Mind, Brain & Behaviour 1
Behavioural Neuroscience

The synapse: mechanisms of communication between neurons

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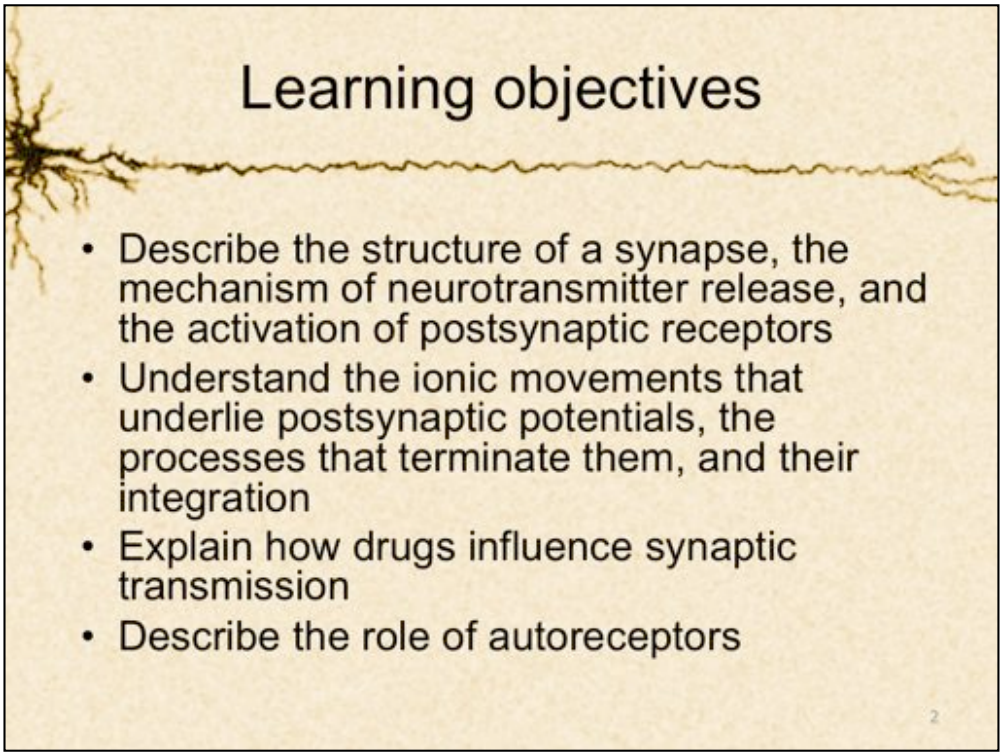
Learning objectives
• Describe the structure of a synapse, the mechanism of neurotransmitter release, and the activation of postsynaptic receptors
• Understand the ionic movements that underlie postsynaptic potentials, the processes that terminate them, and their integration
• Explain how drugs influence synaptic transmission
• Describe the role of autoreceptors
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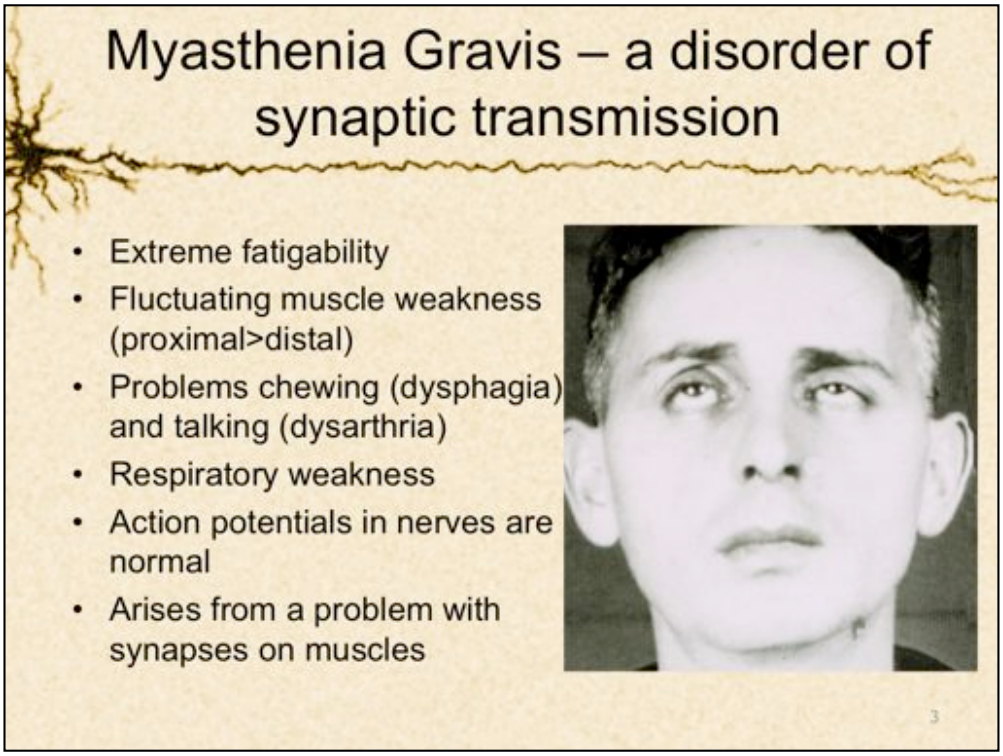


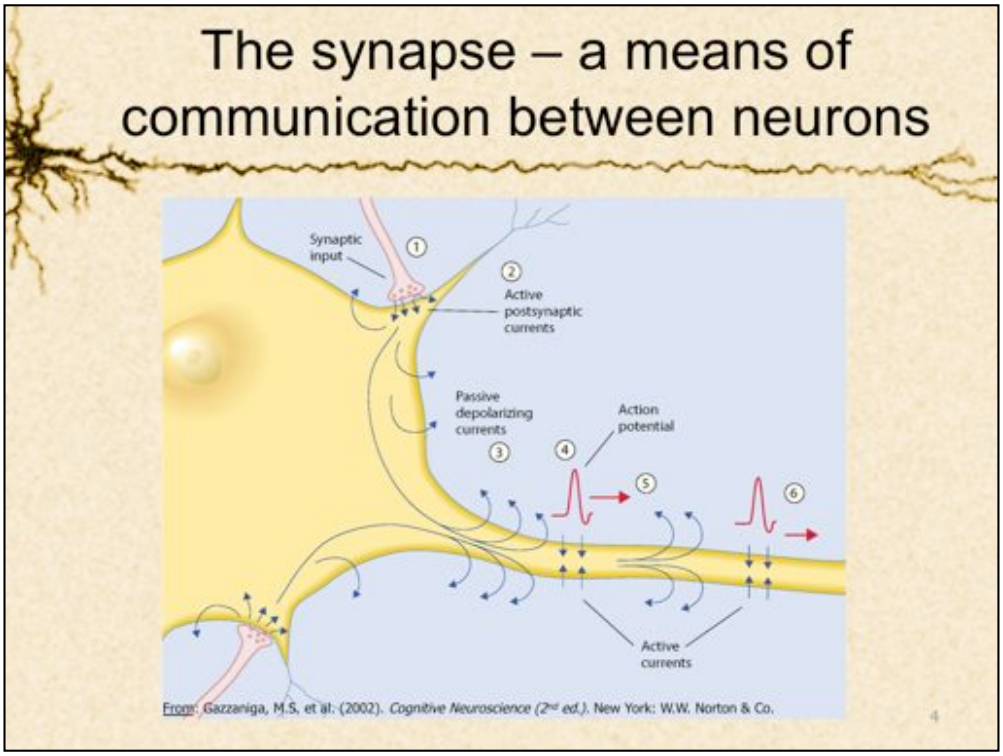
Myasthenia Gravis, meaning 'grave muscle weakness', was first described by **Thomas Willis** in 1672 (you will remember Willis from Lecture 1 – he was the English physician who was the first to suggest that the mind resides in the cerebral cortex and not in the hollow ventricles).

The first symptoms of myasthenia gravis are extreme fatigability and fluctuating muscle weakness. The weakness tends to affect the **proximal** muscles (those of the head, neck and trunk) more than the **distal** muscles (those of the arms and legs).

Eventually sufferers have problems chewing (**dysphagia**) and talking (**dysarthria**) due to weakness of the musculature of the jaw and mouth, respectively.

In severe cases, individuals may experience problems breathing (**respiratory distress**), which can be life-threatening if not treated. Such patients typically are hospitalised and placed on an artificial respirator.

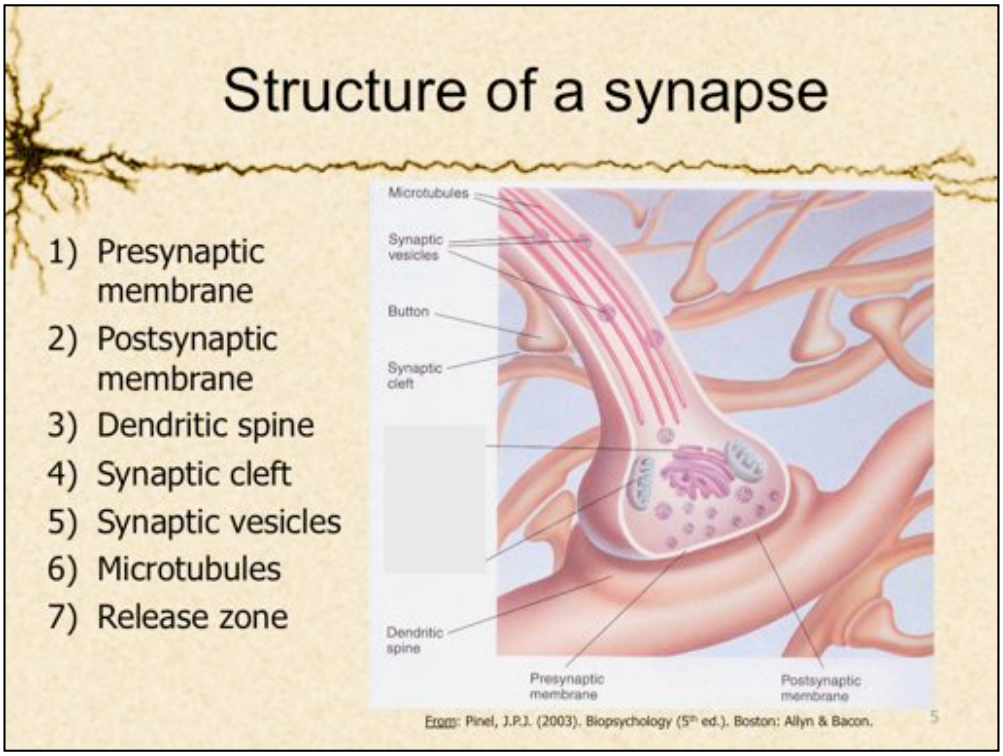
Experimental investigations in sufferers of myasthenia gravis have shown that



You will recall that the transmission of information within a neuron involves the generation of an action potential (AP), which begins at the cell body (or more precisely, at the junction between the cell body and the axon, known as the **axon hillock**). The action potential proceeds along the axon in tiny jumps between the Nodes of Ranvier (the little gaps between the myelinated cells that are wrapped around the axon).

Once the AP reaches the terminal buttons, how does it communicate with the next neuron in the circuit, given that the two are not physically joined?

The answer is that the terminal buttons release a chemical message, called a **neurotransmitter**, which diffuses across the gap (**synaptic cleft**) between the **presynaptic terminal button** (i.e., the terminal button before the synapse) and the dendrite or cell body of the **postsynaptic membrane** (i.e., the membrane of the neuron after the synapse). If the neurotransmitter has an excitatory effect on the postsynaptic cell, then it will depolarise the postsynaptic neuron and generate an action potential. The whole process is then repeated for the next neuron in the circuit. If the neurotransmitter is inhibitory, however, then the postsynaptic cell will become hyperpolarised, and will therefore not fire.



There are three types of synapses, which can be defined on the basis of the places at which they occur:

1) **Axodendritic** – the terminal button synapses with a dendrite of the postsynaptic neuron
2) **Axosomatic** - the terminal button synapses with the cell body (soma) of the postsynaptic neuron
3) **Axoaxonic** - the terminal button synapses with the axon of the postsynaptic neuron

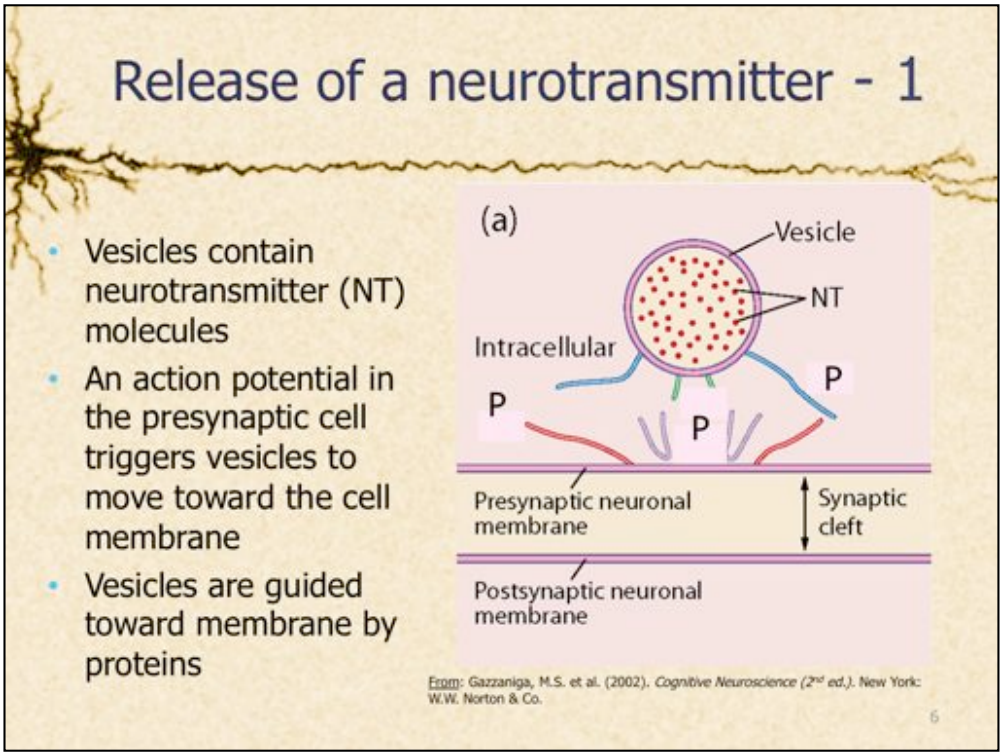
Presynaptic membrane – the membrane of the presynaptic terminal button

Postsynaptic membrane – the membrane of the postsynaptic neuron

Dendritic spine – a ridge on the dendrite of a postsynaptic neuron, with which a terminal button from a presynaptic neuron forms a synapse

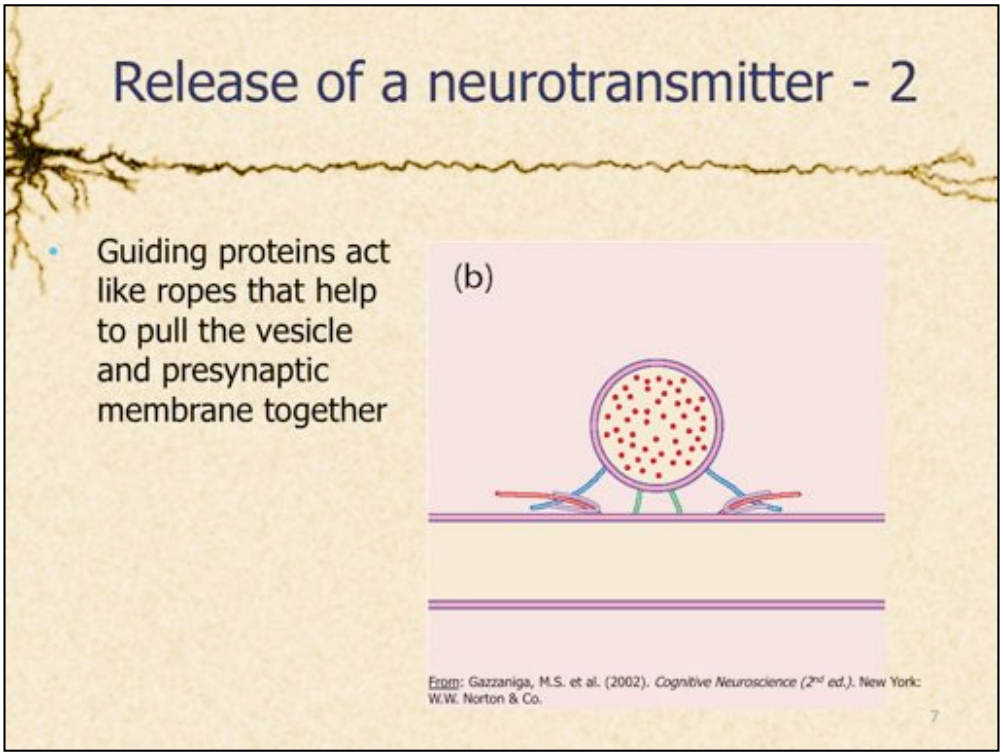
Synaptic cleft – the tiny gap between the presynaptic and postsynaptic membrane (approximately 20 nanometres wide; a nanometre is a billionth of a metre)

Synaptic vesicles – tiny balloons filled with neurotransmitter molecules; found

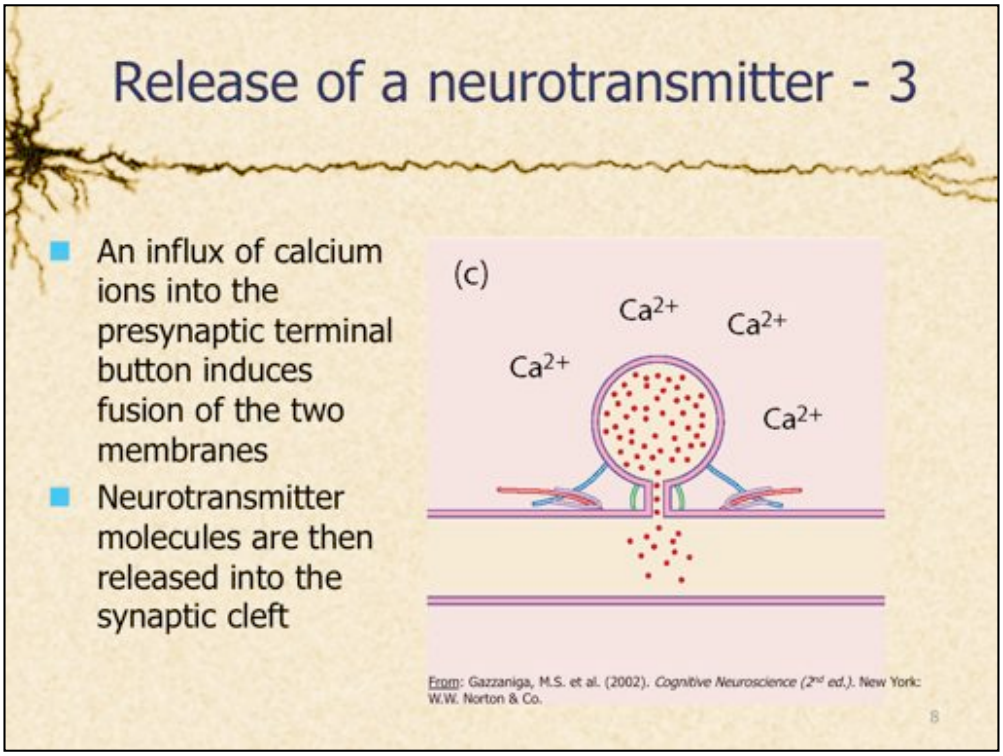


When an action potential is conducted down an axon (including all of its branches), synaptic vesicles located just inside the terminal buttons begin to move toward the release zone of the cell membrane.

The vesicles are guided toward the cell membrane of the presynaptic neuron by a group of **protein structures (P)**

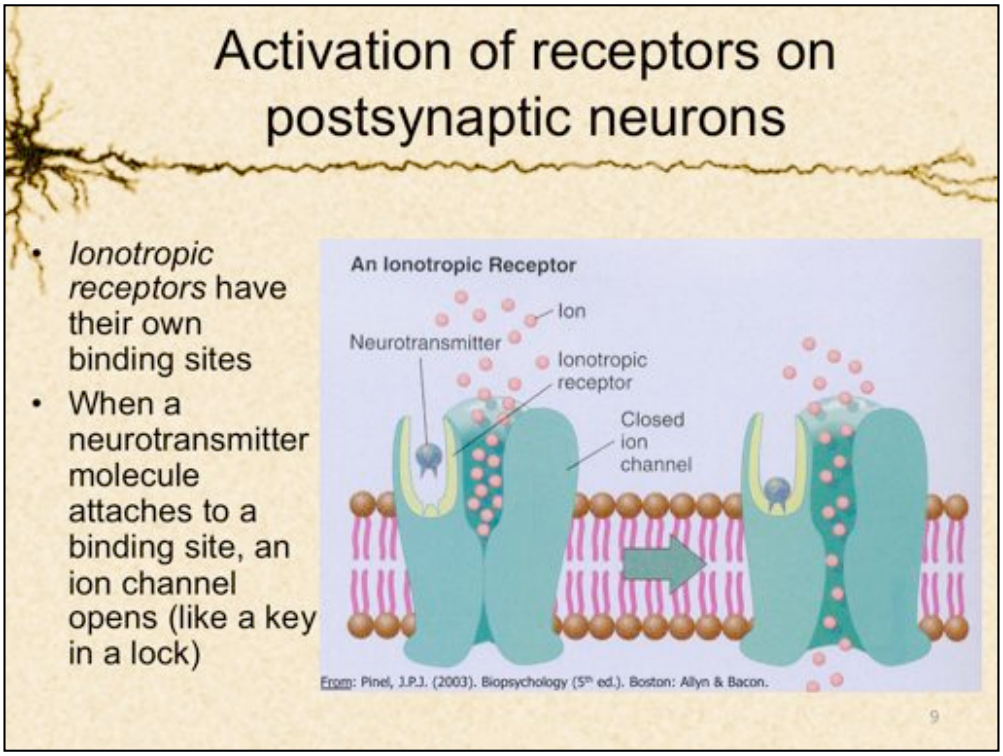


The protein structures act like ropes, helping to pull the vesicles toward the presynaptic membrane.



At this point, there is an influx of calcium Ca^{2+} ions into the presynaptic neuron, which induces fusion of the membranes of the synaptic vesicle and the presynaptic cell.

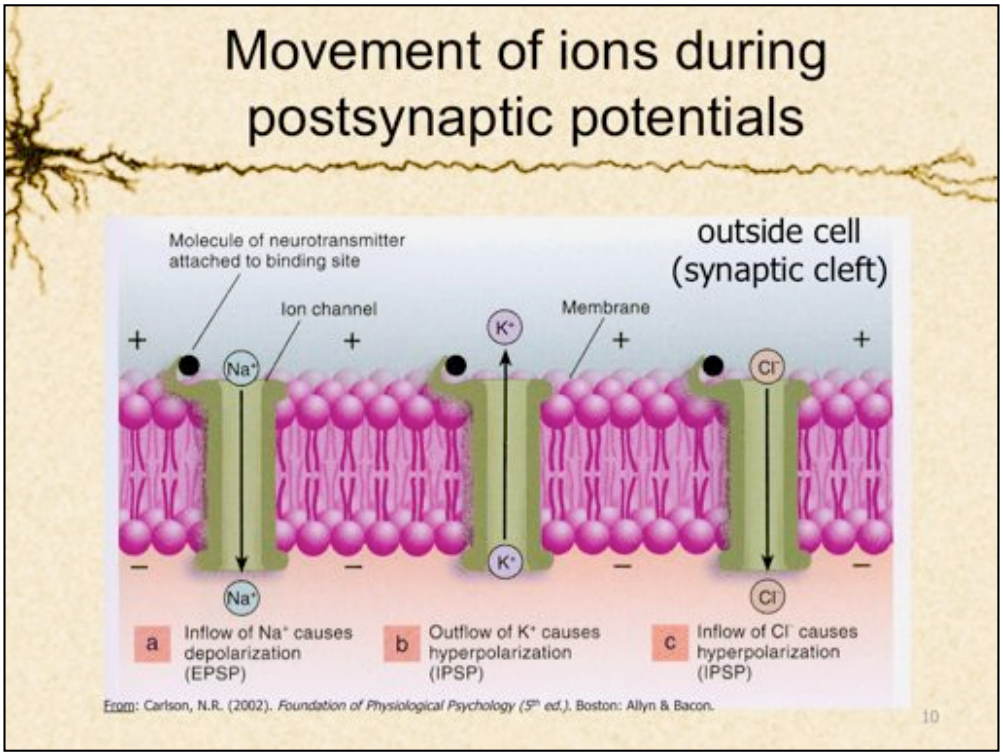
The neurotransmitter molecules carried by the synaptic vesicles are then released into the synaptic cleft. This process occurs very rapidly indeed, within just a few milliseconds (thousands of a second).



How do molecules of the neurotransmitter released by terminal buttons of the presynaptic neuron influence the postsynaptic cell?

Neurotransmitter molecules diffuse across the fluid filled space of the synaptic cleft. Once they reach the other side they attach to specific **binding sites** of the **postsynaptic receptors**, which are located in the membrane of the postsynaptic cell (much like a key in a lock). The neurotransmitter molecules open **neurotransmitter dependent ion channels** in the postsynaptic cell. These channels, once opened, permit the flow of specific ions into and out of the postsynaptic neuron.

Neurotransmitters open ion channels in two different ways, direct and indirect. Here we shall consider only the direct channel, because it is simpler to understand. The direct method involves receptors that are equipped with their own binding sites; these are called **ionotropic receptors**. When a neurotransmitter molecule locks into the binding site, the channel is opened allowing ions to move in or out.



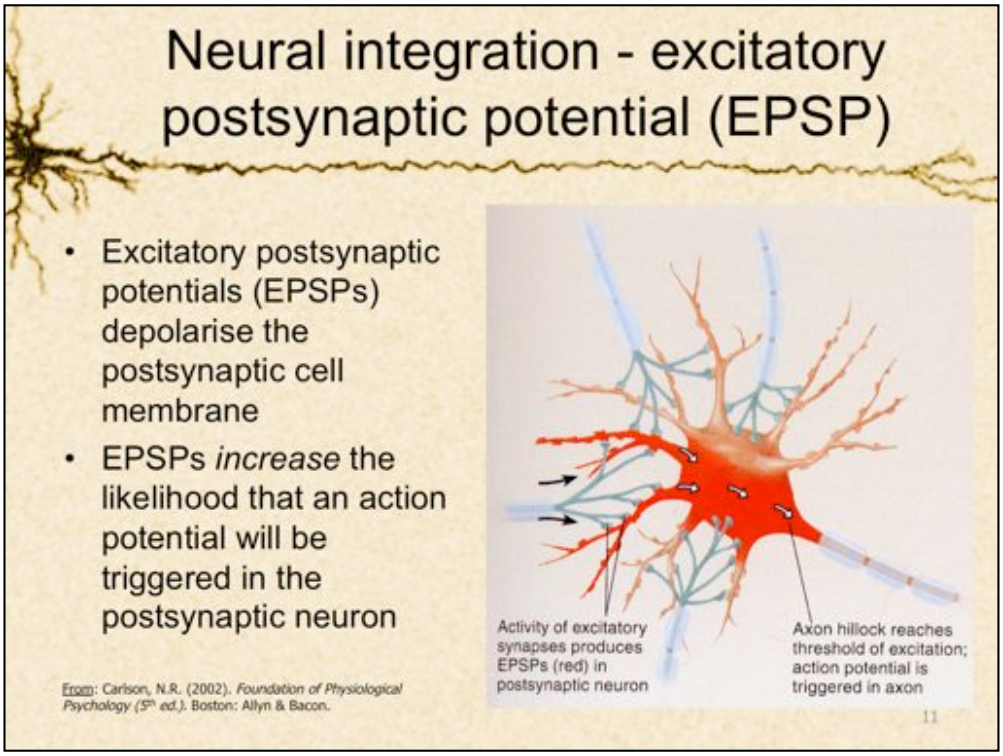
Postsynaptic potentials can be either **excitatory** (increasing the likelihood that the neuron will depolarise, triggering an action potential) or **inhibitory** (increasing the likelihood that the neuron will hyperpolarise, and thus *not* trigger an action potential).

Whether a postsynaptic potential is excitatory or inhibitory is determined not by the neurotransmitter that is released into the synapse, but by the specific ion channel that the neurotransmitter opens.

Three types of neurotransmitter dependent ion channels are found in the postsynaptic membrane:

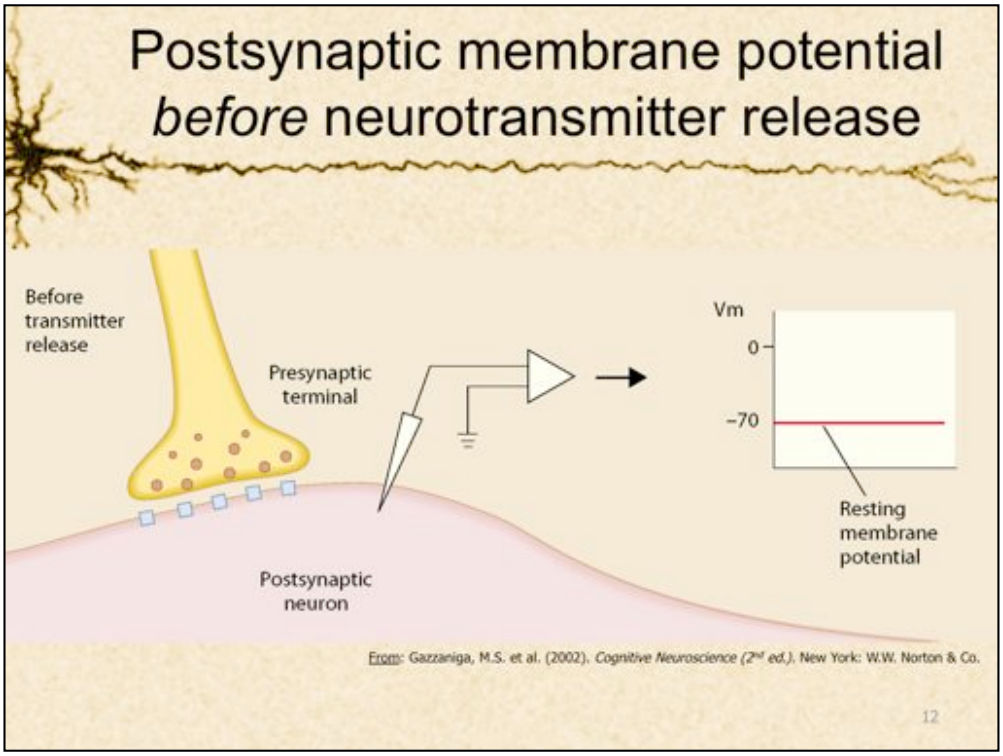
1) Sodium (Na^+)
2) Potassium (K^+)
3) Chloride (Cl^-)

Sodium channels are the most important for triggering excitatory postsynaptic potentials. You will recall that sodium-potassium transporters keep sodium

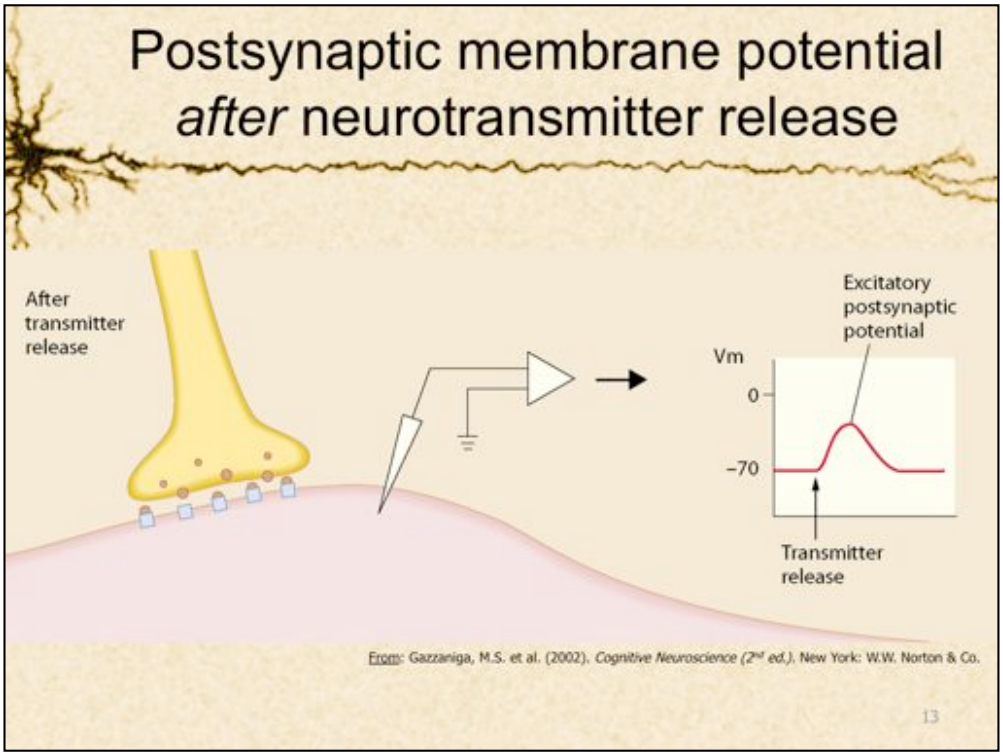


Excitatory postsynaptic potentials (EPSPs) depolarise the postsynaptic cell membrane.

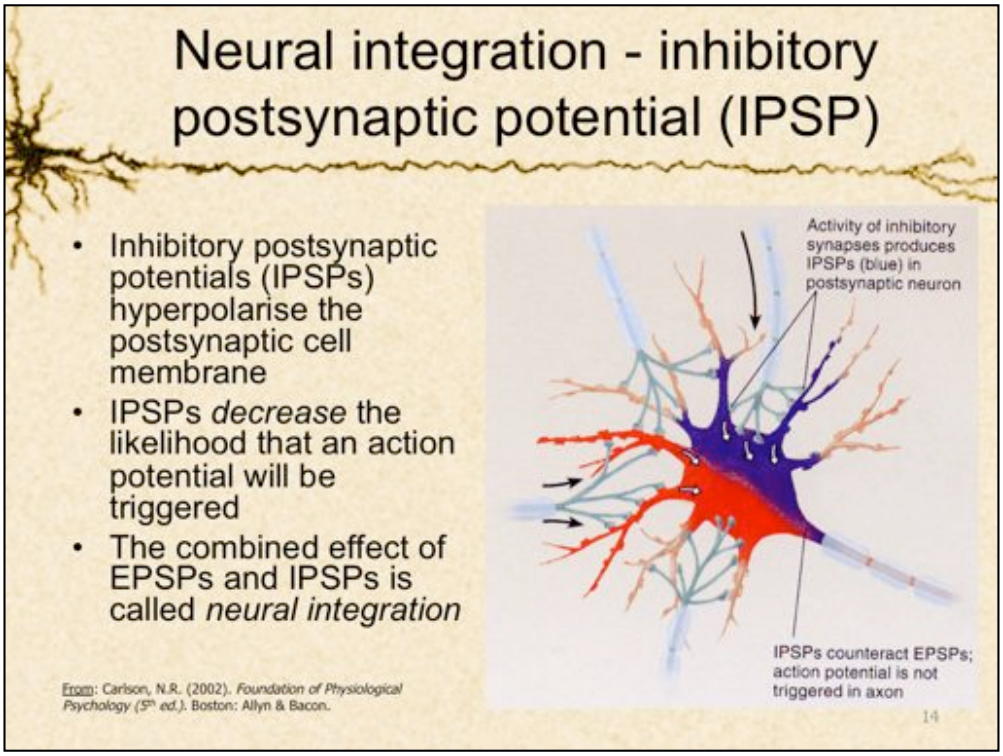
EPSPs *increase* the likelihood that an action potential will be triggered in the postsynaptic neuron.



Prior to the release of neurotransmitter molecules from the presynaptic terminal button, the membrane potential of the postsynaptic neuron is at its resting level (i.e., -70 mV).

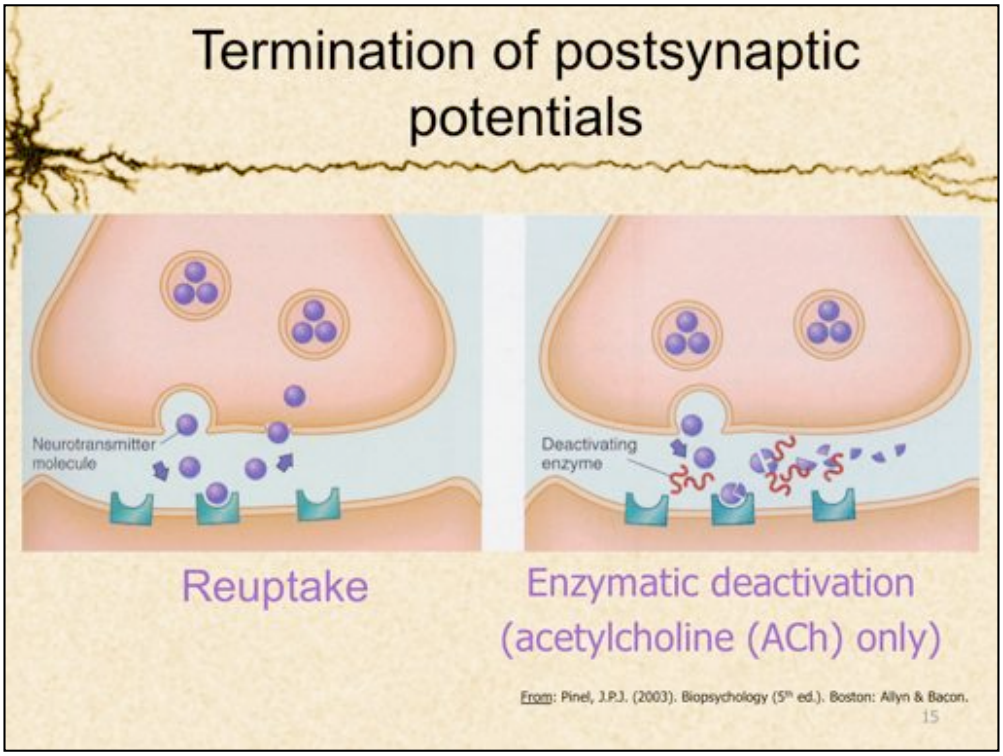


After neurotransmitter molecules are released from the presynaptic terminal button, they diffuse across the synaptic cleft and bind to receptors on the postsynaptic membrane. If the neurotransmitter binds to sodium ion channels, these will allow an inflow of sodium ions, causing a depolarising EPSP in the dendrites of the postsynaptic neuron.



What happens if some of the terminal buttons form inhibitory synapses. Inhibitory postsynaptic potentials are hyperpolarising, and therefore they reduce the likelihood that an action potential will be triggered in the postsynaptic neuron. Thus, IPSPs tend to cancel out the effects of EPSPs.

The interaction between the effects of EPSPs and IPSPs is known as **neural integration**. The rate at which a neuron fires is determined by the relative activity of excitatory and inhibitory synapses on its dendrites and cell body. If the activity of excitatory synapses increases, the firing rate of the postsynaptic neuron also increases. Conversely, if the activity of inhibitory synapses increases, the firing rate of the neuron *decreases*.

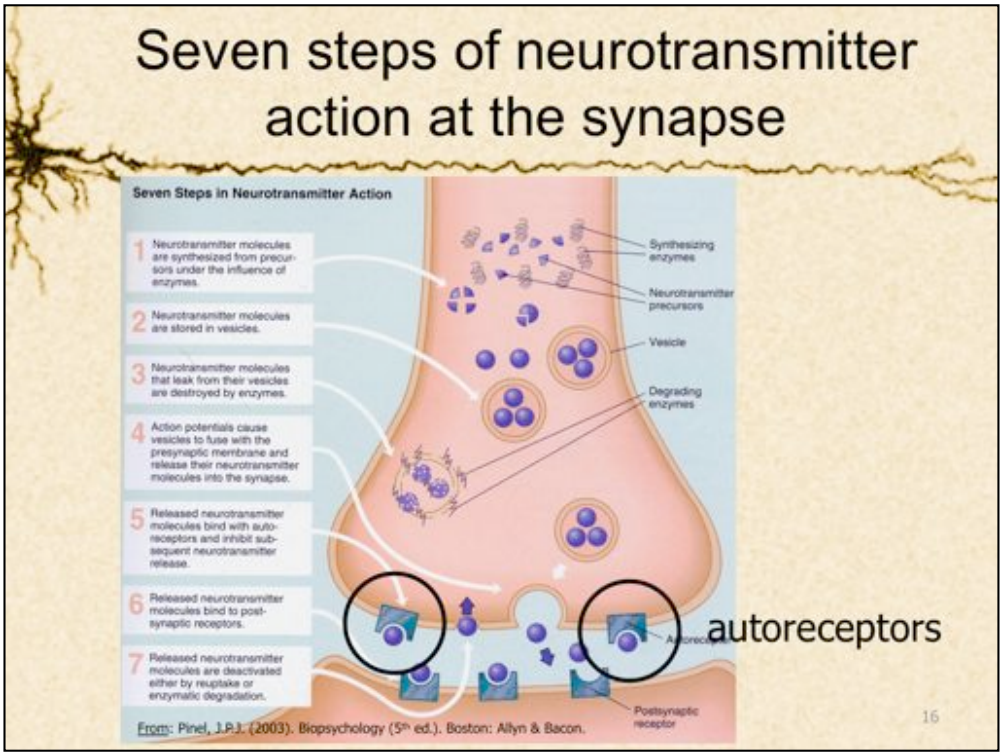


After release of the neurotransmitter and initiation of the postsynaptic potential (either depolarisation of hyperpolarisation), two mechanisms ensure that any excess neurotransmiter substances left in the synaptic cleft are mopped up.

1) **Reuptake** – the neurotransmitter is removed from the synaptic cleft via special **transporter molecules** in the terminal button. These molecules use energy to draw the neurotransmitter back into the cytoplasm of the presynaptic neuron.

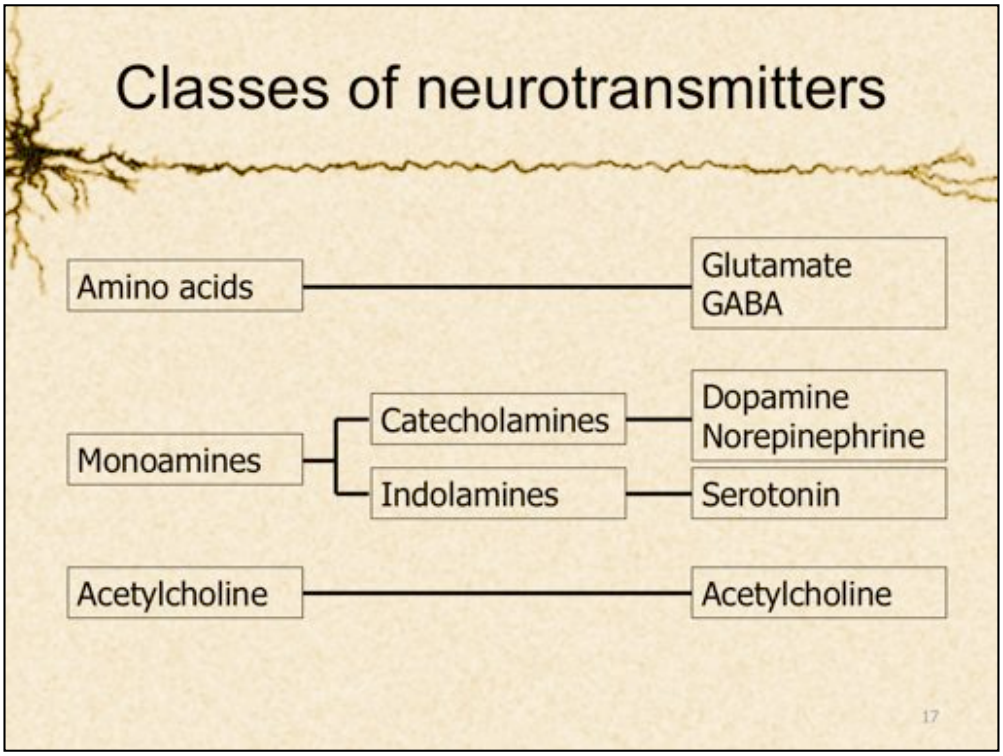
- **Enzymatic deactivation** – an enzyme in the synaptic cleft destroys the remaining neurotransmitter molecules. Such deactivation seems to occur only for one type of neurotransmitter, called **acetylcholine (ACh)**. The enzyme that destroys ACh in the synapse is called **acetylcholinesterase (AChE)**; it does its job by breaking ACh into its constituents, acetate and choline.

These two processes ensure that the postsynaptic receptors are only exposed to the neurotransmitter for a very brief period, thereby allowing many depolarisations and hyperpolarisations to occur in a very short space of



Here is a summary of the seven steps involved in neurotransmitter action at the synapse:

1) Neurotransmitter (NT) molecules are synthesised from their precursors by enzymes
2) NT molecules are stored in vesicles
3) NT molecules that leak from vesicles are destroyed by enzymes
4) Action potentials cause vesicles to fuse with the presynaptic cell membrane, releasing their NT into the synaptic cleft
5) Released NT binds with **autoreceptors** in presynaptic membrane, limiting further release of the NT
6) Released NT binds with receptors on postsynaptic membrane, causing ion channels to open
7) Free NT molecules in the synaptic cleft are taken back up by transporter molecules in the presynaptic membrane, or destroyed by enzymes



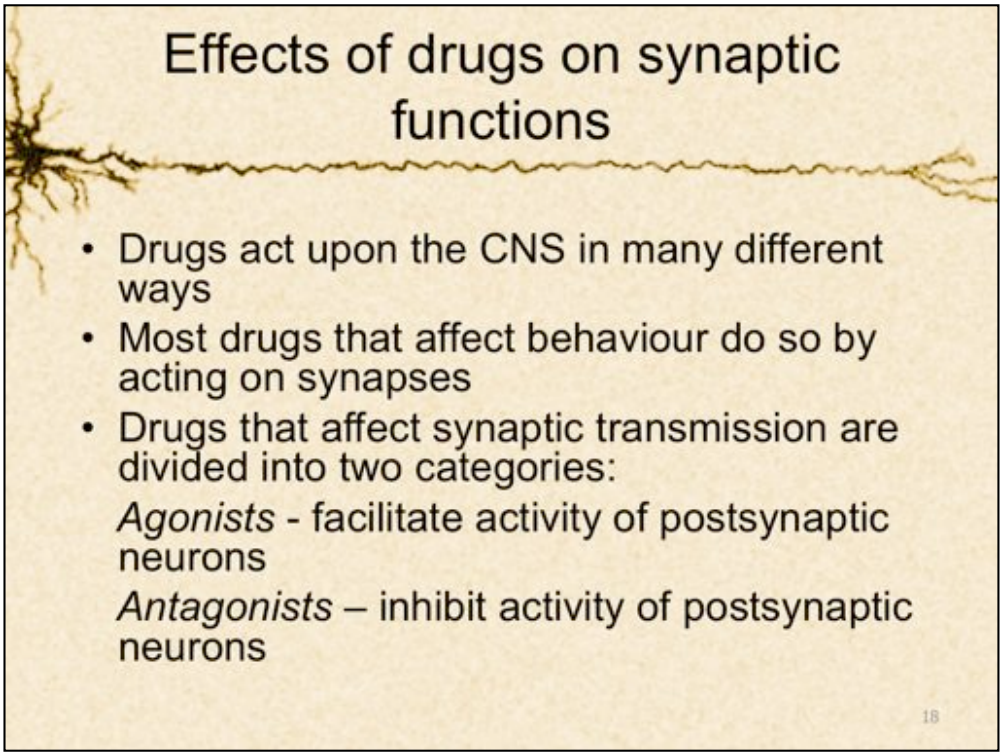
There are four classes of small-molecule neurotransmitters: amino acids, monoamines, soluble gases and acetylcholine. There is one class of large-molecule neurotransmitter: neuropeptides.

Glutamate is the most common excitatory neurotransmitter in the CNS

GABA (gamma aminobutyric acid) is the most common inhibitory neurotransmitter

The **monamines** (**dopamine**, **norepinephrine**, **serotonin**; so named because they are synthesised from a single amino acid) are present in groups of neurons that are located mostly in the brainstem.

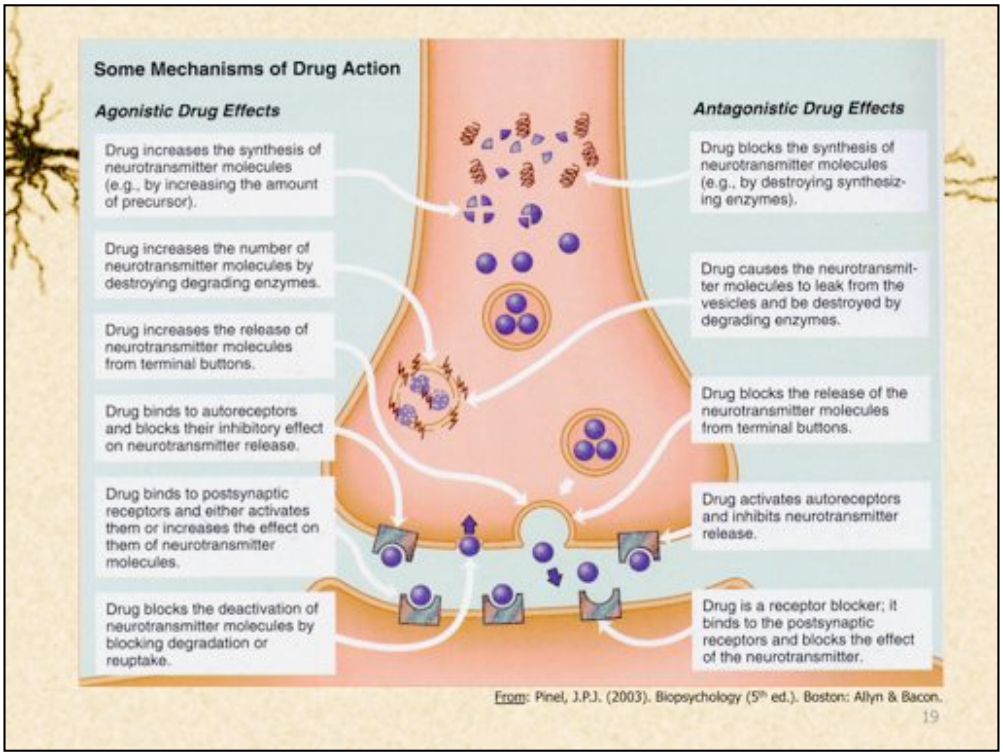
Acetylcholine is the neurotransmitter that operates at synapses with muscles, as well as other parts of the CNS.



Most drugs influence the activity of the nervous system by modulating the activity of the synapse.

If the drug increases the activity of the synapse, it is call an **agonist**.

If the drug decreases the activity of the synapse, it is call an **antagonist**.



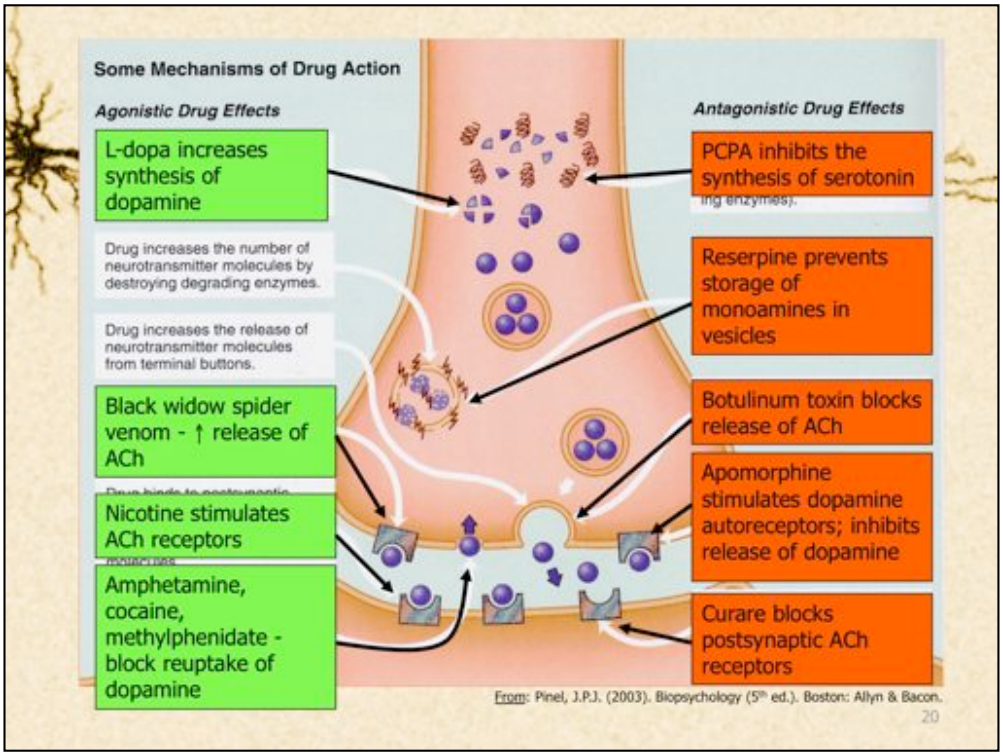
Drugs can influence the the synapse at each of the seven stages of neurotransmitter action

Agonists can do any of the following…

1) Increase the number of neurotransmitter (NT) molecules are synthesised
2) Increase the number of NT molecules that are stored in vesicles
3) Destroy the enzymes that attack NT molecules
4) Increase the number of vesicles that fuse with the presynaptic cell membrane
5) Decrease the activity of autoreceptors
6) Binding directly with the postsynaptic membrane, causing ion channels to open
7) Decreasing the amount of NT that is reuptaken or destroyed by enzymes

Antagonists can do any of the following…

1) Decrease the number of neurotransmitter (NT) molecules are synthesised
2) Decrease the number of NT molecules that are stored in vesicles



Some agonistic drug actions:

L-dopa increases the synthesis of dopamine – this drug is used to treat the symptoms of Parkinson's disease

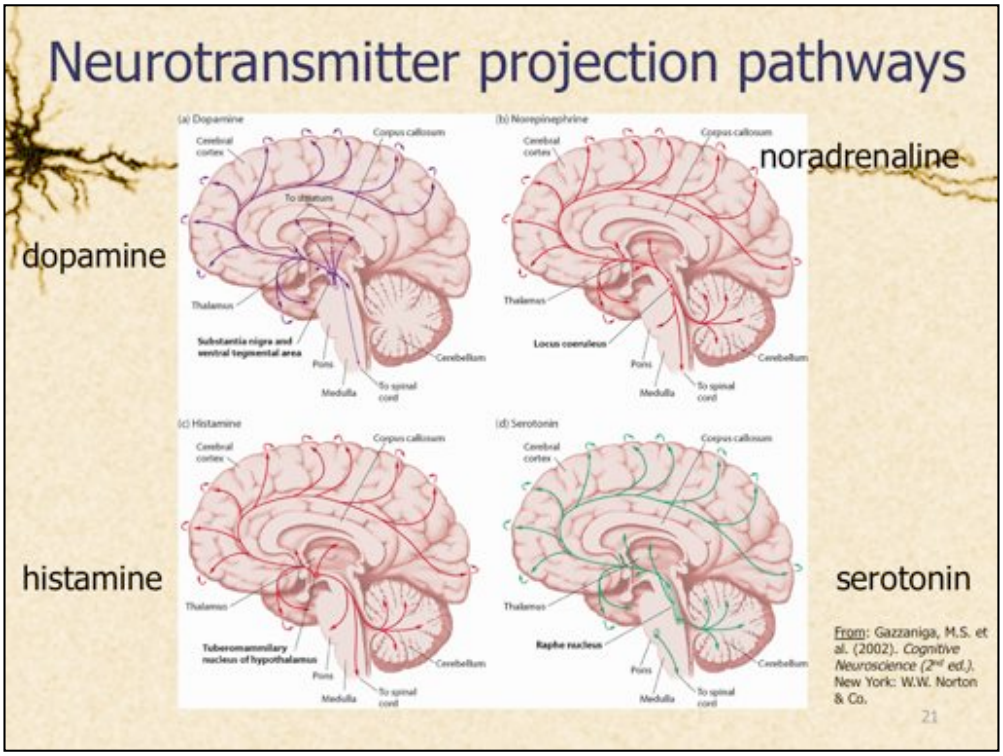
Venom from the black widow spider stimulates the release of acetylcholine (ACh)

Nicotine (e.g., from tobacco) stimulates ACh receptors

Amphetamine, cocaine and methylphenidate block reuptake of dopamine from the synapse. Methylphenidate (Ritalin) is used to treat attention deficit/ hyperactivity disorder in children.

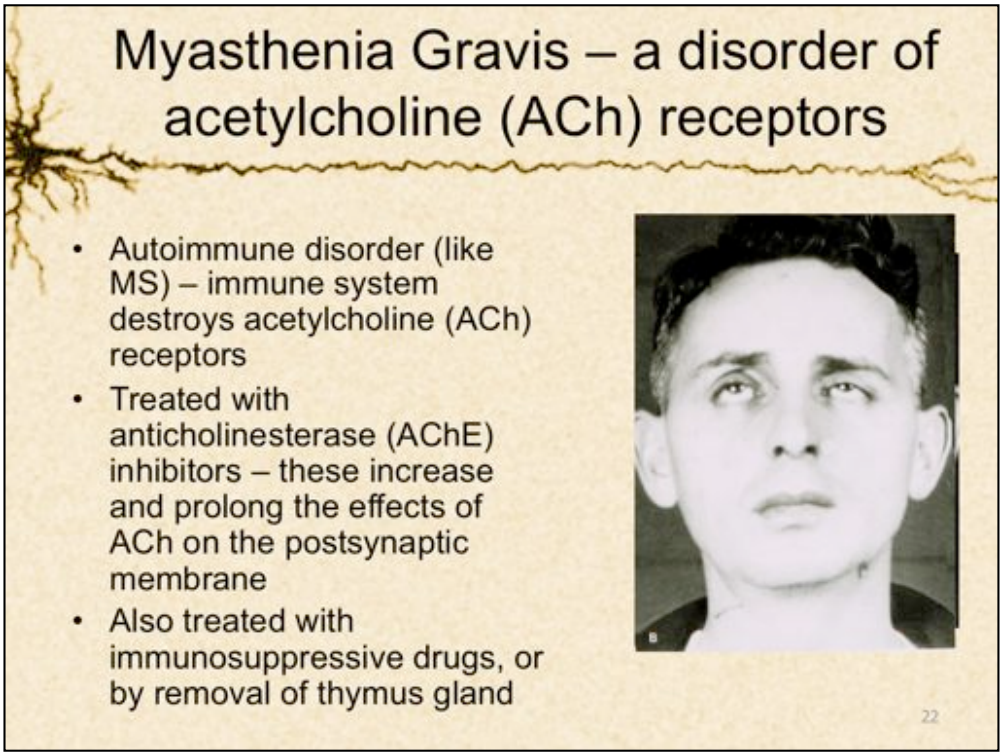
Some antagonistic drug actions:

PCPA inhibits the synthesis of **serotonin** (important in regulating mood and arousal, and in regulating pain)



Different neurotransmitters are produced by particular clusters of neurons and distributed widely in the CNS.

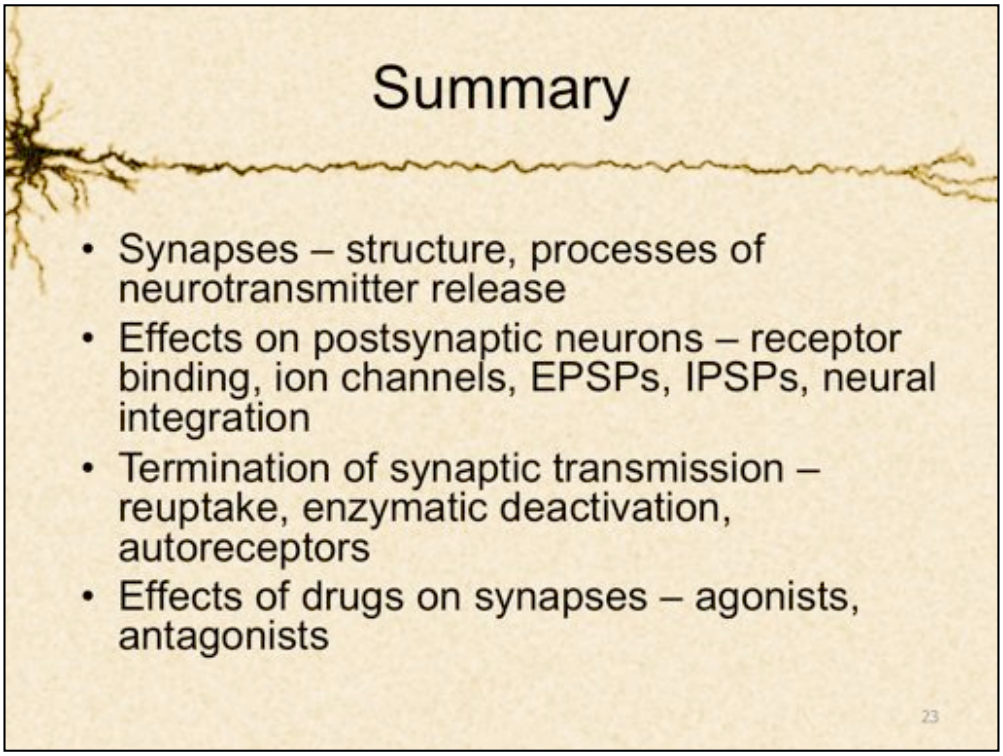
Most of these clusters are in the **brainstem** and **midbrain**.



We can now understand more about myasthenia gravis and how it might be treated.

In this disease the person's own immune system destroys ACh receptors, which are located on synapses with the muscles – this causes weakness.

In 1934 Dr Mary Walker noticed that the symptoms of myasthenia gravis were similar to those of people poisoned with curare. The antidote for curare poisoning is a drug called **physostigmine**, which deactivates acetylcholinesterase (AChE; remember this enzyme mops up ACh from the synapse). By reducing the amount of AChE in the synapse, the amount of ACh in the synapse is increased and prolonged. This helps to increase the strength of synaptic transmission at the muscles, and helps to overcome the muscle weakness.


Summary
• Synapses – structure, processes of neurotransmitter release
• Effects on postsynaptic neurons – receptor binding, ion channels, EPSPs, IPSPs, neural integration
• Termination of synaptic transmission – reuptake, enzymatic deactivation, autoreceptors
• Effects of drugs on synapses – agonists, antagonists
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