LEVODOPA DRUG DELIVERY AND THE ARTIFICIAL BRAIN PACEMAKER

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Brain is simply made up of Systems and Signals
Anatomy of the Brain

Four Lobes

• Pre-frontal Cortex

• Primary Motor Cortex (Pre-central Gyrus)

• Primary Sensory Cortex (Post-central Gyrus)
Anatomy of the Brain

Diencephalon

- Corpus callosum
- Pineal gland
- Thalamus
- Hypothalamus
- Pituitary gland
- Pons
- Medulla
- Cerebellum
Anatomy of the Brain

Limbic System

Hippocampus and fornix (limbic system)

Frontal lobe
Temporal lobe
Cerebellum
Anatomy of the Brain

Basal Ganglia

Figure AB-18: Basal Ganglia

Diagram colors are consistent with Figure AB-19.
Motor and Sensory Pathway in the Brain

- General Overview
- Pathway of Sensory Information in the brain and the Somatosensory Cortex
- Prefrontal Cortex gathers information from the Parietal lobe
Prefrontal Cortex sends out 3 different signals to the Precentral Gyrus, Basal Ganglia, and the Cerebellum

Primary Motor Cortex sends an impulse to the Spinal Cord via the Brainstem

Motor/Sensory Relationship
Prefrontal Cortex decides what to focus on
Thalamus Focuses
Flash light analogy
Examples
Output of Thalamus to the Primary Motor Cortex at the Pre-central Gyrus
Basal Ganglia

General Overview
- Corto-basal ganglia motor loop
  - determines and controls movement
- Basal ganglia
  - channel motor information
  - filter motor information
- Brake hypothesis
  - When sitting
  - When moving from rest
- Small disturbances can cause
  - Unwanted movements
  - Difficulty with intended movements
Basal Ganglia

Relevant Components

- Striatum
  - Putamen in green
  - Caudate nucleus in orange
Basal Ganglia

Relevant Components
- Globus pallidus
  - Myelinated axons \(\rightarrow\) "pale globe"
  - Medial segment – Gpi
  - Lateral segment – Gpe
Basal Ganglia

Relevant Components

- Substantia nigra
  - Pars compacta
  - Another irrelevant ensemble
The thalamus is a “filter”
- Pars oralis or VLo
- Filters motor output to motor cortex
- Control thalamus → control movements usefully
- Stimulation?
- Inhibition?
- Thalamus is under direct pallidal control
Basal Ganglia

Functionality 1 – the Globus Pallidus

- GPI sends major output
- Output is inhibitory
- Revisit the brake hypothesis
  - Thalamus = automobile
  - GPI = all restrictive effects
Basal Ganglia

Functionality 2 – Controlling the GPi

- Indirect pathway = brake pedal
  - Final effect on thalamus is inhibitory
- Direct pathway = gas pedal
  - Final effect on thalamus is excitatory
- Globus pallidus is the breaking effect
- Achieve roundabout management of thalamus
Basal Ganglia

Functionality 3 – Controlling the pathways
- Pathways controlled in striatum
- Mechanism is IMPORTANT
- Simplification of pathway $\rightarrow$ neuron bundles with dopaminergic receptors
  - Implications?
- Different receptors $\rightarrow$ different effect by dopamine
Functionality 4 – Dopamine action on pathways

- D1 receptors on direct pathway
  - Excitatory → ends up stimulating thalamus
- D2 receptors on indirect pathway
  - Inhibitory → ends up lifting inhibition of thalamus
- KEY POINT 1: Dopamine is CRITICAL for the stimulation of the thalamus
- KEY POINT 2: Thalamic stimulation is CRITICAL for regulating voluntary movement
- QUESTION: Where does striatal dopamine come from???
Basal Ganglia

Functionality 5 – Substantia Nigra and Dopamine

- Pars compacta produces dopamine
- Nigrostriatal pathway sends dopamine to striatum
When things go wrong...

Parkinson’s Disease

Huntington’s Disease

Dystonia

Depression
Parkinson's and Dopamine

Dopamine levels in a normal and a Parkinson's affected neuron.

- Normal Neuron
- Parkinson's affected Neuron

Normal movement

Dopamine

Receptors

Movement disorders
Pathophysiology in the Basal Ganglia

- Lack of Dopamine produced in the SNc is the main reason for symptoms

- Recall Break/Acceleration Model

- D2 pathway not inhibited: excited in a sense → not being able to release brakes

- D1 pathway inhibited → cannot accelerate
GPi has much higher neural activity to the Thalamus which is INHIBITORY.

Thalamus has very little neural activity to the Cortex which is EXCITATORY.
Effects of Parkinson’s Disease

- **Akinesia:** not being able to move certain muscles
  - Can not get up from a chair, mask-like facial expression

- **Bradykinesia:** slow movements of muscle
  - Taking small and slow steps to walk

- **Tremor:** Abnormal involuntary movements
  - Shaking of jaw, rubbing of fingers
  - Brake/acceleration model does not apply
    - rest tremor
  - Suggests that the basal ganglia is not functioning properly

- Questions raised about preciseness of pathophysiology
- Possible explanations: Excitatatory path from GPi to the Thalamus?
- Research under progress
1950s - Thalamotomy and pallidotomy are commonly used to correct movement disorders.
Pallidotomy

Overview

- Thermal destruction of tissue
- Reduces tremor, rigidity, bradykinesia and a few other motor symptoms
- Benefits fade over time
- Very risky, especially in the 50’s
- Rarely used
Thalamotomy

Better than Pallidotomy?
- Used less often
- Should be used in conjunction with drugs
- Bilateral surgery is NEVER done.
- Recall that thalamus is CRITICAL to cognitive, speech and sensory pathways.
From Brainstorm to Biomedicine

- 1968 - LDOPA available
  - The medication levodopa (L-dopa) becomes generally available to treat Parkinson's disease.
Substantia nigra is natural drug delivery system

Synthesis:

1. Tyrosine
2. Tyrosine hydroxylase
3. L-DOPA
4. Decarboxylase
5. Dopamine
But this system is compromised
- Low tyrosine hydroxase levels
- Degeneration of nigrostriatal pathway
- Result: low dopamine level in striatum
- Goal of drug remedies: make dopamine more available, of course!
- So why not administer dopamine?
Blood brain barrier (BBB)
- Blocks chemicals
- Tightly packed endothelial cells
- High density restricts passage
- No fenesterations = tight junctions
- Allows lipid soluble molecules or transported molecules
- GENERAL RULE: <=500u
MAIN POINT: Dopamine cannot cross BBB.
We need alternative delivery methods.
Go through the barrier:
- Disruption by osmotic means
- Biochemical disruption – bradykinin is a vasodilator
- HIFU – high intensity focused ultrasound
Go behind the barrier:
- Intracerebral implantation
Not a single one is used in treating Parkinson’s – WHY?

“Through” procedures are invasive

Intracerebral implantation is risky
  - Deliver it to the wrong region
  - Damage grey and white matter to get to right region

Technical expertise required
What do scientists use to supply dopamine?
- Oral drugs
- NOT dopamine
• Passage of an ingested drug
• Absorption through lining into drainage veins
• To liver
• Hepatic veins merge with vena cava and general circulation
For efficient transport, then...

Bioavailability is the issue.

Solubility determines permeability

Transit time in GI tract can
  - Be too long - degrade drug or
  - Too short - inhibit absorption

Protective coating controls absorption location
Recall what the goal is: get dopamine into striatum
Recall the pathway
Precursor - levodopa
Permeates BBB easily
Absent tyrosine hydroxilase no longer a problem.
Enzymatic conversion by?
Best KNOWN method of oral dopamine delivery
Levodopa

- How does it measure up?
- Not very well on its own:
- 30% gets into systemic circulation
- 30% of that actually reaches the brain
- So 1% of ingested levodopa gets to brain!
On its own, two great hindrances:
- METABOLISM in GI tract
- Reduction in blood to dopamine
Solutions

Intravenous infusion
- 100% bioavailability

Orally disintegrating levodopa
- Absorption in the mouth
- Reduces damage in GI tract and blood stream
Most popular - to block degradation of the medication with the coadministration of a decarboxylase inhibitor, such as carbidopa.

THREE-FOLD INCREASE IN % REACHING CIRCULATION
Problem also lies in loss of dopaminergic neurons
Fluctuations in availability of dopamine after long-term usage
Need something...deeper.
Video

- BEFORE AND AFTER VIDEO
1960s and 1970s - While performing surgical lesions to correct movement disorders, neurosurgeons theorize that tremor may be controlled by implanting an electrode.

By the late 1970s, neurologists realize that with long-term use, L-dopa can lose its effectiveness and can contribute to disability in Parkinson's patients.

Neurosurgeons begin implanting stimulating electrodes to treat movement disorders. Published scientific papers describe brain stimulation's results in various patients.

French neurosurgeon Prof. Alim-Louis Benabid and team in Grenoble, France, implant a thalamic stimulation system to control disabling tremor, and begin a pilot study.

First patients enroll in European multicenter clinical study for tremor that includes more than 100 patients.

Medtronic thalamic brain stimulation therapy available commercially in Europe, Canada and Australia for essential tremor and tremor in Parkinson's disease.
First patients enroll in the Medtronic 18-center, global clinical studies of stimulation of the subthalamic nucleus or globus pallidus to control advanced Parkinson's symptoms. Studies include 160 patients in the United States, Europe, Canada and Australia.

Activa Tremor Control Therapy approved in the United States for essential tremor and tremor in Parkinson's disease.

Activa Parkinson's Control Therapy available commercially in Europe, Canada and Australia for advanced Parkinson's disease motor symptoms.

Activa Parkinson's Control Therapy approved in the United States for advanced Parkinson's disease motor symptoms.

Activa Dystonia Therapy receives Humanitarian Device Exemption (HDE) from U.S. Food and Drug Administration for managing the symptoms of primary dystonia.

U.S. Food and Drug Administration designates Activa Therapy as a Humanitarian Use Device (HUD) for the treatment of chronic, treatment-resistant obsessive compulsive disorder (OCD).
Design of the Brain Pacemaker

Internal Components

1. Lead: insulated wire terminating with 4 electrodes
2. Extension: insulated wire that runs below the scalp, behind the ears, down the neck to the pacemaker
3. Pacemaker
   - 7.5 cms wide
   - 1.3 cms thick
   - Runs on a battery
1. A programmer that a physician uses to set the parameters of your pacemaker

2. Handheld magnet to turn the pacemaker on/off.
   - Can control parameters too
Patient injected with very little local anaesthesia
  - Patient is practically awake
Patient’s head is shaved
14 mm hole dug in the skull
Place electrodes in a specific region
  - Need patient response
Use extensions to connect electrodes to pacemaker placed in a ‘pocket’ under the clavicalar bone.
  - Patient under heavy anaesthesia
Stimulate What?

- Stimulate the Thalamus which is equivalent to Thalamotomy.
  - Relief of Essential Tremor

- Globus Pallidus equivalent to Pallidotomy
  - Relief of Parkinson’s

- Subthalamic Nucleus in the Globus Pallidus
  - Relief of Parkinson’s
Implementing the electrodes
MRI imaging
A stereotactic frame is attached to the patient’s head, and the coordinates of the target within the brain are determined relative to the frame’s 3D coordinates.
Record the activity of the GPi and GPe
Specific parts in nucleus activate certain parts of the body
- Communication between patient and doctor is compulsory at this point
- Number of trials
Optic Tract, beneath GPi
Internal Capsule which is posterior and medial to GPi
Contralateral or Bilateral
Target Localization
After targeted position has been found, electrode is placed with a tube that is then removed

4 Platinum Contacts
1.22 mm diameter and 1.5mm in height
Separated by 1.5 mm

\[ R = \frac{\text{Resistivity} \times \text{Length}}{\text{Area}} \]

Leads are then connected as previously stated to the Pacemaker, which the patient can control
Electrodes are placed in regions with heterogeneous populations of neural elements.

- may excite/block cells from A, and/or excite/block cells from B
- different effects of stimulation in cell body A and axon C of the same neuron!
- block or excite axon D
- At ‘E’ can influence both presynaptic and postsynaptic neural elements
- Current Intensity decreases with distance from electrode tip
- Excitability of axons is much more likely than excitability of cell bodies
- Largely myelinated axons are more excitable than less myelinated ones.
HYPOTHESIS:

- Generally, high frequency stimulation results in an override of the underlying pathological neural activity patterns
Frequency can range between 80Hz – 150Hz, depending on patient.

- High frequencies can cause dyskinesias.
- Low frequencies will have the opposite effect.
The amount of current delivered to the tissue is dependent on the electrode impedance. (2CI5, 2CJ4).

Impedance ranges from 500 – 1500 ohms
- What factors cause this variability?
- Research is being done; results obtained are shown next
Factors Contributing to Impedance Values

- \( R = \frac{(\text{Resitivity} \times L)}{\text{Area}} \)
- Assume leads are perfectly cylindrical.
  - Increased in Impedance \( \rightarrow \) Increase in Length of Lead
  - Lead breakage or other mechanical failure
  - Low currents will have minimal effect.
    - Current less than 15mA
- Very low impedance values (<50 ohms) \( \rightarrow \) high currents (0.25mA)
  - Possibility of short circuits
- Sensitive to contact length and diameter
Recall heterogeneous surrounding tissue

Conductivity = 1/Resistance; (of surrounding medium or material)

Increasing conductivity in the bulk tissue medium decreased impedance → larger current can pass, and Vice Versa

Increasing conductivity of the electrode lead encapsulation decreased impedance → larger currents can pass, and Vice Versa
1. **Impulsiveness**
   - Extended research and experiments have shown that patients that have implanted a brain pacemaker think without considering consequences

2. **Do not learn from mistakes**

3. **Surgical complications**
Other Techniques?

- Improved Brain Pacemaker

- Stem cell transplantation
  - involves implanting dopamine-producing cells into the brain to replace those that have been lost in PD

- Infusion of Growth factors
  - factors are infused into specific areas of the brain to stimulate growth of dopamine producing cells in these areas.
References

- Mechanisms of deep brain stimulation, Dostrovsky, Lozano
- Sources and effects of electrode impedance during deep brain stimulation, Butson, Macs, McIntyre
- Extracellular Excitation of Central Neurons, Grill, McIntyre
- The Globus Pallidus, Deep Brain Stimulation, and Parkinson’s Disease, Dostrovsky, Lozano
- Neuropharmacology: Optimizing bioavailability in the treatment of Parkinson's disease
- www.nature.com
- http://www.georgetownuniversityhospital.org/body.cfm?id=1290
- http://www.dukeresearch.duke.edu/database/pagemaker.cgi?992635986
- http://www.firstscience.com/home/articles/humans/deep-brain-stimulation-page-3-1_1299.html
- http://www.popsci.com/popsci/medicine/c0d6c4522fa84010vgnvcm1000004eebccdcrd.html
- http://www.time.com/time/magazine/article/0,9171,1214939,00.html
- http://thebrain.mcgill.ca/flash/a/a_06/a_06_cr/a_06_cr_mou/a_06_cr_mou.html#2
- http://thalamus.wustl.edu/course/cerebell.html