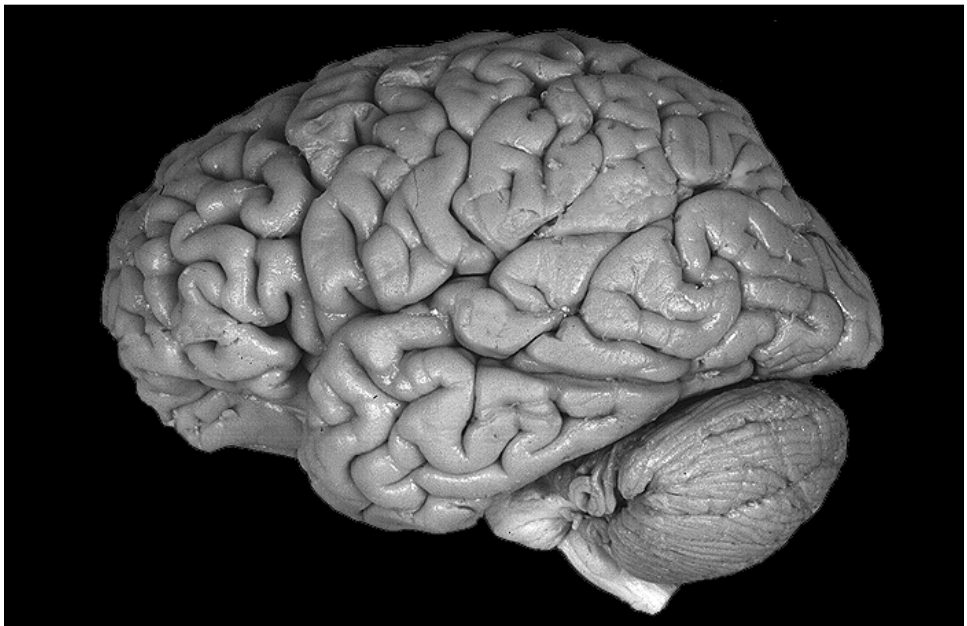
GABA 101

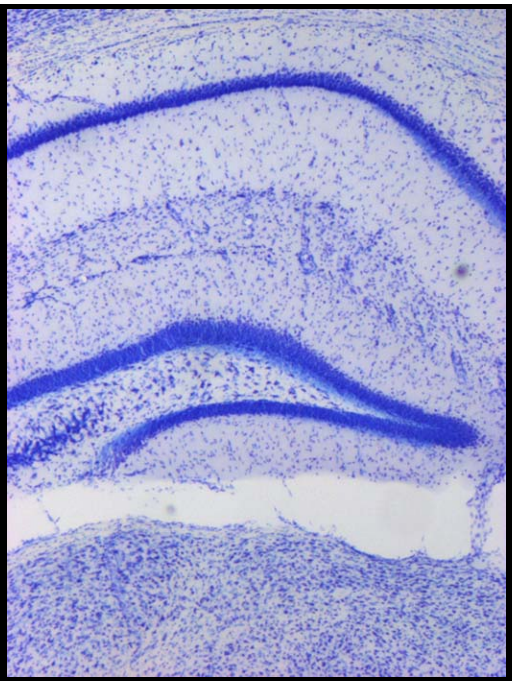
Dr. Amanda Freeman

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?

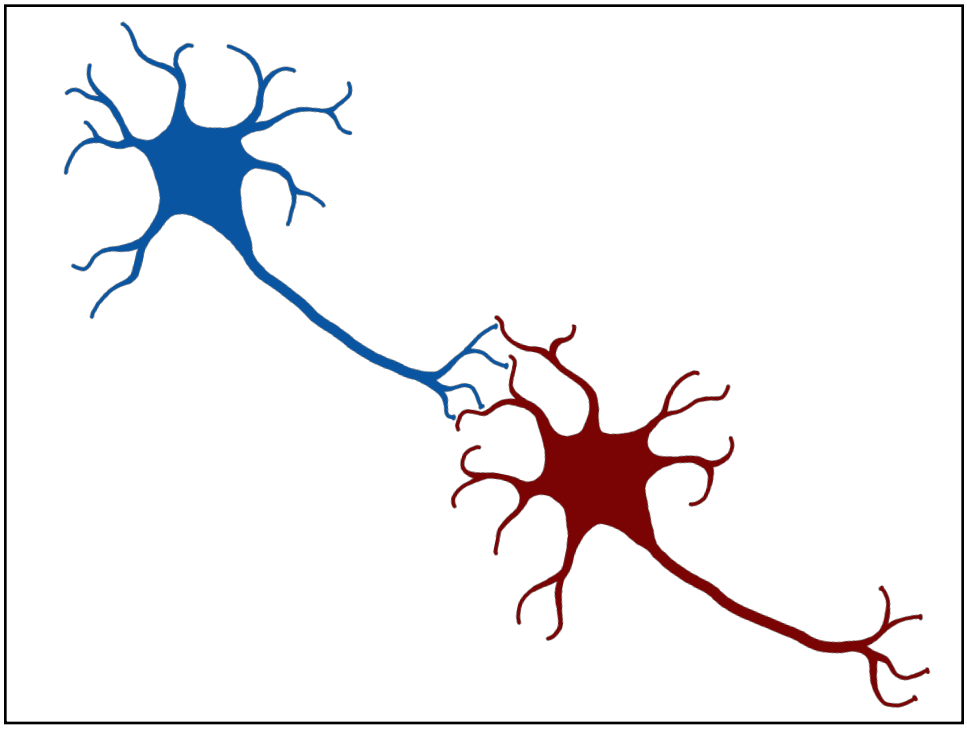


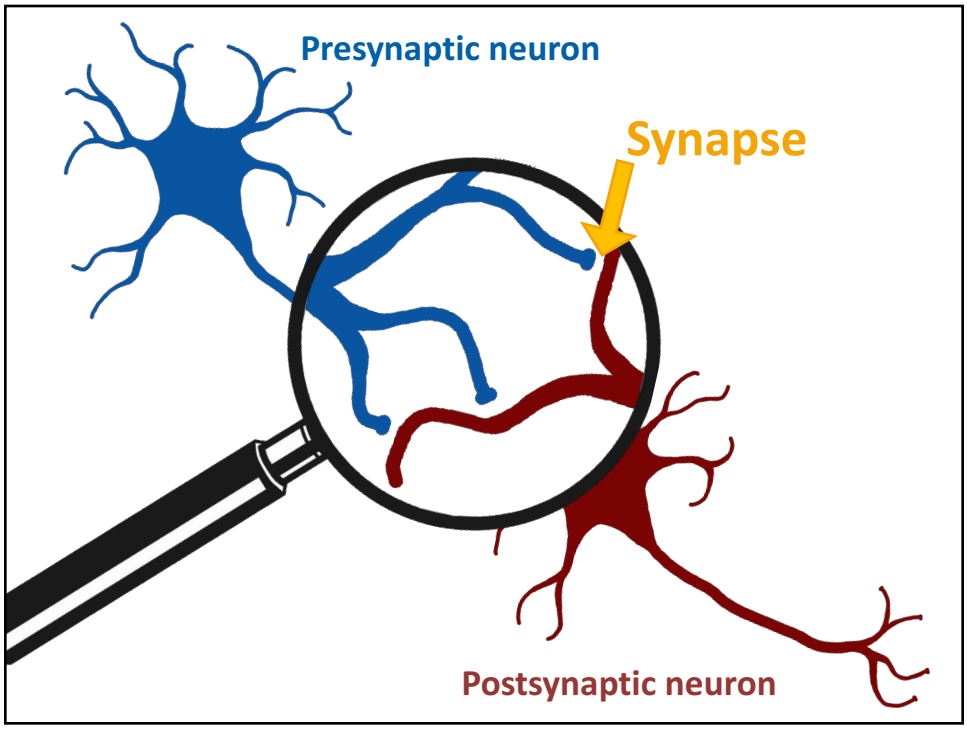
Contains **100,000,000,000** neurons

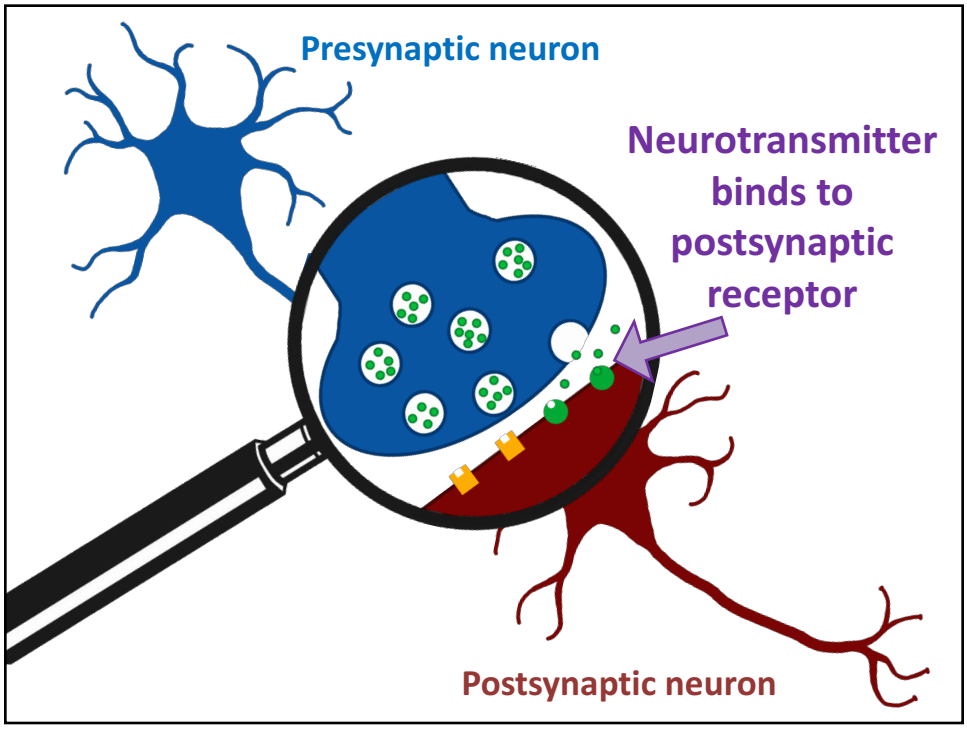


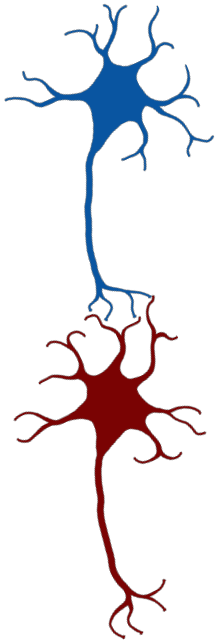
http://d32ogoqmya1dw8.cloudfront.net/images/genomics/units/hippocampus_nissl.jpg

http://vanat.cvm.umn.edu/neurHistAtls/pages/images/Neuron3.jpg

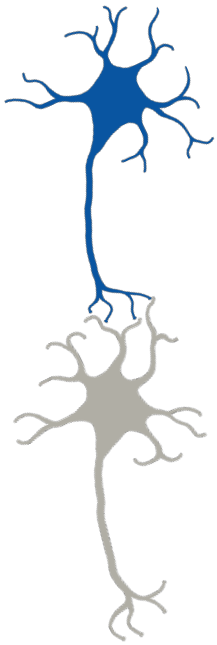



Presynaptic neuron
Synapse
Postsynaptic neuron


Presynaptic neuron
Neurotransmitter binds to postsynaptic receptor
Postsynaptic neuron



Excitatory
neurotransmitters
drive activity
in the postsynaptic
neuron

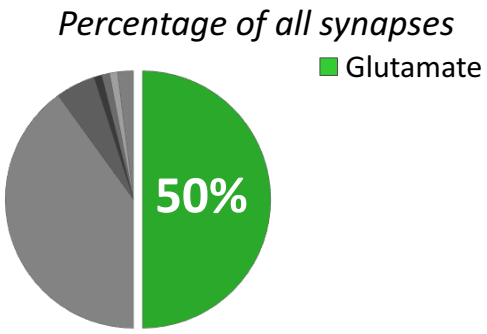


Inhibitory
neurotransmitters
decrease activity
in the postsynaptic
neuron

l-Glutamic acid (Glutamate)

is the principle

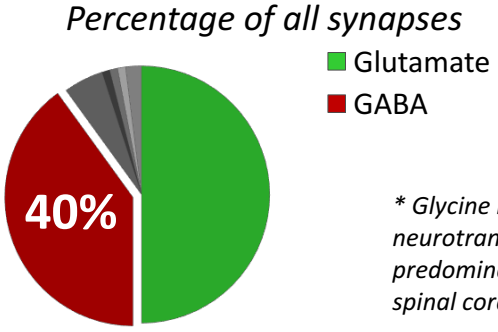
excitatory neurotransmitter



γ-aminobutyric acid (GABA)

is the principle

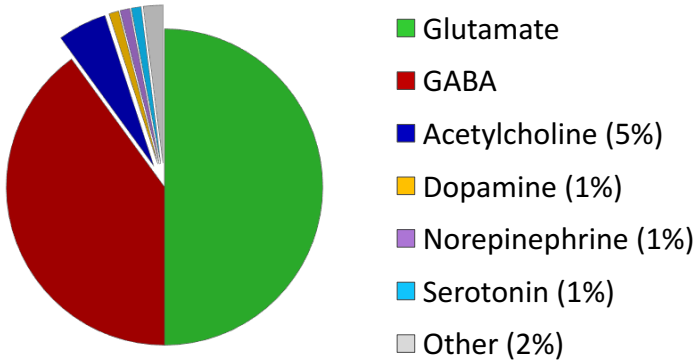
inhibitory neurotransmitter*



** 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



Where does GABA come from?

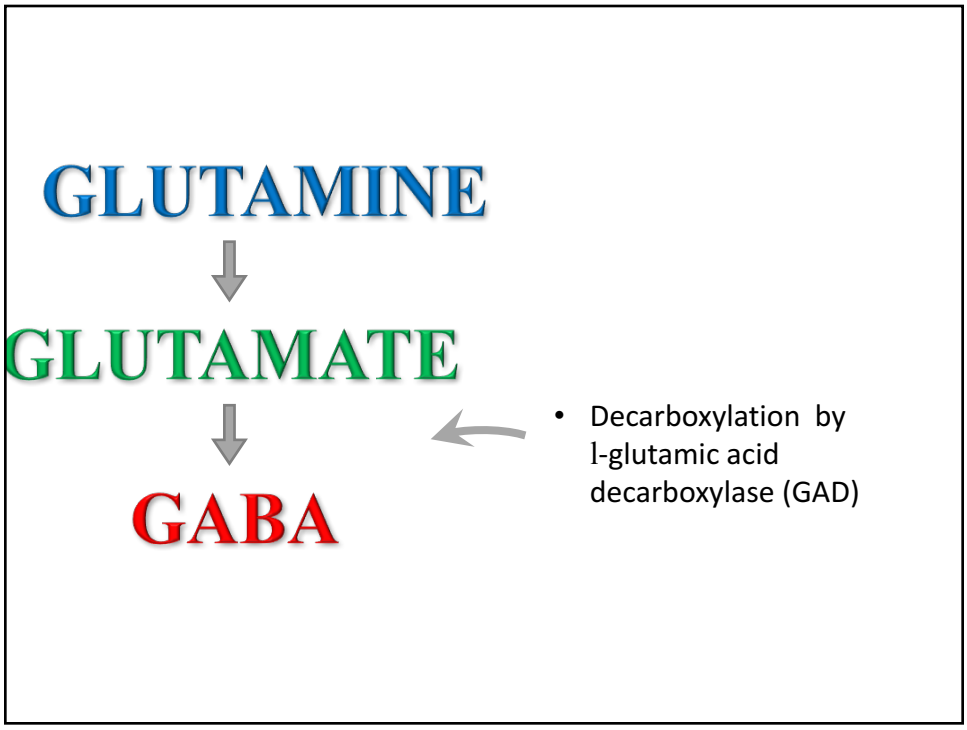
GLUTAMINE

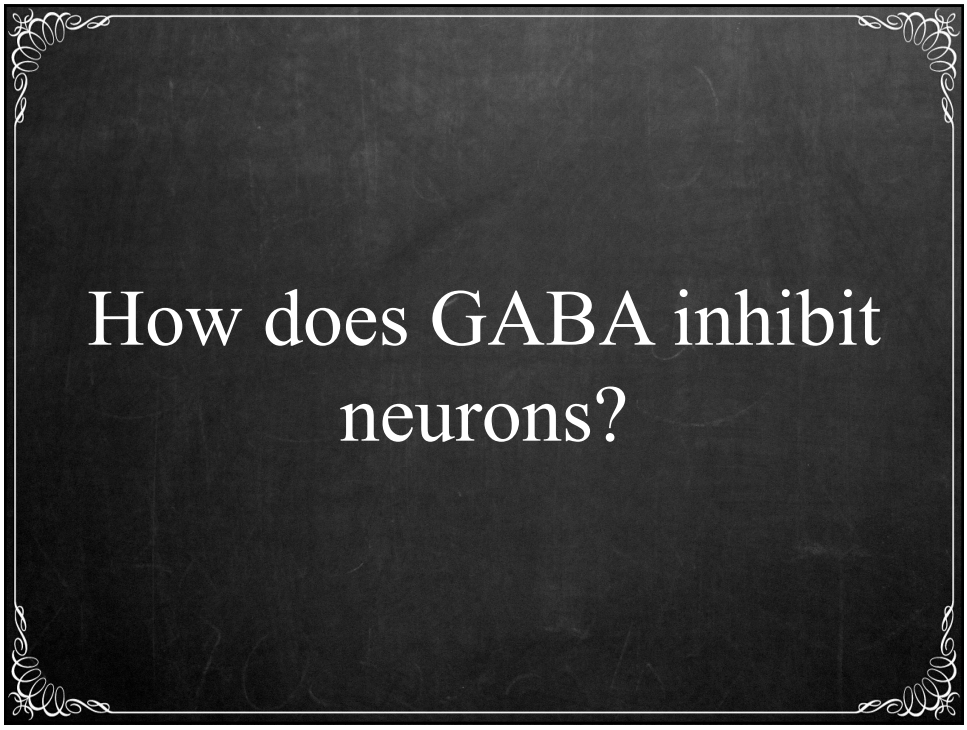
- Major amino acid
- Made by the body or taken in through the diet
- Stored in glial cells

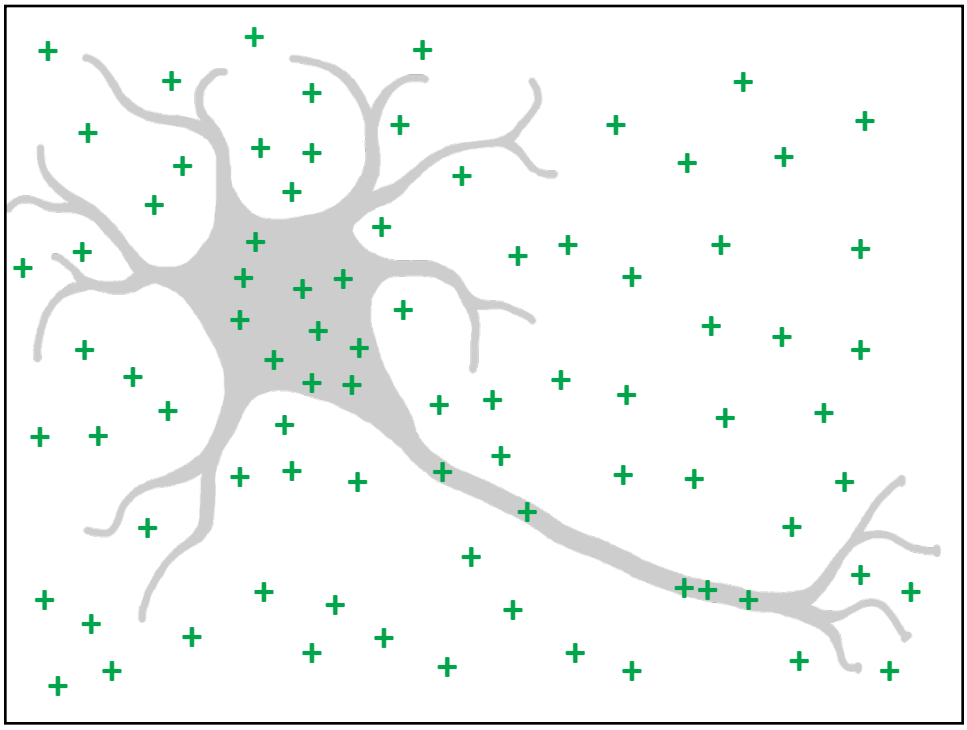
GLUTAMINE

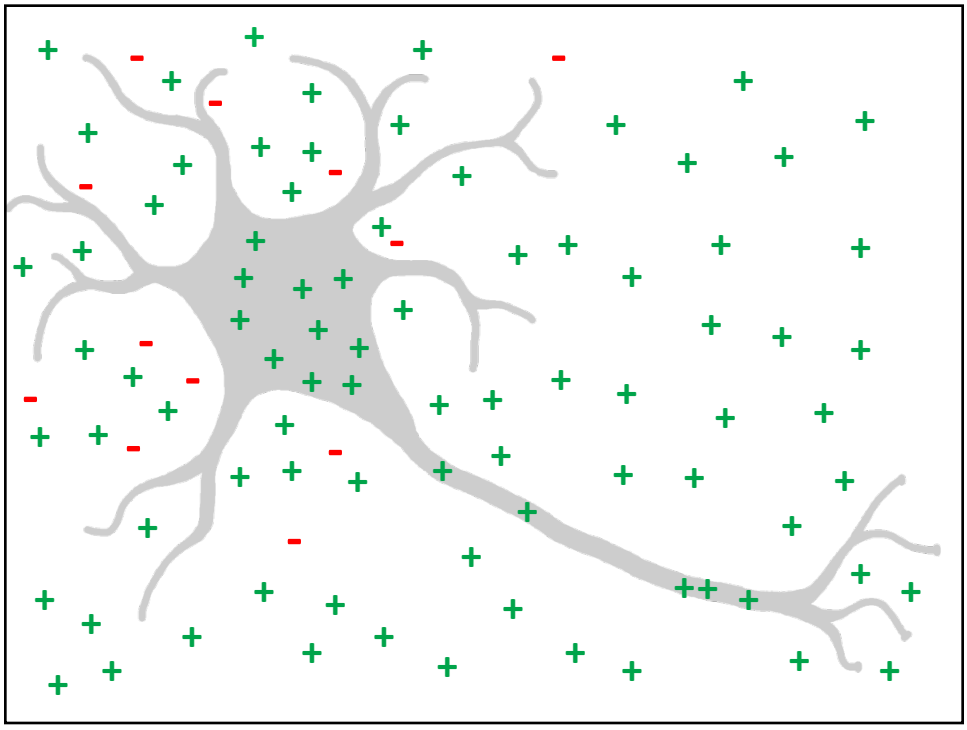
↓

GLUTAMATE

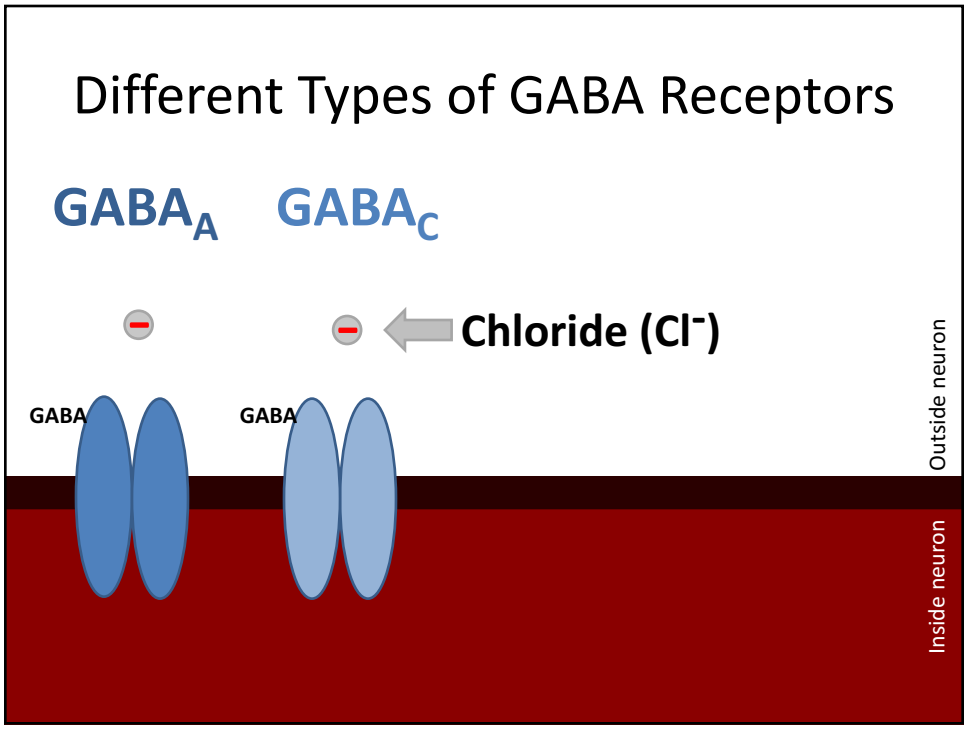

GLUTAMINE
GLUTAMATE
GABA
• Decarboxylation by l-glutamic acid decarboxylase (GAD)

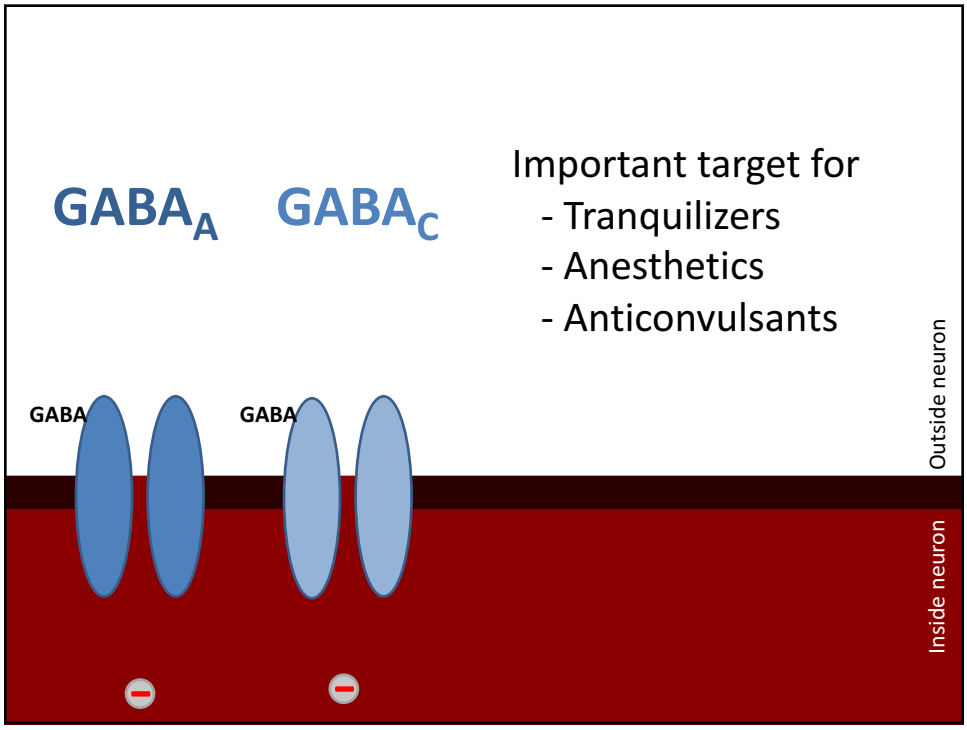

How does GABA inhibit neurons?

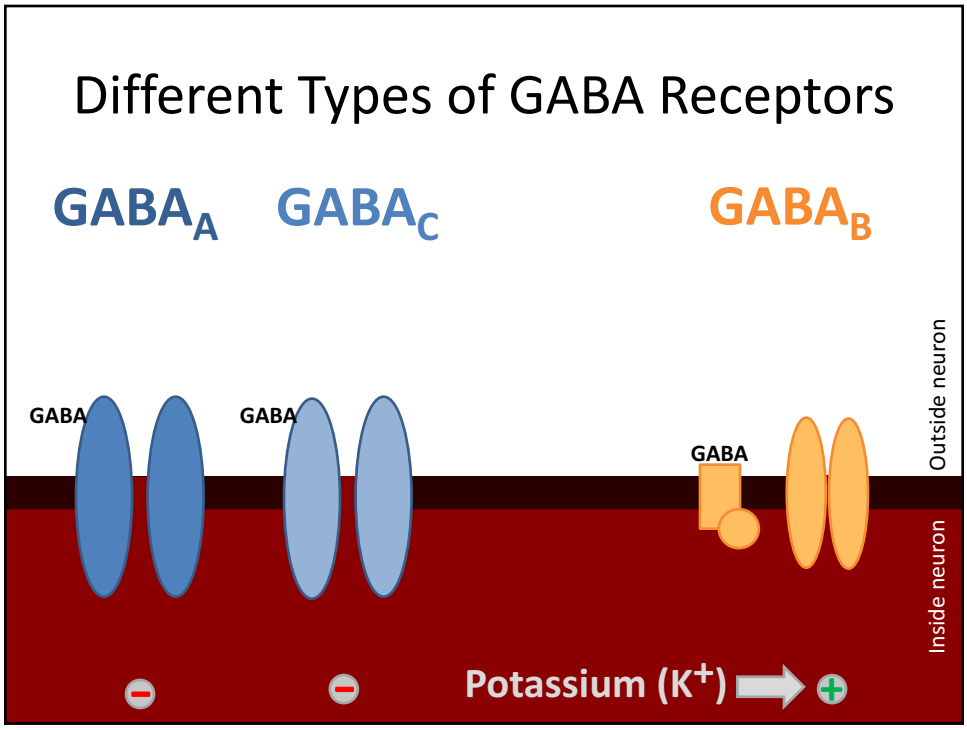


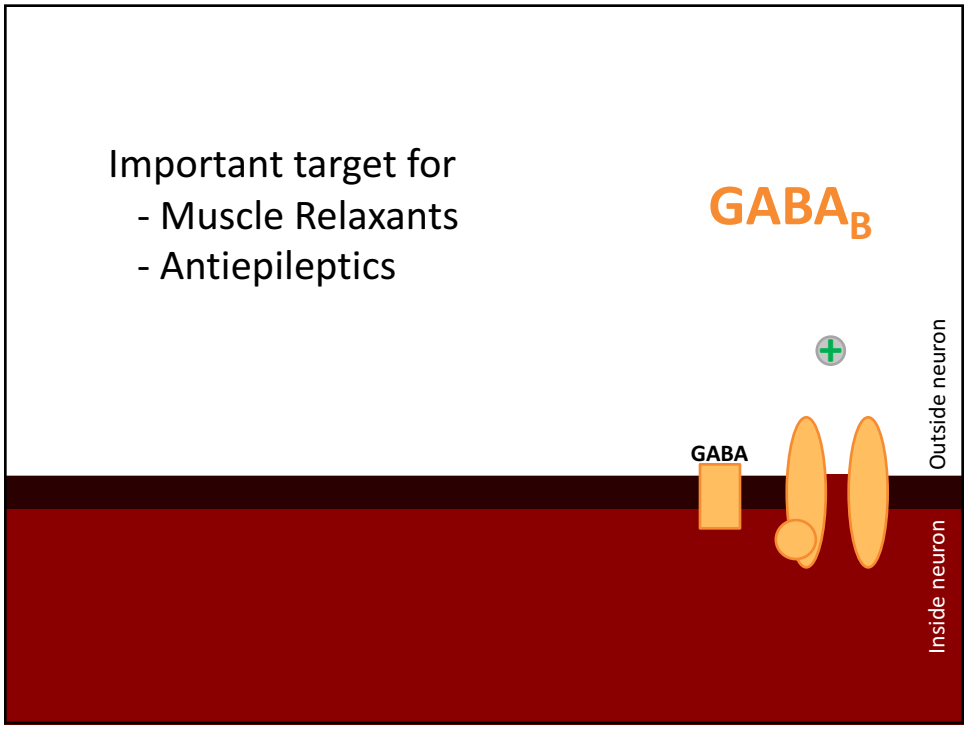


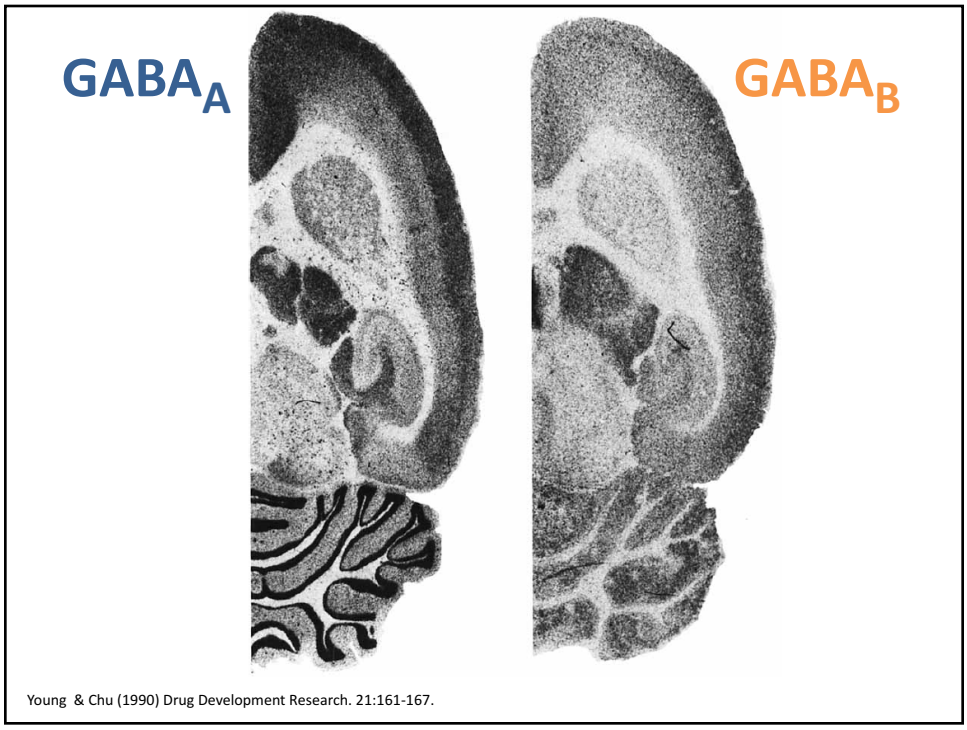
Different Types of GABA Receptors






Different Types of GABA Receptors
GABA$_A$
GABA$_C$
GABA$_B$
GABA
GABA
GABA
Outside neuron
Inside neuron
Potassium (K^+)

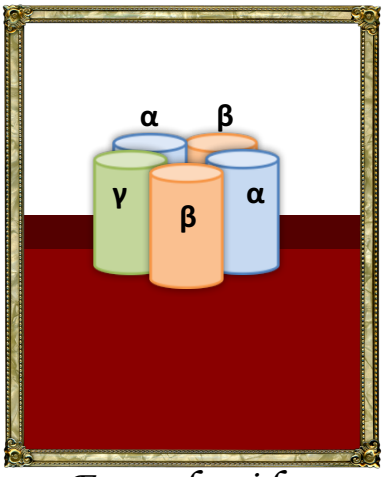

Important target for
- Muscle Relaxants
- Antiepileptics
GABA$_B$
GABA
Outside neuron
Inside neuron



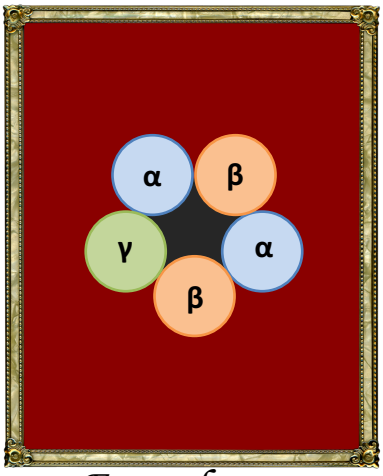
Young & Chu (1990) Drug Development Research. 21:161-167.

How do drugs alter GABA activity?

$GABA_A$ Receptor



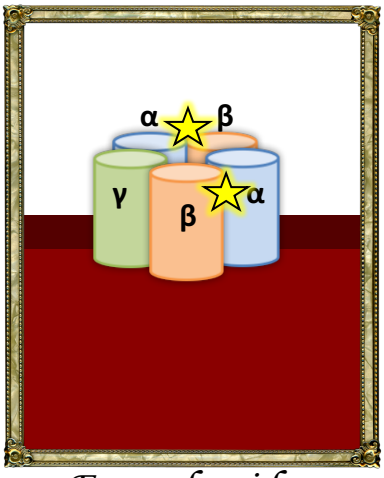
From the side



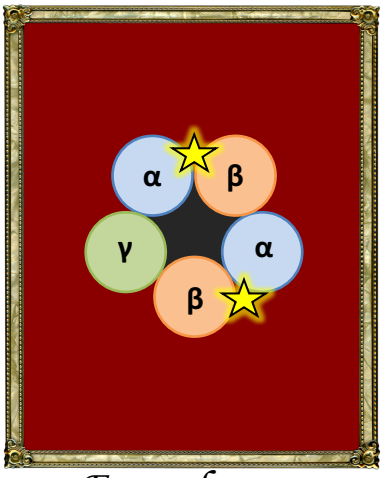
From the top

$GABA_A$ Receptor

☆ *GABA binding sites*



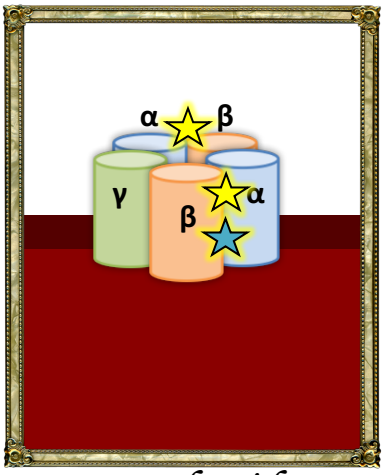
From the side



From the top

$GABA_A$ Receptor

★ *Ethanol and volatile anesthetic binding sites*



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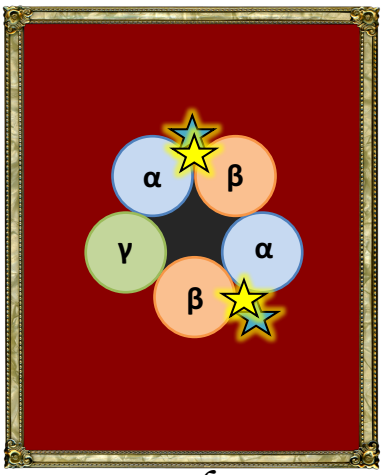
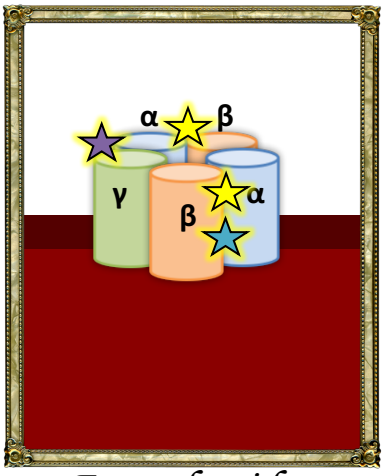


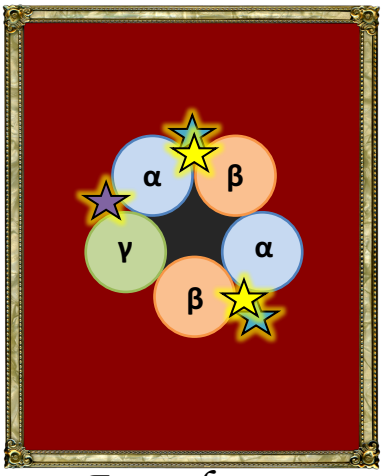
From the top

$GABA_A$ Receptor

★ *Benzodiazepine binding site*



From the side



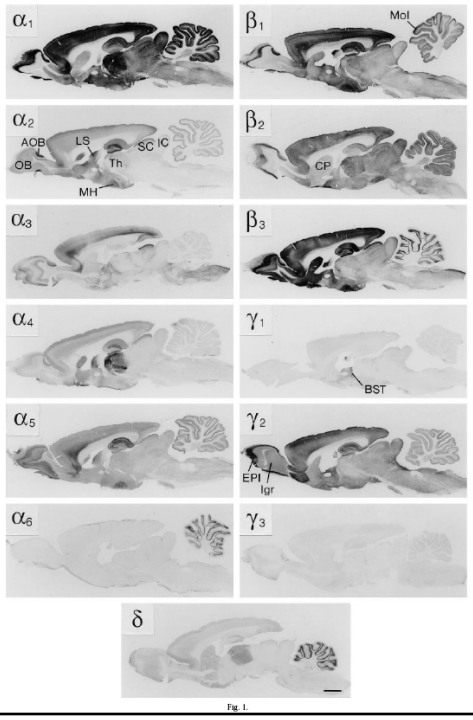
From the top

$GABA_A$ receptor subtype	Percentage of all $GABA_A$ receptors	Function
α_1 ($\alpha_1\beta_2\gamma_2$)	60%	Anesthetics Sedation* Amnesia* Anticonvulsant*
α_2	15-20%	Anxiolytic*
α_3	10-15%	Muscle relaxation* Anxiolytic*
α_5	<5%	Learning and Memory

* *Effects of Benzodiazepines*

Based upon Nutt (2006) Journal of Clinical Sleep Medicine, 2(2):S7-S11.

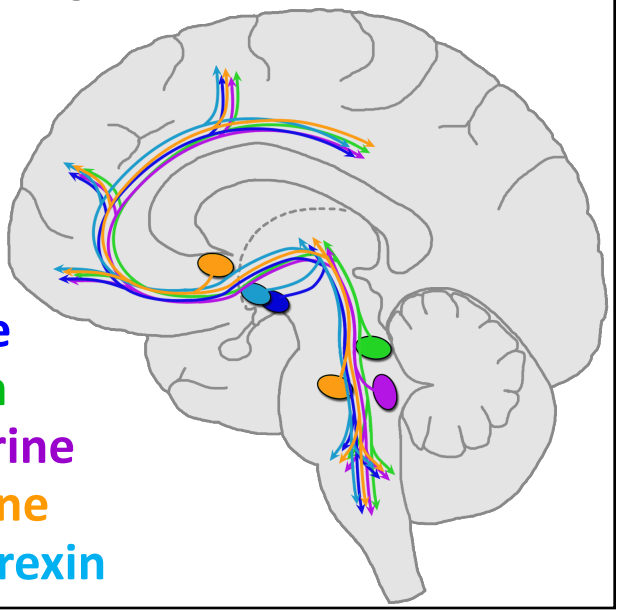
$GABA_A$ receptor subunits



Pirker et al. (2000) Neuroscience . 101(4):815-850.

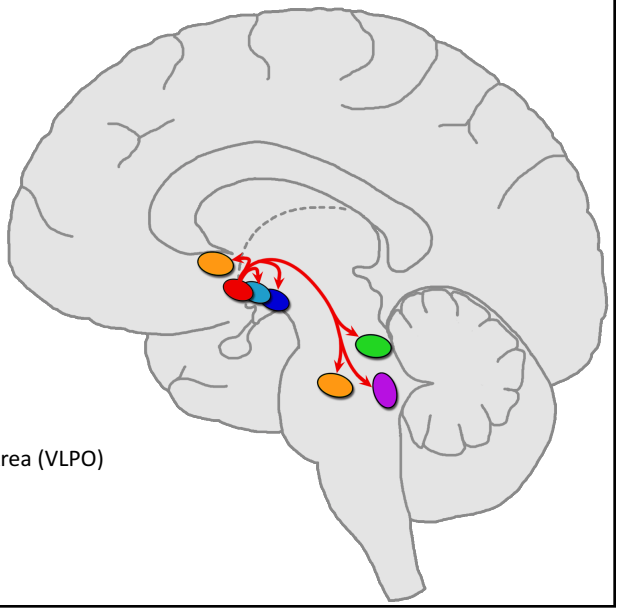
What does GABA have to do with sleep?

Wake Promoting



Histamine
Serotonin
Norepinephrine
Acetylcholine
Hypocretin/Orexin

Sleep Promoting



GABA

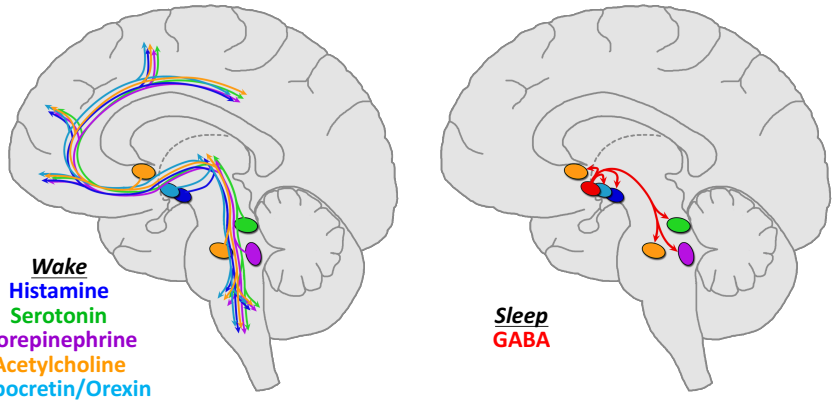
From Ventrolateral Preoptic Area (VLPO)

SLEEP

Modulation of Vigilance in the Primary Hypersomnias by Endogenous Enhancement of $GABA_A$ Receptors

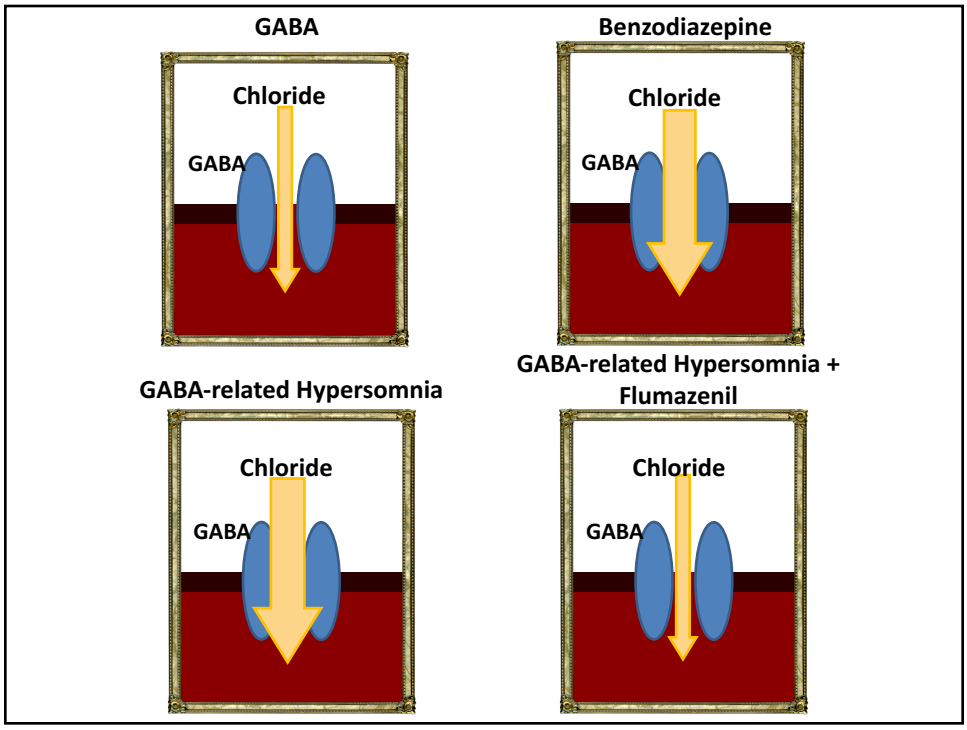
David B. Rye,[1]* Donald L. Bliwise,[1] Kathy Parker,[2] Lynn Marie Trotti,[1] Prabhjyot Saini,[1] Jacqueline Fairley,[1] Amanda Freeman,[1] Paul S. Garcia,[3,4] Michael J. Owens,[5] James C. Ritchie,[6] Andrew Jenkins[3,7]

(2012) Science Translational Medicine 4(161):161ra151



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