulation

1 sec/sweep

1ms/div

Hashimoto et al. J Neurosci. 03

GPi neuronal activity during STN DBS
D3. Antidromic activation of cortex or Gpi

Antidromic spikes recorded in rat cortex during STN-HFS and recorded in Gpi during Gpi-HFS

Li et al. J Neurophysiol. 07

McCairn and Turner. J Neurophysiol. 09
D4. Activation of axons en passant from modeling studies

Stimulation within GPi can influence the STN by activating myelinated and unmyelinated fibres passing from GPe to STN.

Theoretical modeling allow us to predict the effects of stimulation on axons, but these effects have not been demonstrated in humans to date.
In individual patients, STN oscillatory activity in the beta range is suppressed during DBS, and returns when DBS is turned off.
E. GPi DBS in dystonia patients

- Bilateral GPi DBS above 60 Hz is also effective for cervical dystonia, but is ineffective at lower frequencies.
Methods

- **A,** Representative electrode track with 1 mm unit **B,** Recording sites along the track **C,** Example recording

- Stimulation trains at increasing frequencies (1, 2, 5, 10, 20, 30, 50 and 100 Hz, 20-50 pulses each) were delivered via one electrode and neuronal responses were recorded via the other

- Firing rates, fiber volley and evoked field potential (fEP) amplitudes were analyzed before and after short HFS trains (4 X 2 s trains of 100 Hz, 10 s apart)
E. Results

A total of 25 sites were investigated in 13 dystonia patients.

As the fEP amplitude increased, the firing rate decreased in all sites.

Note that mean fEP amplitudes at 50 and 100 Hz were still at 75% and 27% respectively whereas the cell firing was virtually silenced at these high frequencies.
• fEP was driven at the frequency of stimulation and its amplitude decreased for the higher frequency.

• The decrease is likely due to depletion of neurotransmitters.
• Frequency dependent potentiation of fEP. The first fEP amplitude is indicative of the potentiation induced with the previous stimulation frequency.

• Last fEP amplitude of the stimulation train is indicative of the attenuation of fEP.
• Nature of fEP illustrated by the GABAergic anaesthetics, propofol, administered in some patients

• The GABAergic synapses might be potentiated and prevented further stimulation dependent potentiation
In 4 sites, additional long train of 100 Hz stimulation was applied.

Spikes appear to be returning at the end to long train 100 Hz stimulation.

The cell appears to be driven to an increased firing rate.
• Unlike the change in average fEP, the fiber volley amplitude was only significantly decreased at the highest frequency.

• Stimulation can drive the GPi fibers at 100 Hz and therefore can replace the pathological activity.
Evidence for direct excitation of neuronal elements

A. Short, fixed latency and collision-like phenomenon suggest antidromic-like activation

B. Short, fixed latency and persistence at high frequency (100 Hz) stimulation also suggest direct or antidromic-like activation

C. Other short latency excitations with jitter and failure at 30 Hz stimulation suggest synaptically driven spikes
E. Summary of GPi findings

- GABA release is initially involved, but inhibitory synaptic plasticity may be an important mechanism of action of DBS.

- Fiber volleys followed even the high frequency ranges, suggesting that DBS can replace the irregular basal ganglia output with a more regular pattern.

- Single pulse monitoring of fEPs may provide useful signals for closed loop systems... i.e. maximize early fibre volley and minimize later synaptic components.
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Challenges to understanding the mechanisms of DBS

- complex pathways of inputs and outputs from the various nuclei being stimulated

- Large stimulus artifacts during stimulation through DBS contacts can occlude neuronal activity during and immediately after stimulation

- Comparable current densities can be achieved with microelectrodes before implantation with minimal stimulation artifacts.
Hypotheses for the mechanism of DBS - more or less?

- The “less” hypothesis states that DBS silences pathological activity thereby eliminating symptoms. The silencing might be due to pre-synaptic GABA release.

- The “more” hypothesis states that DBS not only silences pathological activity but also replaces it with a new pattern that is driven by DBS.

Garcia et al. Trends Neurosci 05
• High frequency, pulsatile, bipolar electrical stimulation

• Stereotactically placed into target nucleus

• Can be activated and deactivated with an external magnet

• Exact mechanisms unknown but likely complex and varied