Brain Inhibition: Function, Disorders, and Therapeutic Targeting

By Kirill Zavalin, PhD Candidate
Vanderbilt Brain Institute
Objectives

• Understand the role inhibition plays in our brain
• Understand how inhibition works on the level of cells and synapses
• Learn of disorders that arise from improper inhibition
• Learn which drugs target the inhibitory system
Neurons Compose Our Brain

Lizzie Renck, 2015, https://dancingastronaut.com/2015/05/music-improves-cognitive-function-productivity-heres/
Neurons Communicate by Releasing Chemical Signals onto One Another
Circuits of Neurons in Our Brain Comprise a Complex, Interconnected System
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- Many different types of neurons
Circuits of Neurons in Our Brain Comprise a Complex, Interconnected System

- Many different types of neurons
- Many different brain regions
Inhibitory Cells Control Signal Transduction of Other Neurons
Local “Interneurons” Control Long-Range Signals Sent by Excitatory Cells


Hanns Mohler, 2002
Local “Interneurons” Control Long-Range Signals Sent by Excitatory Cells


Hanns Möhler, 2002

Feed-Forward Inhibition

**Excitation**

**Inhibitory interneuron**

**Excitation Comes to Inhibitory and Projecting Neuron**
Local “Interneurons” Control Long-Range Signals Sent by Excitatory Cells


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**Feed-Forward Inhibition**

- **Excitation**
- **Inhibitory interneuron**
  - Signal Is Passed On By Projection Neuron

Hanns Möhler, 2002
Local “Interneurons” Control Long-Range Signals Sent by Excitatory Cells

Feed-Forward Inhibition

Inhibitory Neuron Shuts Off Projection Neuron


Hanns Möhler, 2002
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Feedback Inhibition

Projecting Neuron Receives Excitatory Signal

Hanns Möhler, 2002
Local “Interneurons” Control Long-Range Signals Sent by Excitatory Cells


Feedback Inhibition

Signal Is Passed On By Projection Neuron

BUT also activates an inhibitory neuron
Local “Interneurons” Control Long-Range Signals Sent by Excitatory Cells

Feed-Forward and Feedback Inhibition Are Common Motifs Used to Regulate Circuits of Neurons

Roles of Inhibition in the Central Nervous System

• Involved in most neural circuits
• Regulates which signals are sent
• Works to prevent anxiety and seizure activity
• Cortex: interneurons regulate projection neurons
• Basal Ganglia: long-range inhibitory signals regulate movement initiation
• Thalamus: inhibition disconnects cortex from sensory signals
• Spinal Cord: interneurons inhibit motor neurons to relax muscles
• Involved in other circuits too
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Regions Outside of Cortex Can Send Long-Range Inhibitory Signals

Hanjing Emily Wu et al, 2018

https://scienceofpd.files.wordpress.com/2016/02/pathways.jpg?w=830
Basal Ganglia Controls Movement Initiation Through Inhibition

Excitation
Inhibition

Dopamine

Normal

Hanjing Emily Wu et al, 2018

https://scienceofpd.files.wordpress.com/2016/02/pathways.jpg?w=830
Basal Ganglia Controls Movement Initiation Through Inhibition

Regions of basal ganglia communicate with inhibitory cues to initiate movement
Parkinson’s Disease: Movement Initiation is Prevented by Increased Inhibition of Thalamus by Basal Ganglia
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![Diagram showing normal and Parkinson's disease pathways](https://scienceofpd.files.wordpress.com/2016/02/pathways.jpg?w=830)
Parkinson’s Disease: Movement Initiation is Prevented by Increased Inhibition of Thalamus by Basal Ganglia

In normal conditions, the thalamus excites the cortex to initiate movement. However, in Parkinson's disease, the inhibition of the thalamus is too strong, preventing the thalamus from exciting the cortex. As a result, the cortex cannot tell the muscle to contract, leading to movement initiation problems.
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Many Diseases and Disorders Occur Because of Disrupted Inhibition

• Epilepsy
• Anxiety Disorders
• Sleep Disorders
• Schizophrenia
• Autism Spectrum Disorders
How Inhibitory Signaling Occurs: Neurotransmitter GABA Activates GABA Receptors

Bg Patel, 2015
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How Inhibitory Signaling Occurs: Neurotransmitter GABA Activates GABA Receptors

GABA (gamma-aminobutyric acid)

$\text{HO} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{NH}_2$

Bg Patel, 2015
How Inhibitory Signaling Occurs: Neurotransmitter GABA Activates GABA Receptors

GABA (gamma-aminobutyric acid)

GABA Receptors
- GABA\textsubscript{A} receptor
- GABA\textsubscript{B} receptor

BG Patel, 2015
How Inhibitory Signaling Occurs: Neurotransmitter GABA Activates GABA Receptors

GABA (gamma-aminobutyric acid)

Presynaptic nerve terminal

GABA Receptors

- GABA<sub>A</sub> receptor
- GABA<sub>B</sub> receptor

Postsynaptic neuron

Synaptic (IPSC)

Extrasynaptic (tonic current)

Bg Patel, 2015
GABA_\text{A} Receptors Mediate Quick Inhibitory Signals

Jacob et al, 2008

Bg Patel, 2015
GABA\textsubscript{A} Receptors Mediate Quick Inhibitory Signals

- Formed from Five Different Pieces ("Subunits")
- 19 known subunits make many combinations possible
  - Different combinations work differently
- Some drugs selectively target specific combinations

Jacob et al, 2008
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Mutations in GABA$_A$ Receptor Subunits Are Often Causes of Genetic Epilepsies

GABA noncoding region mutations:

- $\gamma_2$(IVS6+2T→G)
  - CAE, FS
- GABBR3 exon 1a haplotype 2 promoter
  - CAE
- $\gamma_2$ (Q390X)
  - GEFS+, FS, Dravet syndrome

Modified from Macdonald et al., J Physiol, 2010
Defective GABA Receptors Can Create Too Little Inhibition, Causing an Imbalance in Neural Circuits That Can Cause Seizures
Seizure Medication Restores Balance By Decreasing Excitation or Increasing Inhibition

- Excitation
- Inhibition

Action of Anti-seizure Drugs:
- Decrease Activity of:
  - Voltage-gated Sodium Channels
  - Voltage-gated Calcium Channels
  - Glutamate Receptors

Increase GABA Receptor Transmission
Abnormal Inhibitory Function in Prefrontal Cortex Might Cause the Cognitive Disturbances in Schizophrenia
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GABA_A receptors
Target of Many of Our Most Useful Medications
GABA_A receptors
Target of Many of Our Most Useful Medications

Valium (anxiolytic, sedative, antiseizure)

Diazepam

Alcohol

Ethanol

Neurosteroid

5α-pregn-3α-ol-20-one

Inhaled Anesthetic

S-Isoflurane

IV Anesthetics

R-(-)-Etomidate

Propofol

Barbiturate Anesthetic

Thiopental

Jacob et al, 2008; Andre Lagrange presentation
GABA<sub>A</sub> receptors
Target of Many of Our Most Useful Medications

Valium (anxiolytic, sedative, antiseizure)

Many of these have different binding sites!

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Jacob et al, 2008; Andre Lagrange presentation
GABA$_A$ receptors
Target of Many of Our Most Useful Medications

- Many of these have different binding sites!

- Target different subunit combinations
- Have different effect (anxiolytic/sedative vs anesthesia).

Valium (anxiolytic, sedative, antiseizure)

Alcohol

Diazepam

Neurosteroid

Inhaled Anesthetic

IV Anesthetics

Barbiturate Anesthetic

Jacob et al, 2008; Andre Lagrange presentation
During Embryonic Development, GABA$\textsubscript{A}$ Receptors Are Actually Excitatory!
If this condition occurs in the adult brain, it can cause epilepsy (for instance, this contributes to temporal lobe epilepsy)
Summary

• Specialized neurons inhibit other neurons by releasing neurotransmitter GABA to activate inhibitory GABA receptors

• Inhibition 1) sends signals and 2) regulates other neurons
  • Cortex and throughout CNS: Interneurons regulate signal transmission of projecting neurons
  • Thalamus: controls relay of sensory information (sleep and attention)
  • Basal Ganglia: controls movement initiation
  • Spinal Cord: relaxes muscles
  • Many other examples
Summary

- Specialized neurons inhibit other neurons by releasing neurotransmitter GABA to activate inhibitory GABA receptors.
- Inhibition 1) sends signals and 2) regulates other neurons.
- If inhibition goes wrong:
  - Anxiety
  - Sleep Disorders
  - Epilepsy
  - Schizophrenia
  - Autism Spectrum Disorders
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- Inhibition 1) sends signals and 2) regulates other neurons
- If inhibition goes wrong:
  - Anxiety
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  - Epilepsy
  - Schizophrenia
  - Autism Spectrum Disorders
- Many drugs target GABA$_A$ receptors (sedative, anxiolytic, muscle relaxant, anti-seizure, anesthesia)
  - Alcohol
  - Benzodiazepines (e.g. Valium)
  - Barbiturates
  - Neurosteroids (Progesterone)
  - Anesthetics (Propofol)
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- Many drugs target GABA\textsubscript{A} receptors (sedative, anxiolytic, muscle relaxant, anti-seizure, anesthesia).
- Drugs can also target other parts of GABA signaling machinery:
  - GABA\textsubscript{B} receptors
  - Machinery that regulates how much GABA is released by inhibitory cells.
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• Drugs can also target other parts of GABA signaling machinery
  • GABA$_B$ receptors
  • Machinery that regulates how much GABA is released by inhibitory cells

• GABA is excitatory during brain development and in epileptic neurons
Thank you for your time! Questions?