Drugs and the Brain

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ESP Splash (Saturday)

These slides are available online, along with fun 5-minute quizzes and other materials:

http://datb.mit.edu/

Are You in the Right Room?

This is **Drugs and the Brain (DATB),** if you are supposed to be somewhere else you may leave now.

Please Reuse These Slides

Outline

1. How the Brain Works
2. Terminology
3. Specific Neurotransmitters

   Glutamate (Glu), GABA, serotonin (5-HT), norepinephrine (NE), dopamine (DA), opioids

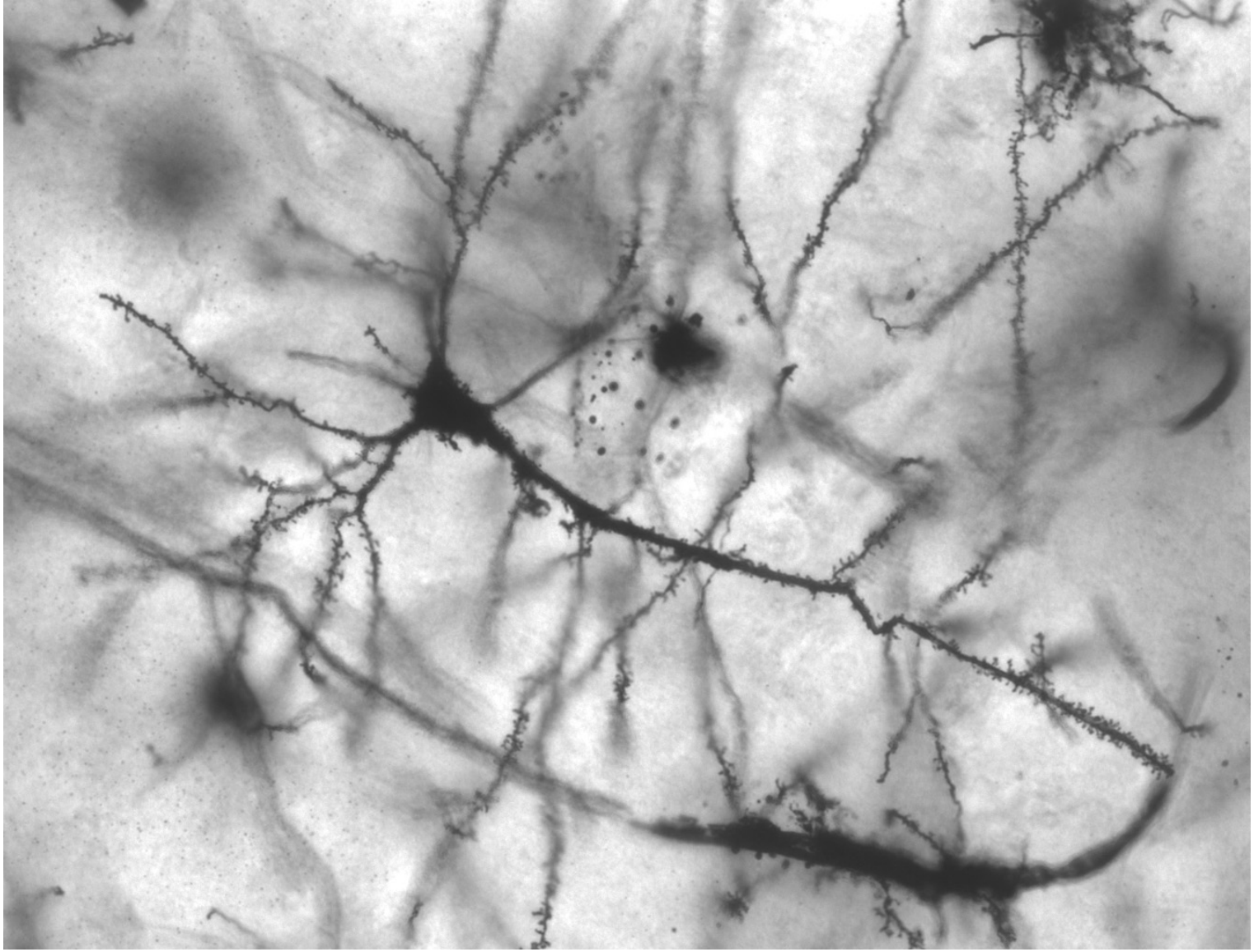
4. Drug Mechanisms
5. Addiction

How the Brain Works

200 billion neurons (brain cells)

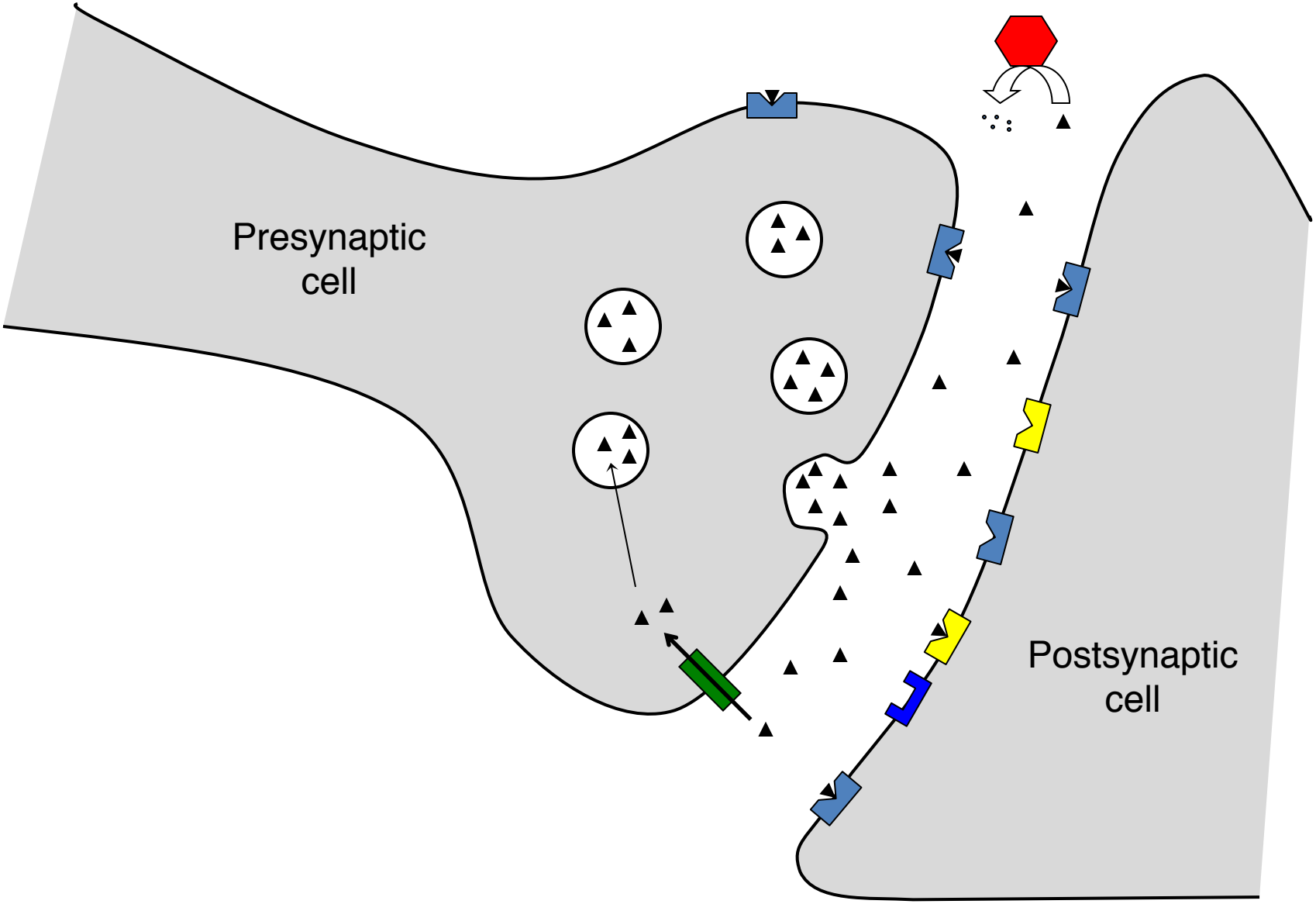
Roughly 1,000 synapses per neuron, but highly variable. The pyramidal cells in the cerebral cortex often have 10,000 synapses.

125 trillion synapses in the cerebral cortex alone



One pyramidal neuron from the hippocampus of a human.
CC-BY-SA by MethoxyRoxy, source.

One Synapse



Action Potentials

Neurons make computations and send signals using electrical signals called **action potentials.**

Information is encoded in the frequency of action potentials.

Millions of synchronized action potentials cause **brain waves,** which are voltage changes on the scalp measured by EEG.

Neurotransmitters

A neurotransmitter is a chemical released by one neuron to transmit a message to another neuron.

Neurotransmitters travel across the synapse.

There is a muddy line between neurotransmitters and **hormones,** and many chemicals are both.

Receptors

Receptors are proteins (large molecules) that bind to neurotransmitters and drugs and pass along the signal.

Neurotransmitters and drugs are called **ligands** because they bind to receptors. *Ligand* comes from the Latin *ligare*, to bind or tie, and it is a cognate with *ligament* and *ligature*.

Receptors

A ligand (neurotransmitter or drug) fits inside a receptor **like a key inside a lock.** The fit is very specific, most molecules do not fit most receptors.

Receptors are **chemical sensors,** just like:

- Pregnancy tests
- Litmus paper
- Your taste buds
- Your nose

Excitatory vs. Inhibitory

Excitatory: Tends to increase action potential firing.

Inhibitory: Tends to decrease or block action potentials.

Receptors are classified as excitatory or inhibitory. Some neurotransmitters can be classified this way, but many are both.

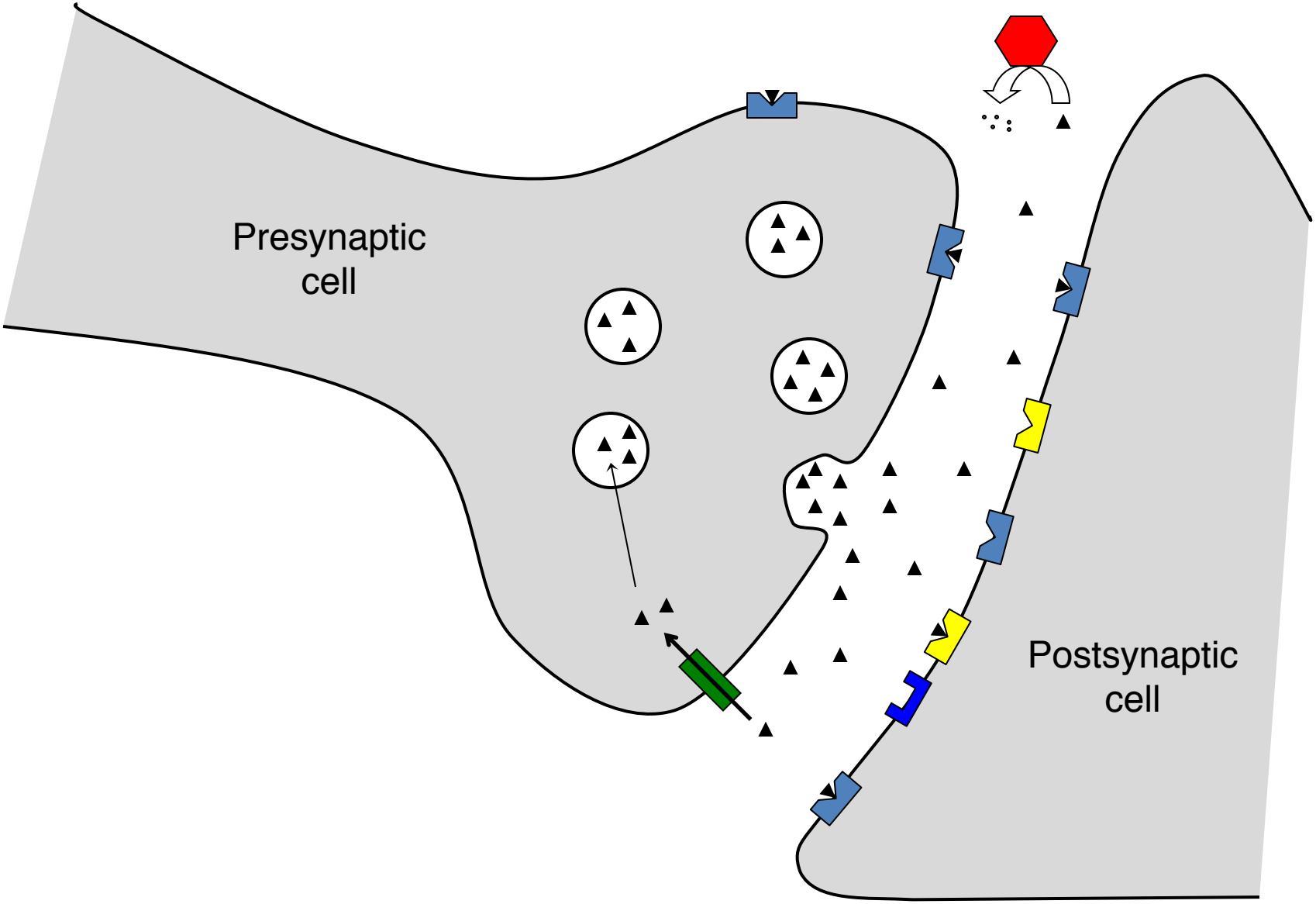
Agonist vs. Antagonist

Agonist: Binds to a receptor and sends the “normal” signal (either excitatory or inhibitory).

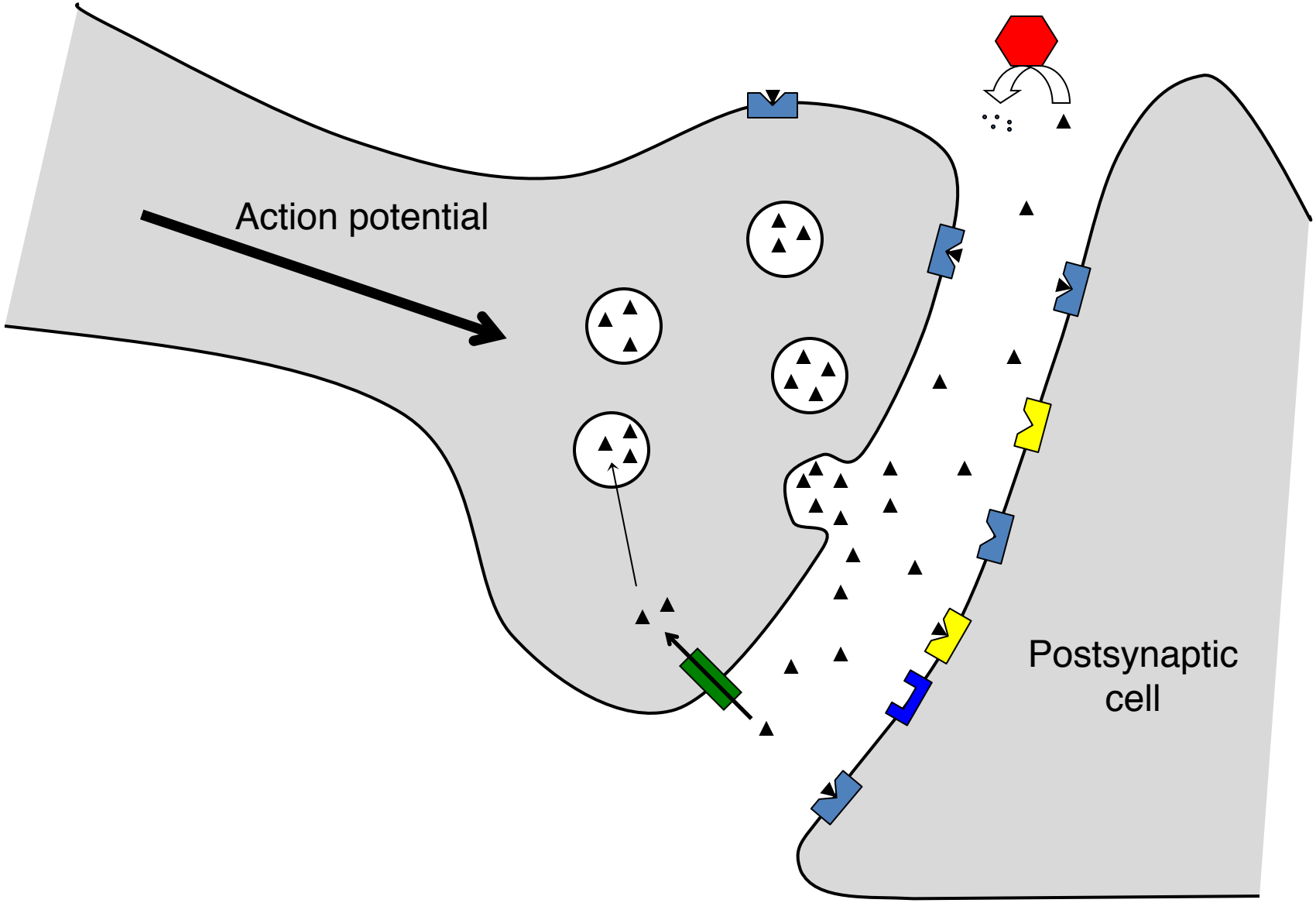
Antagonist: Binds to a receptor and *does not* send a signal. Antagonists block receptors and prevent agonist binding.

A ligand can be classified as an agonist or antagonist at a particular receptor.

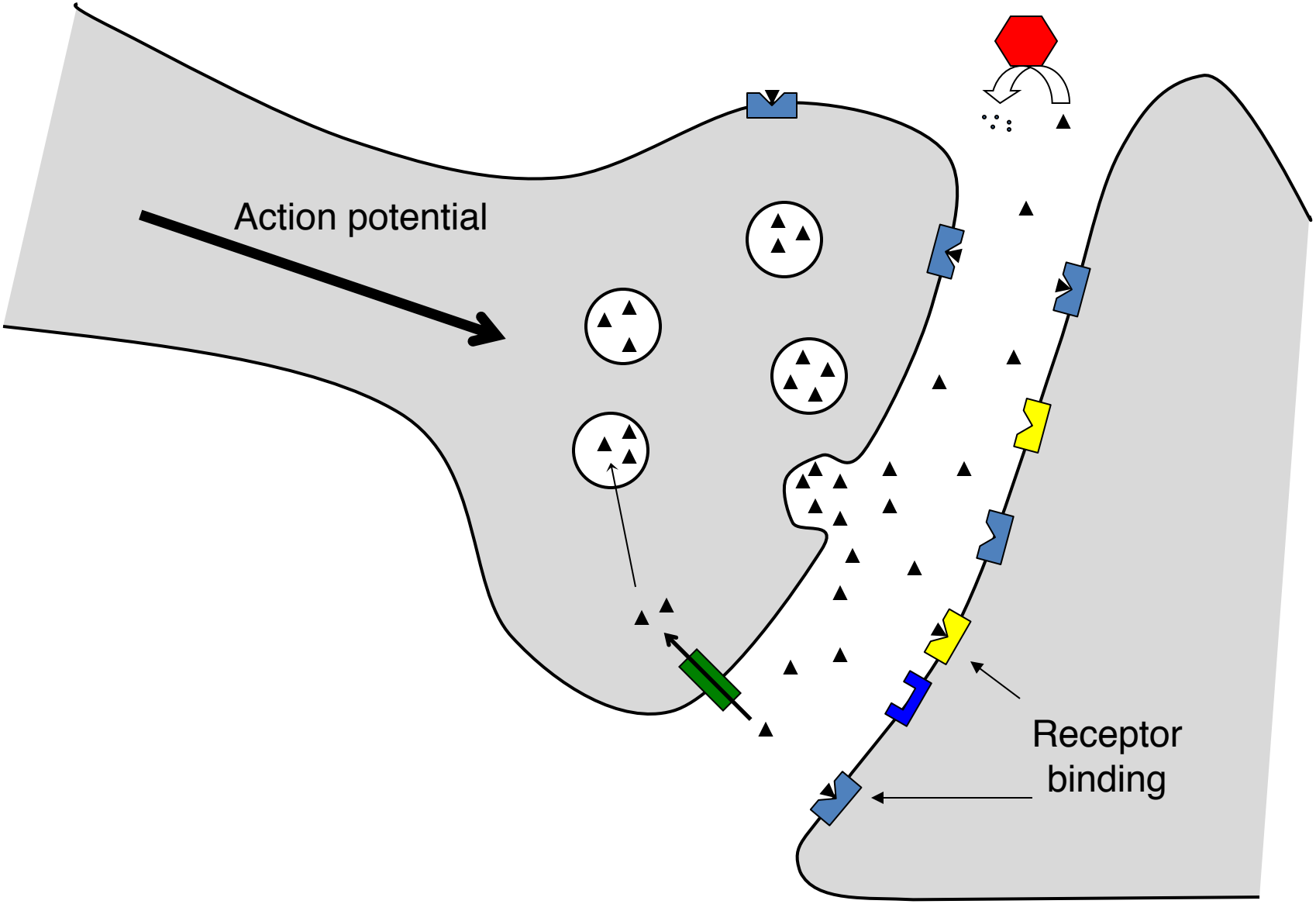
One Synapse



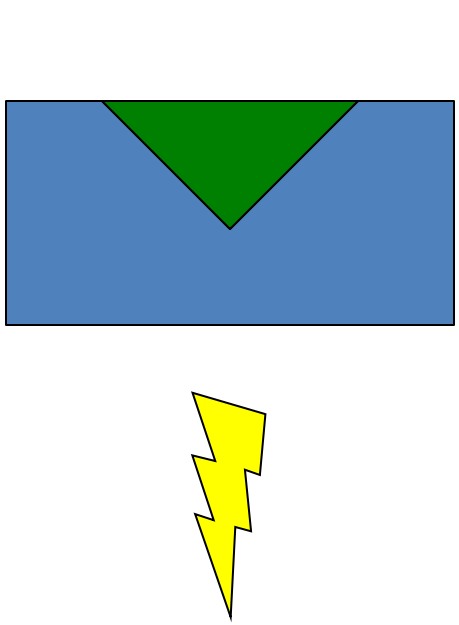
One Synapse



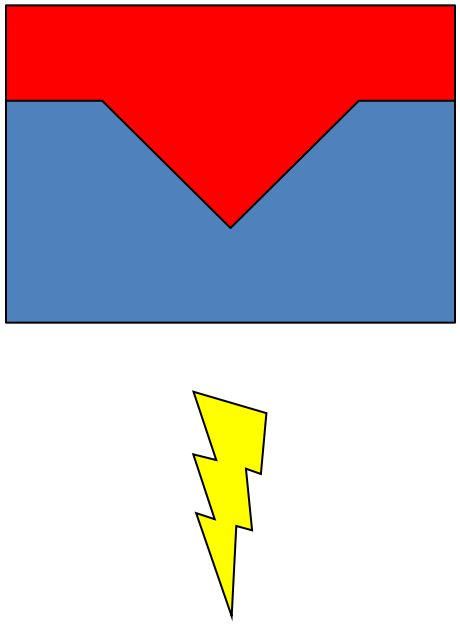
One Synapse



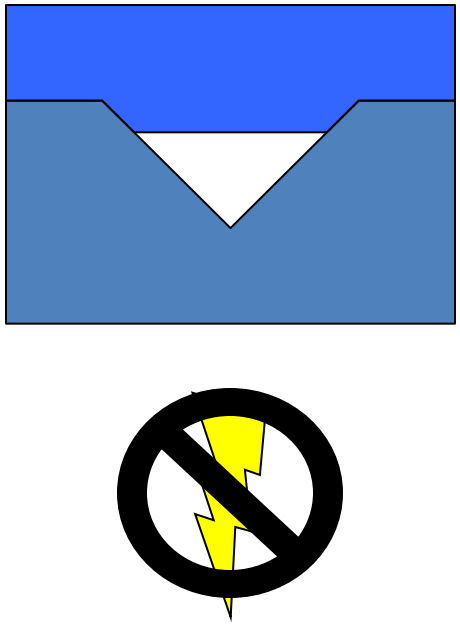
Agonist vs. Antagonist



Neurotransmitter



Agonist (drug)



Antagonist (drug)

2 × 2 Table Quiz

	Excitatory receptor:	Inhibitory receptor:
Agonist:	**Cell 1:** Will this ligand (neurotransmitter or drug) cause **more signal** or **less signal?**	**Cell 2:** And this?
Antagonist:	**Cell 3:** And this?	**Cell 4:** And this?

2 × 2 Table Quiz

	Excitatory receptor:	Inhibitory receptor:
Agonist:	**More Signal** **+ + + +**	**Cell 2:** And this?
Antagonist:	**Cell 3:** And this?	**Cell 4:** And this?

2 × 2 Table Quiz

	Excitatory receptor:	Inhibitory receptor:
Agonist:	More Signal + + + +	**Less Signal** **- - - -**
Antagonist:	**Cell 3:** And this?	**Cell 4:** And this?

2 × 2 Table Quiz

	Excitatory receptor:	Inhibitory receptor:
Agonist:	More Signal + + + +	Less Signal - - - -
Antagonist:	**Less Signal** **- - - -**	**Cell 4:** And this?

2 × 2 Table Quiz

	Excitatory receptor:	Inhibitory receptor:
Agonist:	More Signal + + + +	Less Signal - - - -
Antagonist:	Less Signal - - - -	**More Signal** **+ + + +**

	Excitatory receptor:	Inhibitory receptor:
Agonist:	Drugs here may be **stimulants,** promoting wakefulness, alertness, and fast thinking, but also **seizures.**	Drugs here may be **sedatives,** promoting relaxation and sleep.
Antagonist:	May be **sedatives.**	May be **stimulants.**

	Excitatory receptor:	Inhibitory receptor:
Agonist:	Stimulants of this type: Nicotine Psychedelics (LSD, psilocybin mushrooms, mescaline)	Sedatives of this type: Ethanol (alcohol) Barbiturates Benzodiazepines (Valium, Klonopin, Xanax, Ativan)
Antagonist:	Sedatives of this type: Diphenydramine (Benadryl) Antipsychotics (Haldol, Thorazine, Seroquel)	Caffeine

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   Glutamate (Glu), GABA, serotonin (5-HT), norepinephrine (NE), dopamine (DA), opioids

4. Drug Mechanisms
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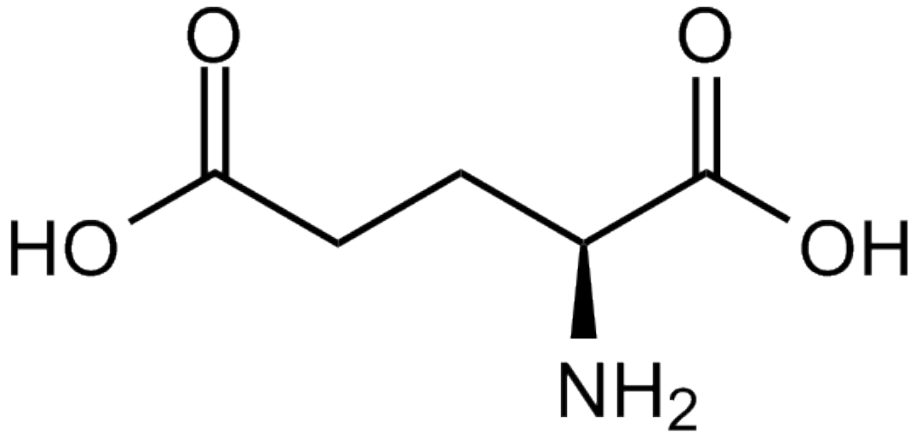
Glutamate (Glu)



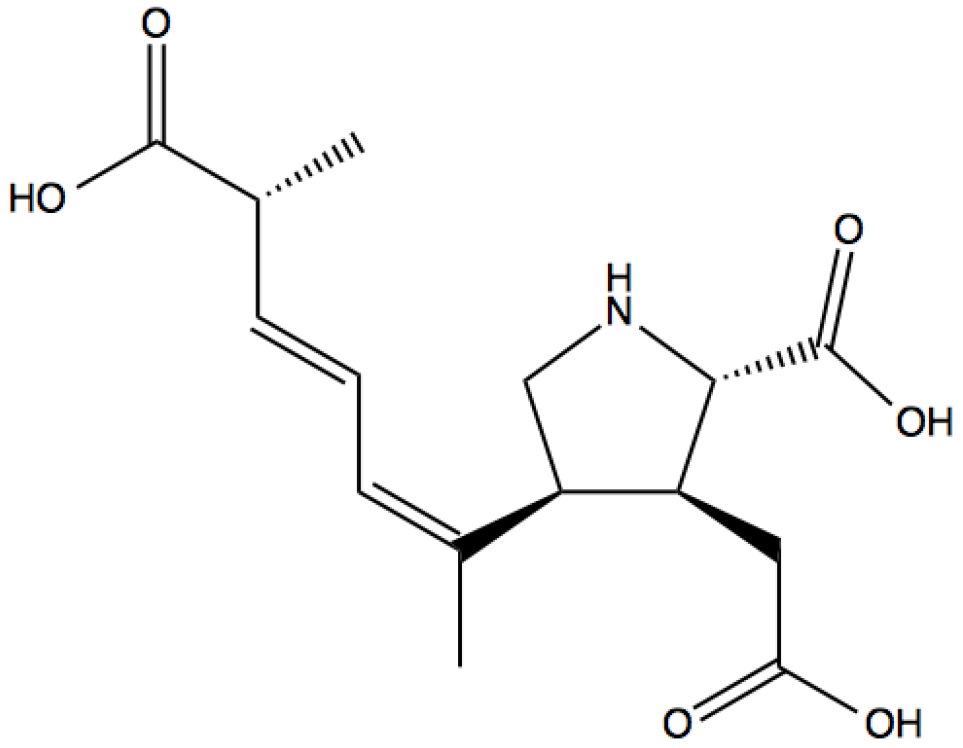
The most common excitatory neurotransmitter

Glutamate is released by 80% of neurons

Learning

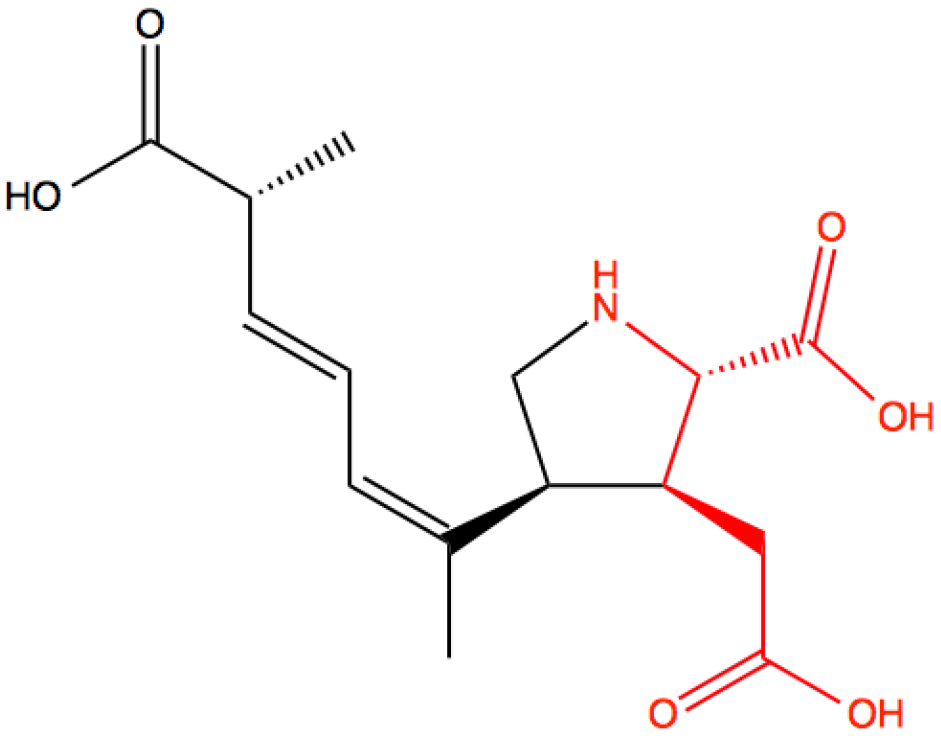
Memory

Glutamate Agonist: Domoic Acid



Glutamate agonists usually cause **seizures**, and domoic acid is no exception. Domoic acid also causes **permanent brain damage.**

Glutamate Agonist: Domoic Acid



Domoic acid actually *contains* glutamate, which is probably why it binds to glutamate receptors. I have highlighted glutamate in red above.

Amnesic Shellfish Poisoning (ASP)

Amnesic shellfish poisoning is the disease caused by domoic acid.

Domoic acid is produced by photosynthetic single-celled organisms called diatoms. These are a type of plankton. They are eaten by shellfish, and the shellfish are eaten by humans.

Domoic acid is not destroyed by cooking or freezing and cannot be washed off with water. There is no known way to clean tainted shellfish.

Amnesic Shellfish Poisoning (ASP)

Ingesting tainted shellfish causes headache, seizures, tremors, and sometimes death.

Victims who survive often lose the ability to form new memories, they have **permanent anterograde amnesia,** which is the source of the name.

Victims who survive often have other signs of brain damage, such as **very low IQ.**

Glutamate Antagonists

There are many important glutamate antagonists.

NMDA antagonists act at a special subtype of glutamate receptor called the NMDA receptor.

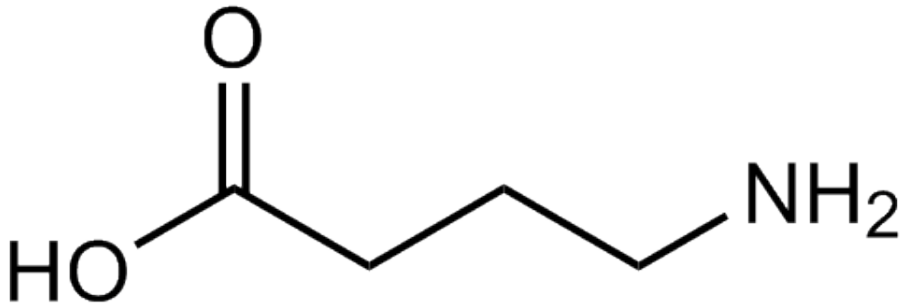
NMDA antagonists are sedatives, as you would expect, and they are used as general anesthetics.

NMDA Glutamate Antagonists

NMDA antagonists include:
- Ketamine
- PCP
- Dextromethorphan (Robitussin)

NMDA antagonists cause:
- Convincing and absorbing hallucinations
- Euphoria
- Addiction
- Nausea
- Dulled sensory perception (dissociation)
- Coma

GABA



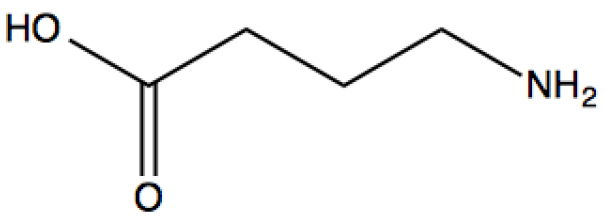
GABA is the primary inhibitory neurotransmitter

GABA stands for **g**amma-**a**mino**b**utyric **a**cid

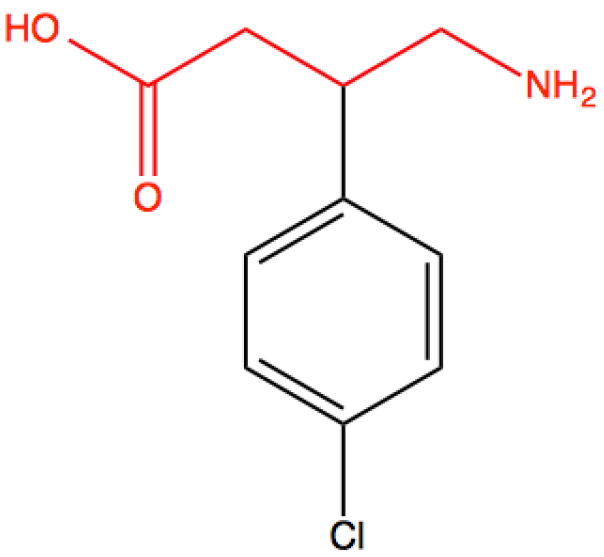
Sleep, muscle relaxation, anxiety relief, memory impairment

Example GABA Drugs

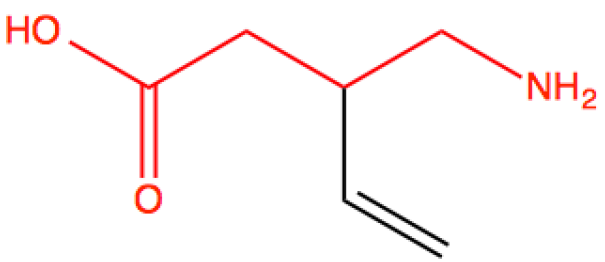
GABA



Baclofen



Vigabatrin



Baclofen is a GABA agonist. Vigabatrin inhibits GABA breakdown. Both drugs contain GABA itself, which is highlighted.

GABA Agonists: Sedatives

GABA agonists are almost always sedatives. Here are some famous GABA agonists:

Ethanol (alcohol) – Note that ethanol has other mechanisms, it does not act solely through GABA.

Barbiturates – Examples include phenobarbital (Luminal) and pentobarbital (Nembutal).

Benzodiazepines – Examples include diazepam (Valium), clonazepam (Klonopin), alprazolam (Xanax), and lorazepam (Ativan).

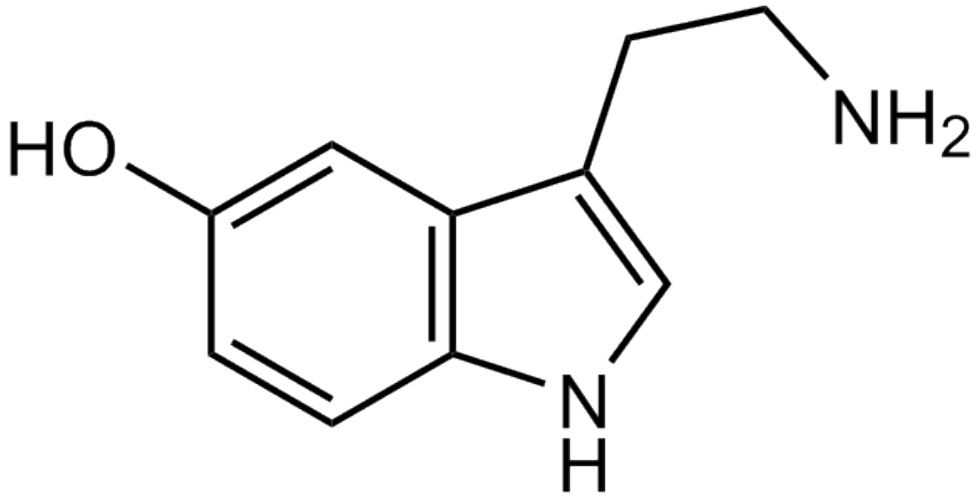
GABA Antagonists: Convulsants

GABA antagonists are almost universally **convulsants,** meaning they induce seizures. At lower doses, they cause anxiety.

Pentylenetetrazol (PTZ) – May have additional non-GABAergic mechanisms

Benzodiazepine inverse agonists – Interesting side effects

Serotonin (5-HT)



The Satiety Neurotransmitter

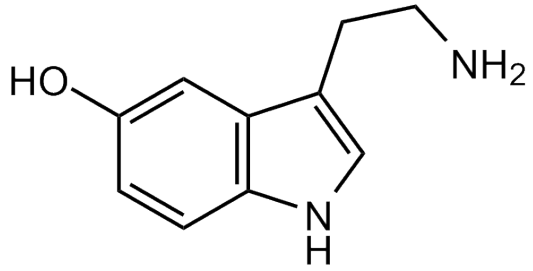
5-HT stands for 5-hydroxytryptamine

Feelings of fullness, contentment

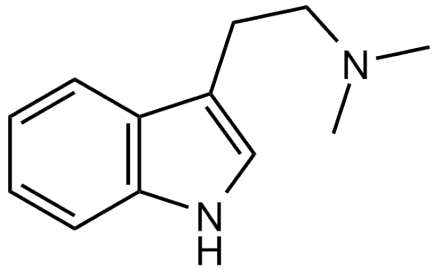
Relieves depression

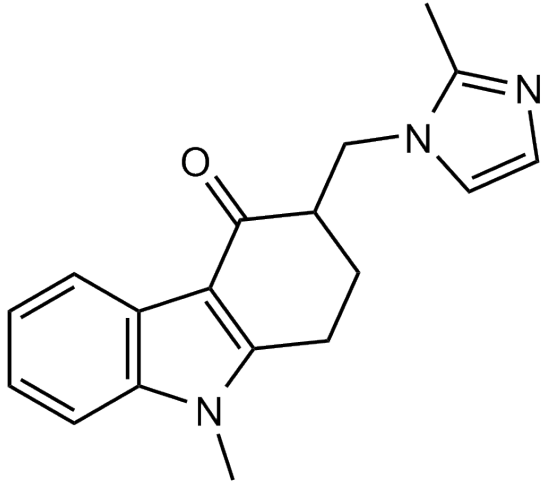
Serotonergic Drugs I

Serotonin

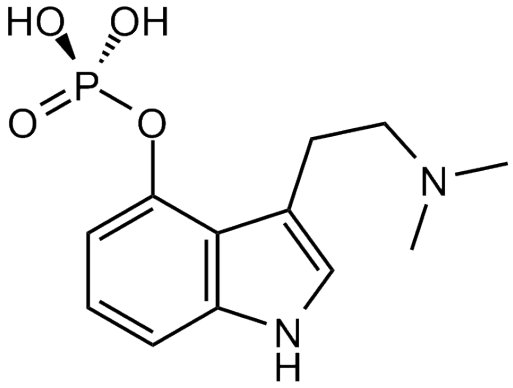


Dimethyltryptamine
DMT



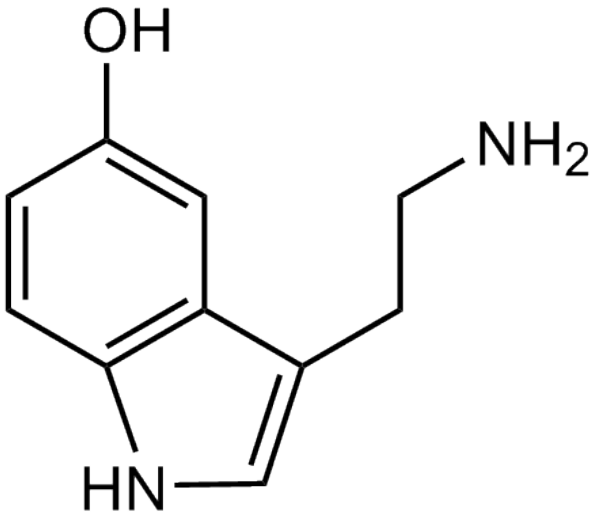


Ondansetron
Zofran

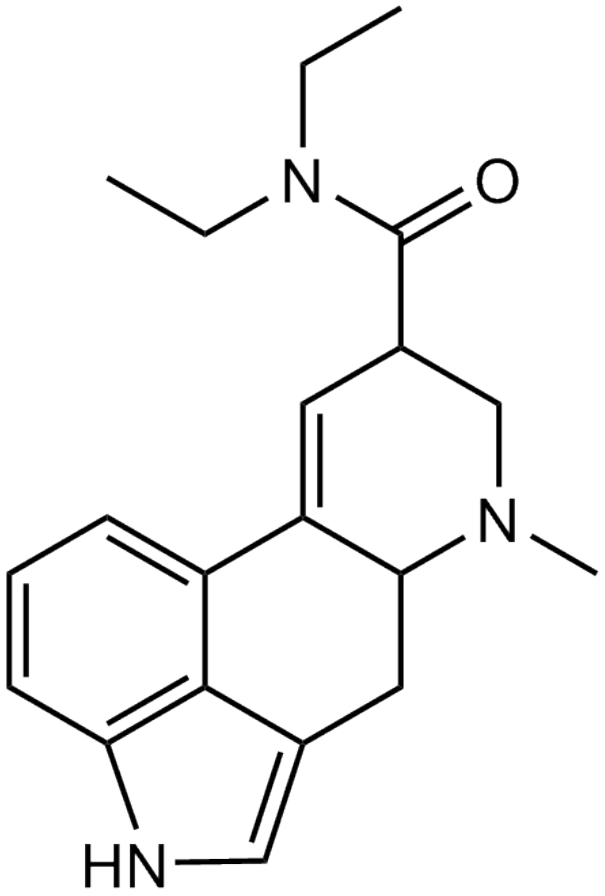


Psilocybin

Serotonergic Drugs II

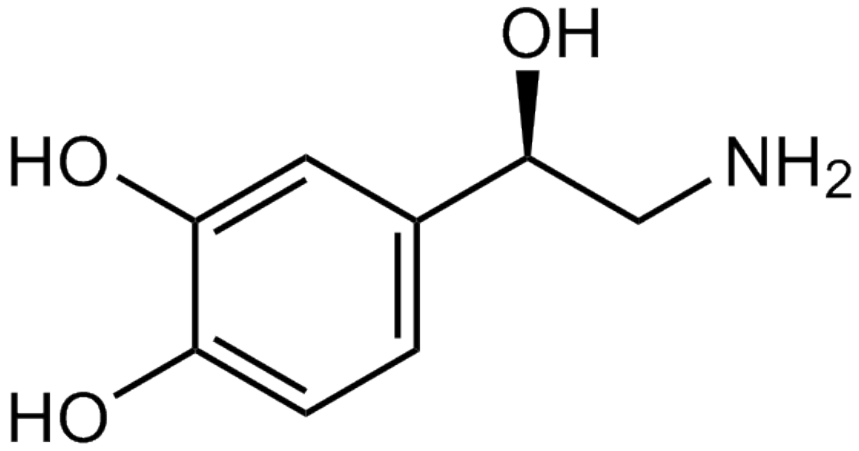


Serotonin



Lysergic Acid Diethylamide

Norepinephrine (NE)



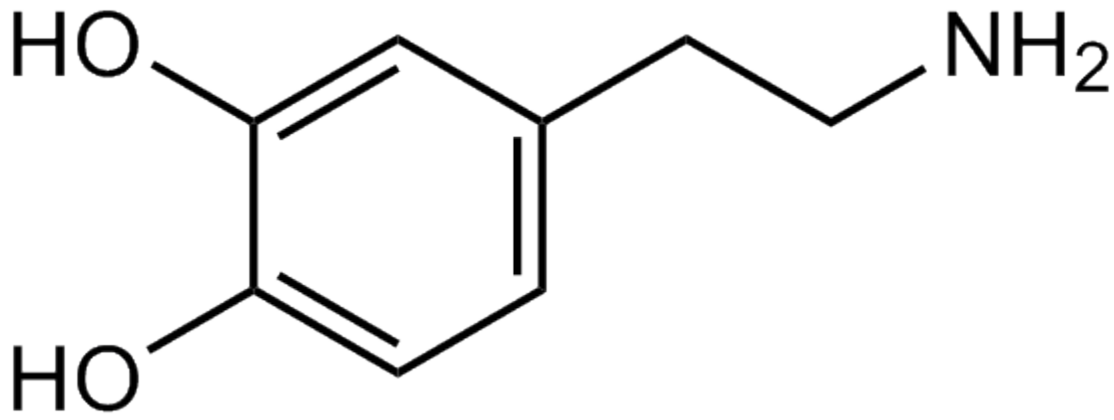
The Fight-or-Flight Neurotransmitter

Also called **noradrenaline**

Excitement, fear, alertness

As a hormone, it increases heart rate, blood pressure, and blood sugar

Dopamine (DA)

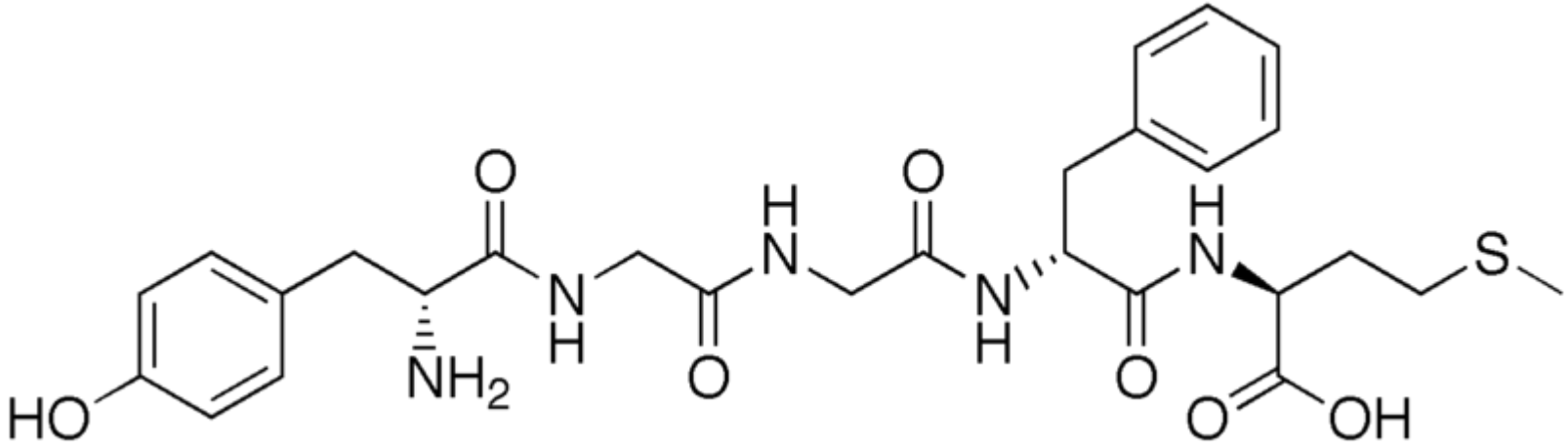


The Salience Neurotransmitter

Rewards eating, sex

Increases alertness, happiness, motivation

Opioids



Relieve pain, anxiety

Induce sleep

Important for pleasure

Slow the digestive tract

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