Drugs and the Brain Teaser

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How the Brain Works

You have about 100 billion brain cells, which are called neurons.

Each neuron has about 1,000 connections, called synapses. (This number is extremely variable.)

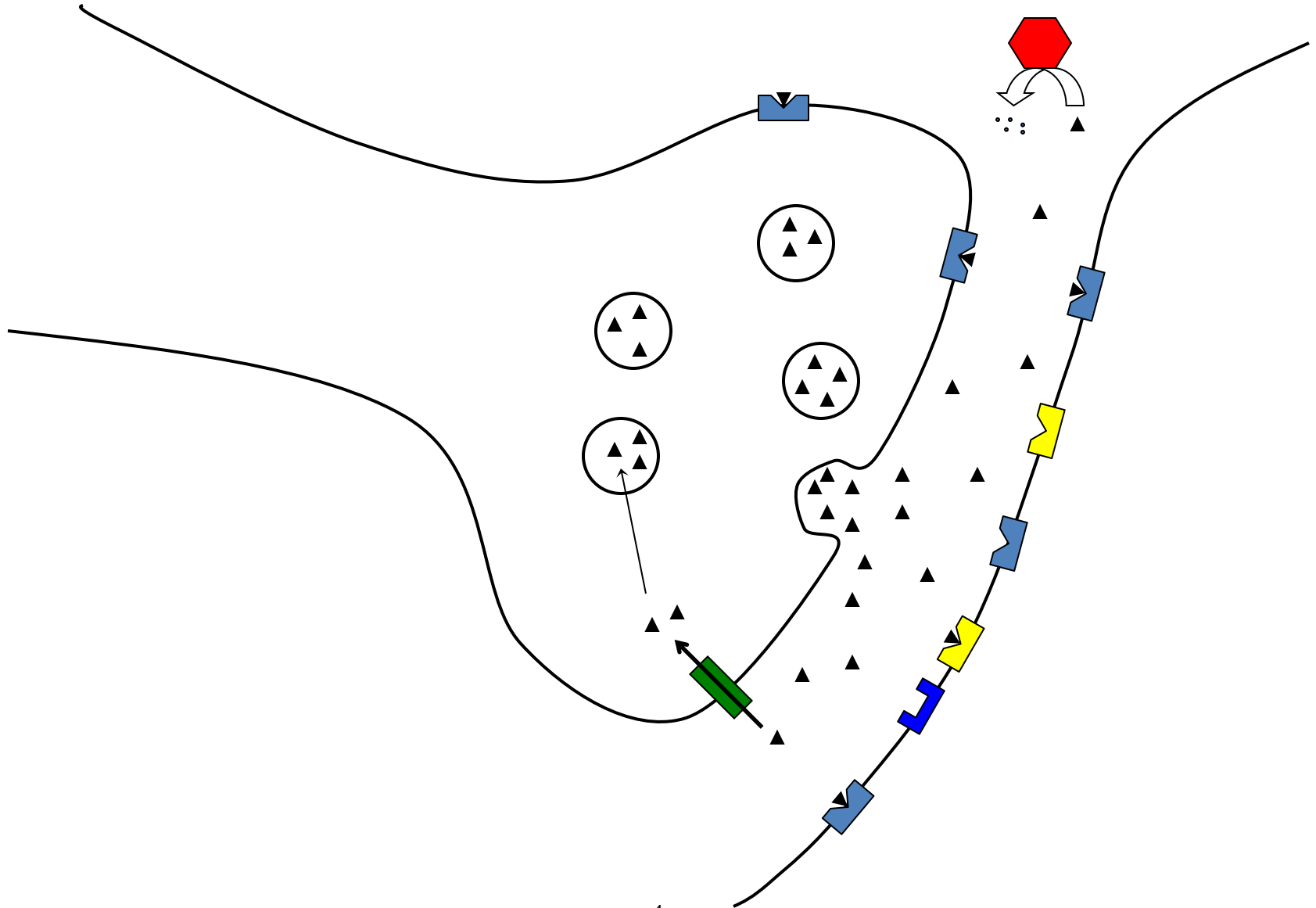Neurons fire action potentials, which are electric signals.

Neurons release chemicals called neurotransmitters, these chemicals carry signals across the synaptic cleft.
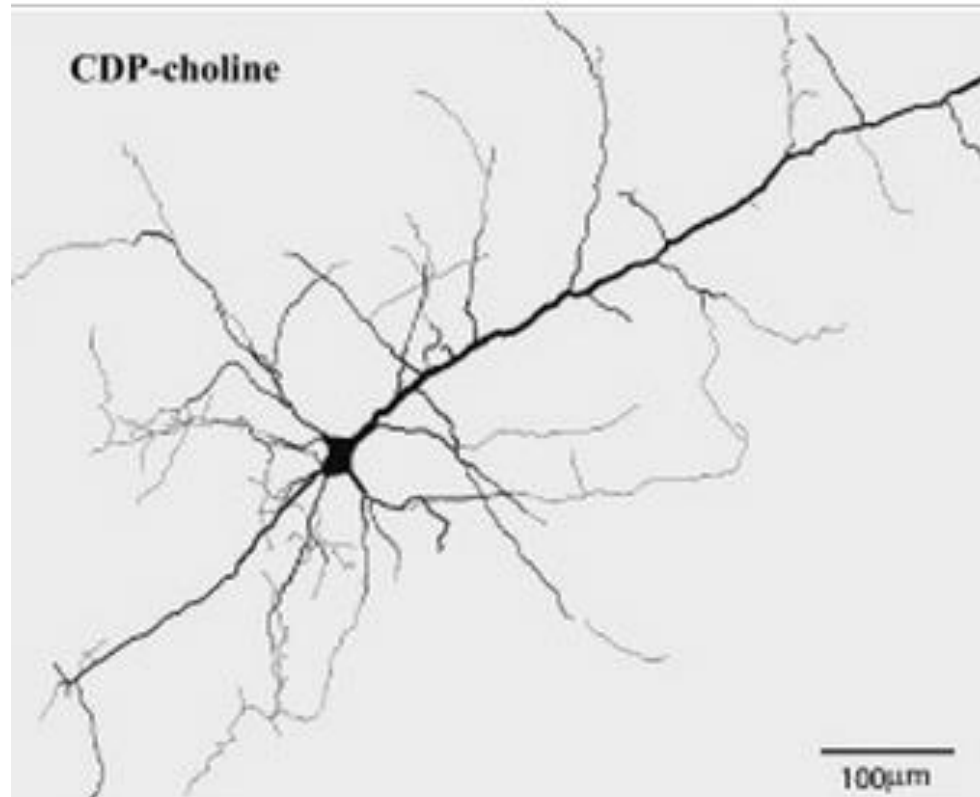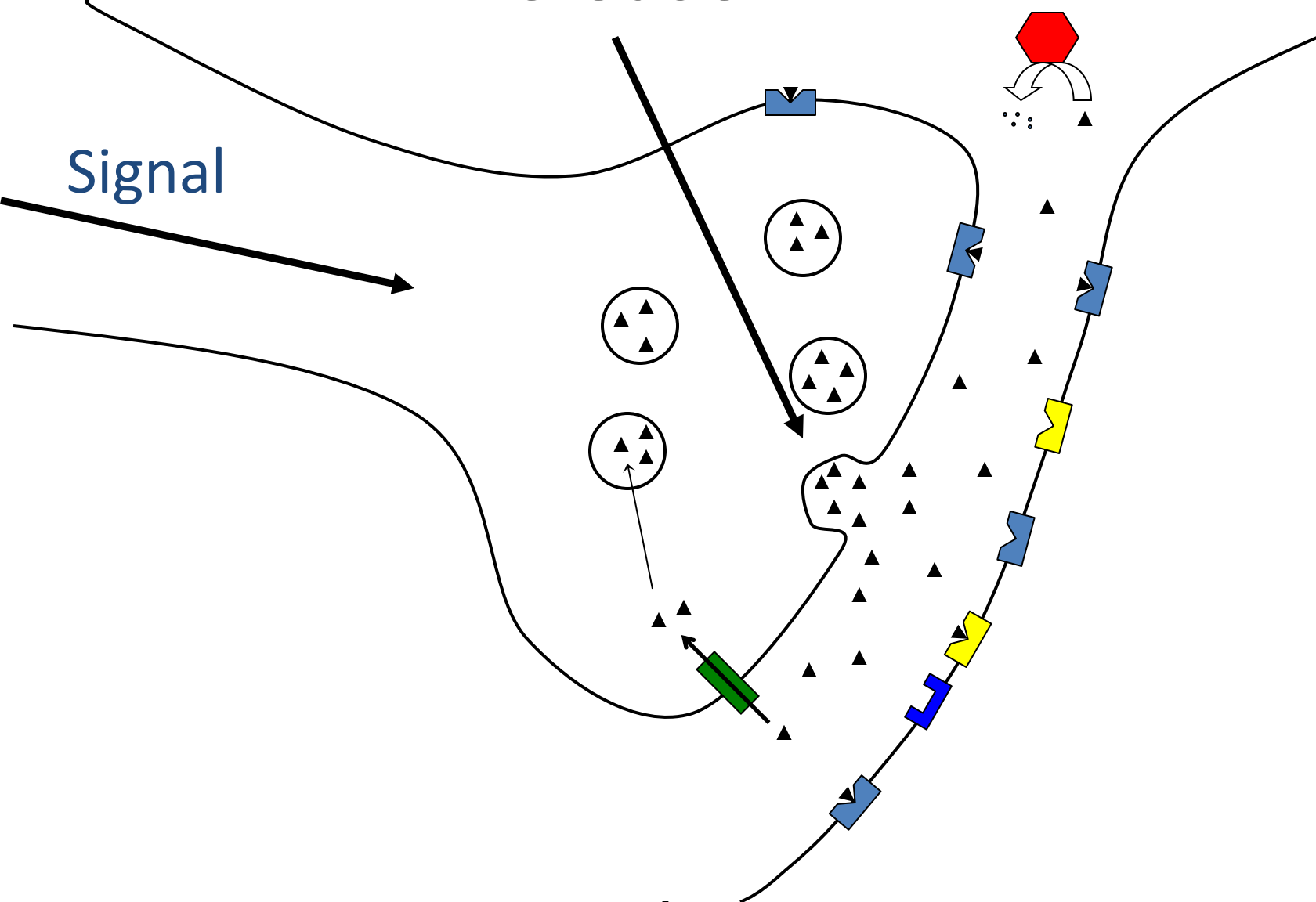
Pyramidal neuron, Golgi stain.

Background: The Synapse

Release

Signal

Receptor binding
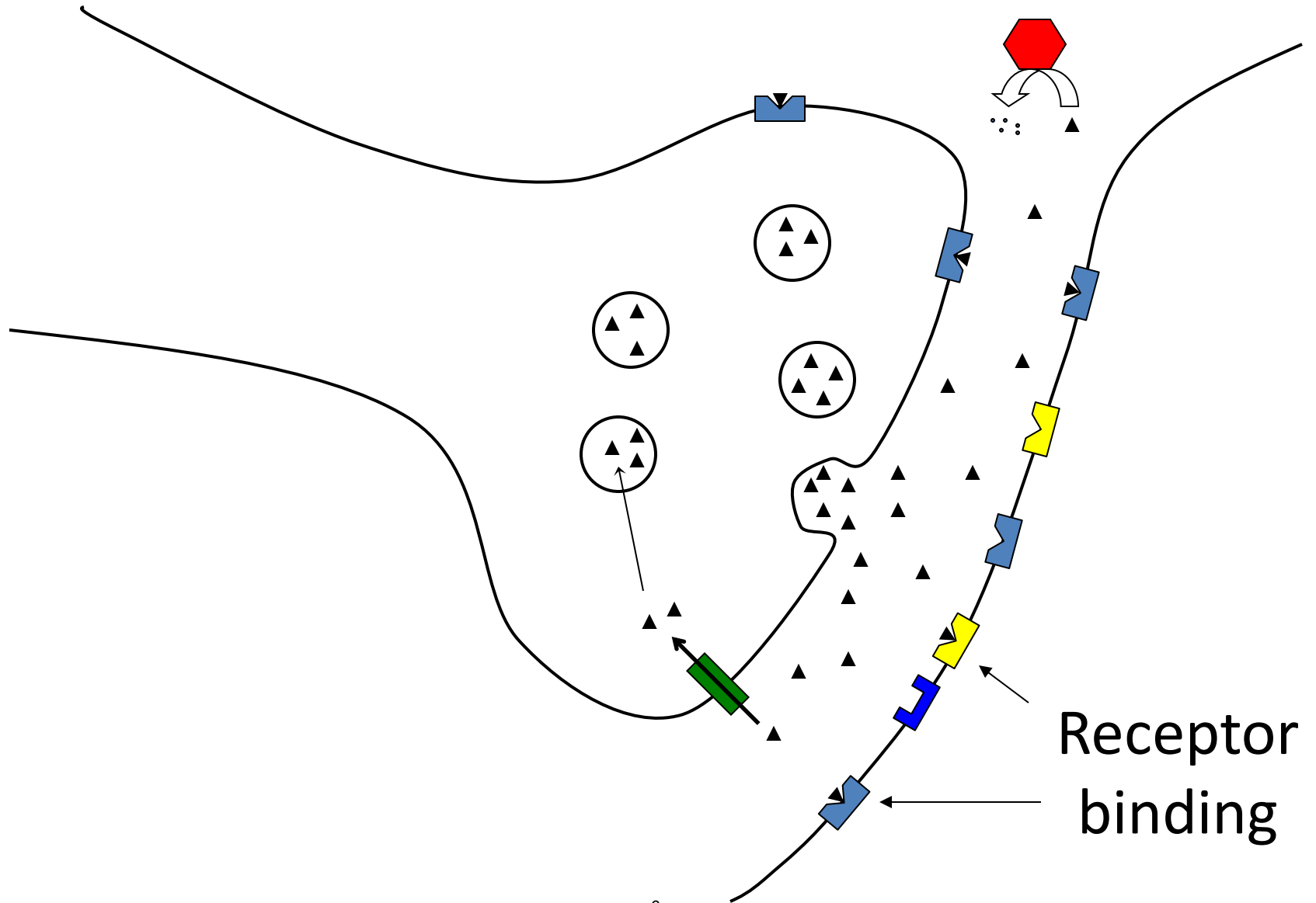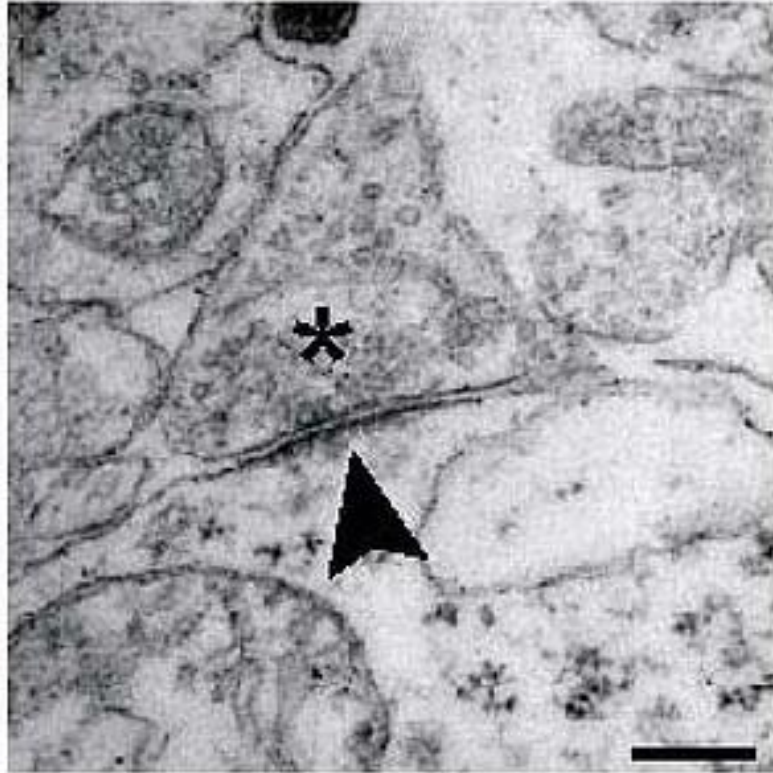
A real synapse!

Vocabulary

Neurotransmitter: A signaling molecule, it crosses the synapse

Hormone: Another type of signaling molecule. The border between neurotransmitter and hormone is blurry, many chemicals are both.

Receptor: A protein that detects a specific chemical, by binding to it

Ligand: A molecule that binds to a receptor

Vocabulary II

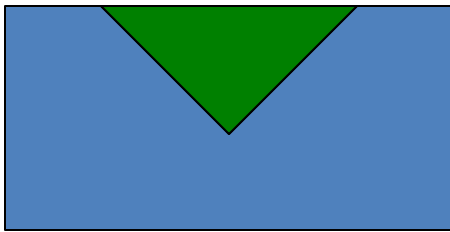**Excitatory:** Something that increases action potentials (increases neuron firing)

Inhibitory: Something that decreases action potentials

Agonist: A ligand that stimulates a receptor
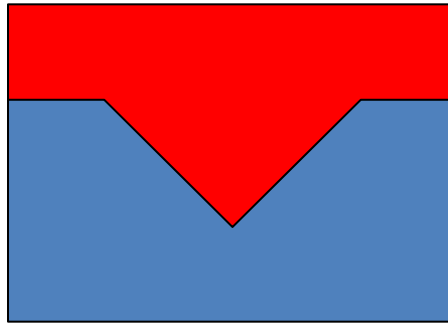
Antagonist: A ligand that binds to a receptor but does not stimulate it. Antagonists *block receptors*, and they counteract agonists.

Agonists and Antagonists

Neurotransmitter

Agonist (drug)
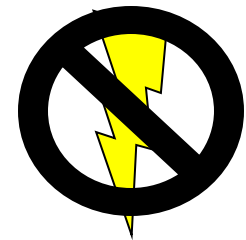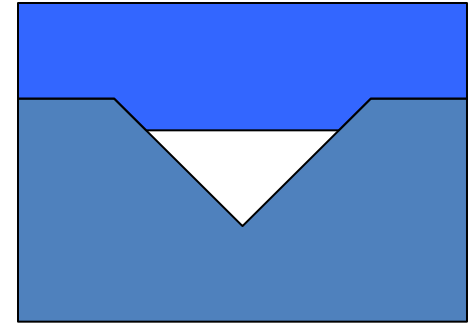
Antagonist (drug)

Little quiz

What would each of the following do?:

	Excitatory receptor	**Inhibitory receptor**
Agonist		
Antagonist		

Little quiz

What would each of the following do?:

	Excitatory receptor	**Inhibitory receptor**
Agonist	+++ More signal	--- Less signal
Antagonist	--- Less signal	+++ More signal

Example drugs

What would each of the following do?:

	Excitatory receptor	Inhibitory receptor
Agonist	+++ Nicotine	--- Alcohol
Antagonist	--- Benadryl	+++ Caffeine

Mechanism 1: Receptor Agonist

Here are some famous receptor agonists:

Morphine (also heroin, methadone, OxyContin): These drugs are full agonists at the mu opioid receptor. These drugs cause pain relief, anxiety relief, sedation, nausea, constipation, addiction.

Alcohol: This is a GABA agonist, but it has other mechanisms which are also important.

Mechanism 2: Receptor Antagonist

Here are some famous receptor antagonists, they block receptors:

PCP (also ketamine, dextromethorphan): These drugs are NMDA receptor antagonists. The NMDA receptor is a type of glutamate receptor. These drugs cause convincing and absorbing hallucinations, pain relief, coma, and nausea. These drugs are moderately addictive.

Mechanism 2: Receptor Antagonist

More examples:

Scopolamine (also diphenhydramine, atropine): These drugs block muscarinic acetylcholine receptors. These drugs cause convincing and absorbing hallucinations, memory loss (including retrograde memory loss), dry mouth, rapid heart rate, and dilated pupils. Hallucinogenic doses are extremely dangerous. Diphenhydramine is better known as **Benadryl**.
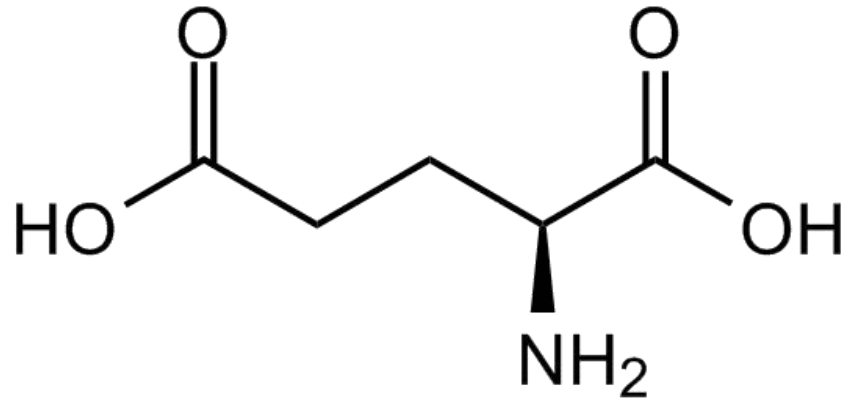
Mechanism 2: Receptor Antagonist

More examples:

Caffeine

Antihistamines are histamine antagonists (or inverse agonists)

Antipsychotics are dopamine antagonists (and sometimes also serotonin antagonists)

Glutamate (Glu)

Glutamate is the most common excitatory neurotransmitter in the human brain.

Glutamate is about 1,000 times more common than serotonin, dopamine, or norepinephrine.

Glutamate is released by 80% of neurons.

Glutamate Drugs

PCP, ketamine, and dextromethorphan are all glutamate antagonists. They act at the NMDA glutamate receptor.

Memantine (Namenda) is also an NMDA antagonist, it is approved for the treatment of Alzheimer's disease.

Glutamate agonists tend to cause seizures. This makes sense, because glutamate is excitatory and seizures are caused by excess excitation.

GABA
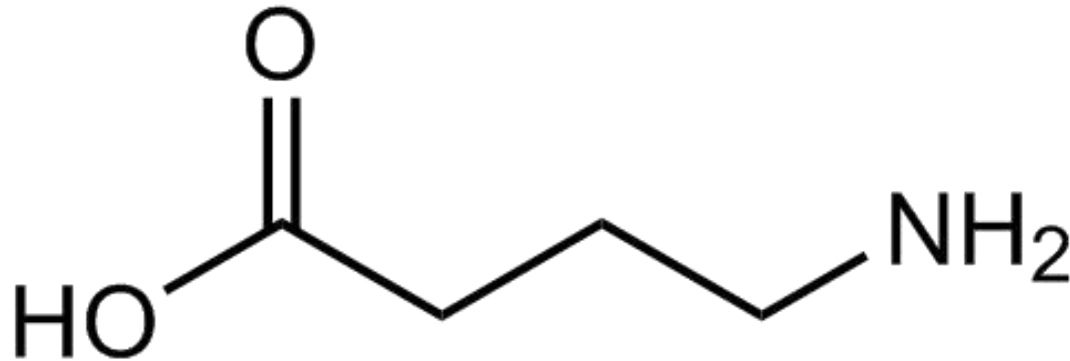
GABA stands for gamma-aminobutyric acid.

GABA is the most common inhibitory neurotransmitter in the human brain.

GABA agonists cause sleep, anxiety relief, muscle relaxation, and memory impairment.

GABA Drugs

Muscimol: Muscimol is a $GABA_A$ agonist found in *Amanita muscaria* mushrooms. It causes nausea, sedation, and perceptual anomalies.

Amanita muscaria mushroom
Image courtesy of Harry-Harms on Flickr. CC-BY-NC-SA

Mechanism 3: Partial Agonist

A partial agonist is like an agonist, but it causes only partial effects. Partial agonists are often safer in overdose than full agonists. Partial agonists may have fewer side effects.

Buprenorphine (brand name Suboxone): This is a mu opioid partial agonist. Like a full agonist (e.g. heroin), it relieves pain and opioid withdrawal. Unlike a full agonist, overdose does not usually cause death.

Mechanism 3: Partial Agonist

More partial agonists:

Psychedelics, such as LSD, psilocybin (in mushrooms), and mescaline (in peyote cactus). Psychedelics are 5-HT$_{2A}$ partial agonists. 5-HT is synonymous with serotonin. Psychedelics cause perceptual distortions and strange thinking. However, unlike certain other *hallucinogens*, psychedelics do not tend to cause convincing and absorbing hallucinations.

More about Psychedelics

Here is an explanatory example: Psychedelics may make you see a wolf in a patterned carpet. However, psychedelics generally will not allow you to have a conversation with a purple dragon. In contrast, PCP and ketamine can facilitate a conversation with a purple dragon. This is what I call a **convincing and absorbing hallucination**.

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