GABA 101

Dr. Amanda Freeman

Outline

• How do neurons communicate?
• Where does GABA come from?
• How does GABA inhibit neurons?
• How do drugs alter GABA activity?
• What does GABA have to do with sleep?
Contains 100,000,000,000 neurons

http://d32ogoqmya1dw8.cloudfront.net/images/genomics/units/hippocampus_nissl.jpg
Presynaptic neuron

Postsynaptic neuron

Synapse

Presynaptic neuron

Neurotransmitter binds to postsynaptic receptor

Postsynaptic neuron
Excitatory neurotransmitters drive activity in the postsynaptic neuron.

Inhibitory neurotransmitters decrease activity in the postsynaptic neuron.
**l-Glutamic acid (Glutamate)**

is the principle *excitatory* neurotransmitter

Percentage of all synapses
- Glutamate: 50%

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**γ-aminobutyric acid (GABA)**

is the principle *inhibitory* neurotransmitter*

Percentage of all synapses
- Glutamate
- GABA: 40%

*Glycine is another inhibitory neurotransmitter, but is predominately located in the spinal cord*
Other neurotransmitters can be **excitatory** or **inhibitory** depending upon the receptor present

**Percentage of all synapses**

- Glutamate
- GABA
- Acetylcholine (5%)
- Dopamine (1%)
- Norepinephrine (1%)
- Serotonin (1%)
- Other (2%)

Where does GABA come from?
GLUTAMINE

- Major amino acid
- Made by the body or taken in through the diet
- Stored in glial cells

GLUTAMINE

GLUTAMATE
How does GABA inhibit neurons?

Decarboxylation by l-glutamic acid decarboxylase (GAD)
Different Types of GABA Receptors

$\text{GABA}_A$  $\text{GABA}_C$

Inside neuron

Outside neuron

Chloride (Cl$^-$)

Important target for
- Tranquilizers
- Anesthetics
- Anticonvulsants
Different Types of GABA Receptors

- $\text{GABA}_A$
- $\text{GABA}_C$
- $\text{GABA}_B$

Inside neuron: $\text{GABA}_B$

Potassium ($K^+$) outside neuron

Important target for
- Muscle Relaxants
- Antiepileptics
How do drugs alter GABA activity?

$\text{GABA}_A$ Receptor

*From the side*

*From the top*

$\text{GABA}_A$ Receptor

$\star \text{GABA binding sites}$

*From the side*

*From the top*
GABA_\text{A} Receptor

**Ethanol and volatile anesthetic binding sites**

From the side

From the top

GABA_\text{A} Receptor

**Benzodiazepine binding site**

From the side

From the top
<table>
<thead>
<tr>
<th>GABA&lt;sub&gt;A&lt;/sub&gt; receptor subtype</th>
<th>Percentage of all GABA&lt;sub&gt;A&lt;/sub&gt; receptors</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>α&lt;sub&gt;1&lt;/sub&gt; (α&lt;sub&gt;3&lt;/sub&gt;β&lt;sub&gt;2&lt;/sub&gt;γ&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>60%</td>
<td>Anesthetics Sedation* Amnesia* Anticonvulsant*</td>
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<tr>
<td>α&lt;sub&gt;2&lt;/sub&gt;</td>
<td>15-20%</td>
<td>Anxiolytic*</td>
</tr>
<tr>
<td>α&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10-15%</td>
<td>Muscle relaxation* Anxiolytic*</td>
</tr>
<tr>
<td>α&lt;sub&gt;5&lt;/sub&gt;</td>
<td>&lt;5%</td>
<td>Learning and Memory</td>
</tr>
</tbody>
</table>

* Effects of Benzodiazepines


What does GABA have to do with sleep?

Wake Promoting

- Histamine
- Serotonin
- Norepinephrine
- Acetylcholine
- Hypocretin/Orexin
Sleep Promoting

GABA
From Ventrolateral Preoptic Area (VLPO)

Modulation of Vigilance in the Primary Hypersomnias by Endogenous Enhancement of GABA<sub>A</sub> Receptors

David B. Rye,¹,² Donald L. Blwise,¹ Kathy Parker,² Lynn Marie Trottii,¹ Prabhjyot Saini,¹ Jacqueline Fairley,¹ Amanda Freeman,¹ Paul S. Garcia,²,³ Michael J. Owens,⁵
James C. Ritchie,⁶ Andrew Jenkins,²,³,⁷


Wake
Histamine
Serotonin
Norepinephrine
Acetylcholine
Hypocretin/Orexin

Sleep
GABA
Summary

- GABA is the principle inhibitory neurotransmitter in the brain
- The influx of Cl- (or outflux of K+) makes neurons less likely to be activated
- Function and localization of GABA receptors varies based upon the subtype
- GABA promotes sleep through inhibition of wake promoting brain regions