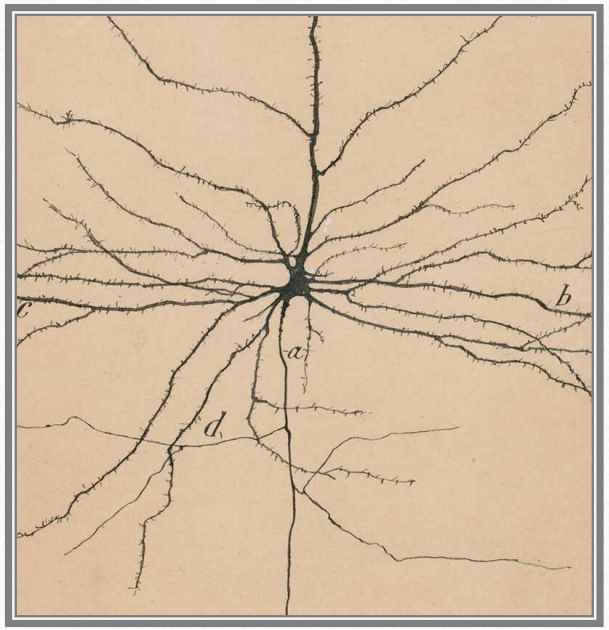
An Introduction to Neurotransmission for Psychology Teachers

EFPTA Conference, Spring 2024

Why study neurotransmission?

- It had been suspected since the 19th century that neurons communicate with each other and other tissues → neurons form a network with discontinuities between cells.
- For the nervous system to function properly, transmission must also be possible in a discontinuous network → synapses occur between individual neurons.
- Synapses may be functionally divided into two groups, chemical and electrical synapses.
- In chemical synapses, where there is no mechanical connection between neurons, transmission is based upon neurotransmitters and other neurochemicals. In this case, a microscopically small *synaptic cleft* occurs between two cells.
- In electrical synapses, the cells are directly coupled to each other via *gap junctions*. Electrical synapses occur mostly outside the central nervous system, the best known example being the cardiac muscle.
- Synapses are of central importance from an information modification perspective: in effect, a single synapse "decides" whether transmission will proceed, and in which direction. This is comparable with how the central component of the digital computer, the transistor, functions. The fine structure of synapses was only resolved in the 1950s, owing to the introduction of electron microscopy.



Basic properties of synapses

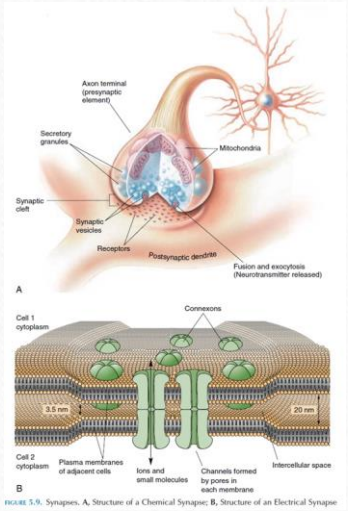
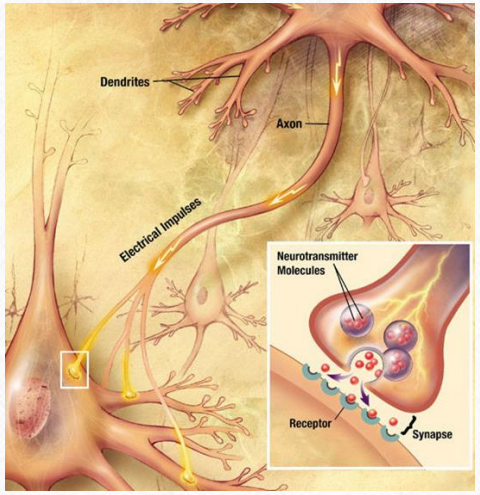
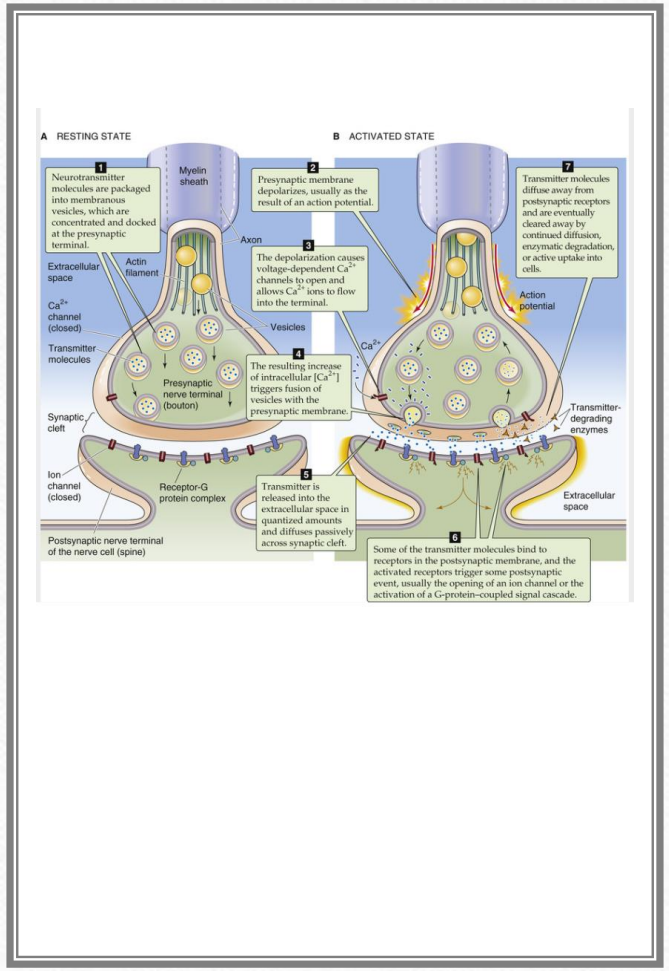


FIGURE 5.9. Synapses. A, Structure of a Chemical Synapse; B, Structure of an Electrical Synapse

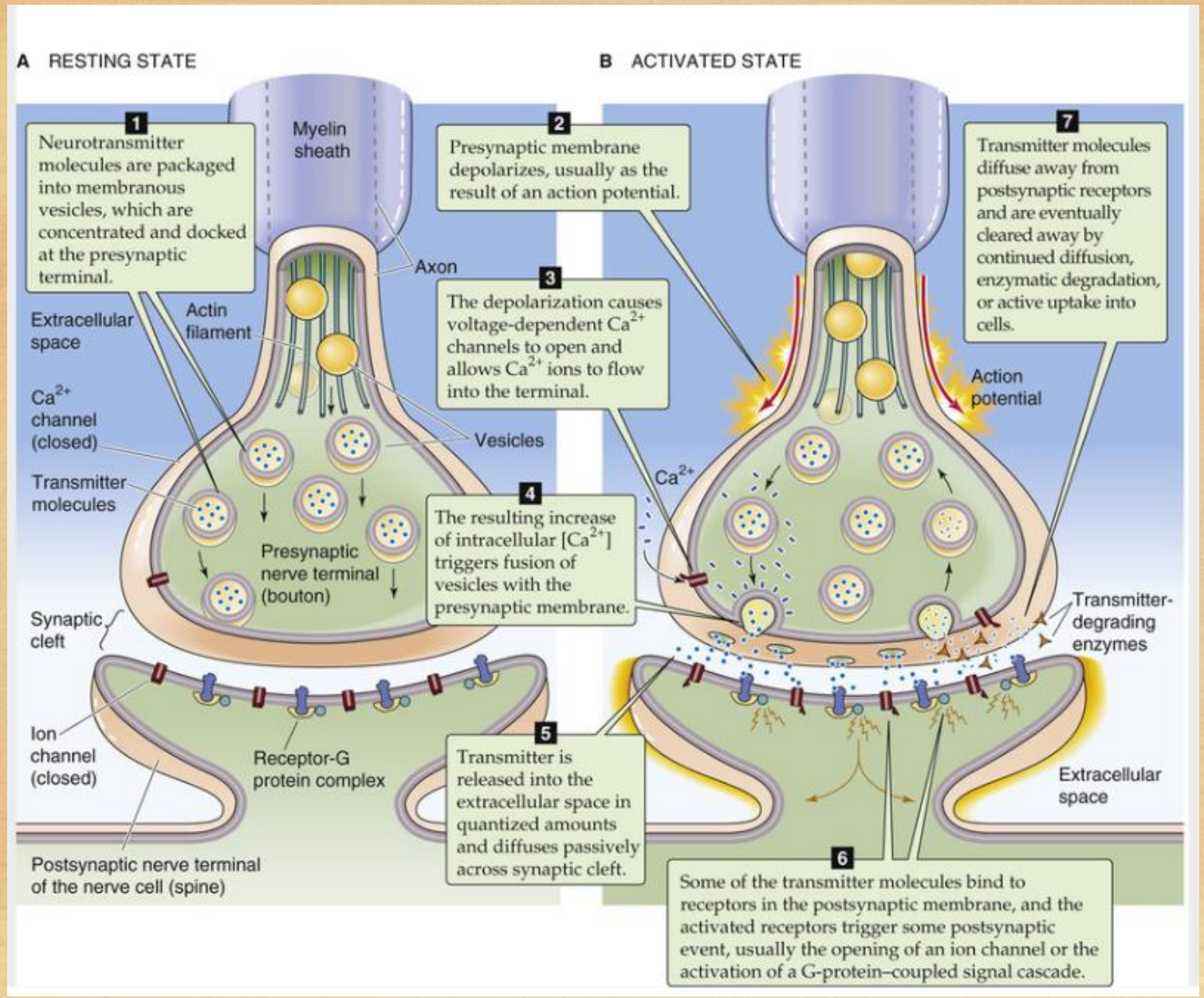


- From a historical perspective, an important model system in the study of synapses has been the *neuromuscular junction*. In skeletal muscle, the neurotransmitter is *acetylcholine*. Later research has revealed that other types of synapses differ significantly from both neuromuscular junctions and each other.
- In the 19th century, it had been discovered that biological systems exhibit electrical signaling. This observation unraveled a major conceptual issue: were if not for the neurotransmission machinery between cells, it can be shown mathematically that the signal would be attenuated to about one ten-thousandth of its original amplitude, making transmission impossible.
- Two major theories emerged regarding the nature of neurotransmission: the reticular theory postulated a network of neurons directly connected to each other, whereas, according to the synaptic theory, neurotransmission would necessitate a chemical agent. In retrospect, both theories were essentially correct.
- In electrical synapses, the neural cell membranes (neurolemmae) are in direct apposition with a distance of approximately three nanometers between cells. Macroscopically, it seems as if the cells were connected by a discoid structure, but in fact, as revealed by electron microscopy, this is a gap junction. The gap junction consists of connexons, each of which consists of six connexin molecules.
- In a chemical synapse, the transcellular distance is much larger, approximately 30-50 nanometers. A special feature of chemical synapses are the neurotransmitter vesicles on the presynaptic side. These are spherical membrane vesicles that contain one or more neurotransmitters in high concentration.



Synaptic structure reflects function

- In electrical synapses, changes in transmembrane voltage are directly conducted between cells, whereas in chemical synapses, neurotransmisson is dependent upon diffusion of a neurotransmitter. The normal function of a synapse may be schematically described by multi-stage transmission cycle.
- Our knowledge regarding chemical synapses is older than that regarding electrical synapses: it was shown already in the early 20th century that extracts from the adrenal cortex can modify heart rate and/or blood pressure. In 1921, Otto Loewi showed that the parasympathetic vagus nerve (*n. vagus*, lit. “meandering nerve”) produces acetylcholine, which slows the heart rate. This is considered the first indisputable piece of evidence regarding the existence of chemical neurotransmission.



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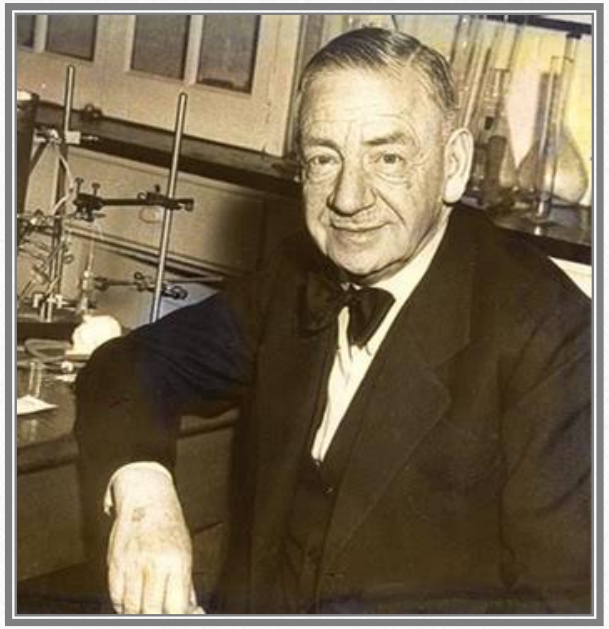
The Loewi experiment and the diversity of synaptic transmission

- Loewi and colleagues made two important observations: firstly, secretions collected from an isolated frog heart slowed another heart when treated with it. On the other hand, the *same* transmitter had the "opposite" effect on skeletal muscle. This substance was later identified as acetylcholine. In retrospect, this reveals that the diversity of synaptic transmission is due to diversity in both neurotransmitters and their receptors. Loewi and colleagues were granted the 1936 Nobel Prize in Physiology.



In electrical synapses, the cytoplasms of adjacent neurons are directly connected

- Direct electrical neurotransmission was only first observed in the late 1950s. In 1959, Furshpan and Potter showed that direct electrical neurotransmission takes place in the abdominal nerve of the European crayfish (*astacus astacus*) without a measurable synaptic delay (*chemical* neurotransmission is associated with a characteristic synaptic delay due to the operation of the synaptic machinery). In other words, in electrical synapses, genuine structural continuity exists between two cells. In these synapses, the connexons form a pathway facilitating the movement of charge carriers (in practice, ions). Electrical synaptic transmission may be either uni- or bidirectional, with the directionality dependent upon the connexin molecules expressed in each synapse. Some isoforms of connexin molecules are said to be *voltage-gated*, which means that the transsynaptic voltage determines whether the channel is open or not. This, however, is not a universal property of electrical synapses.

Electrical synapses have also been discovered in the central nervous system

- From our discussion thus far, one might surmise that being faster, electrical synapses would constitute a "better" technical solution than chemical synapses. However, empirical evidence shows that chemical synapses by far outnumber electrical ones. Why is this?

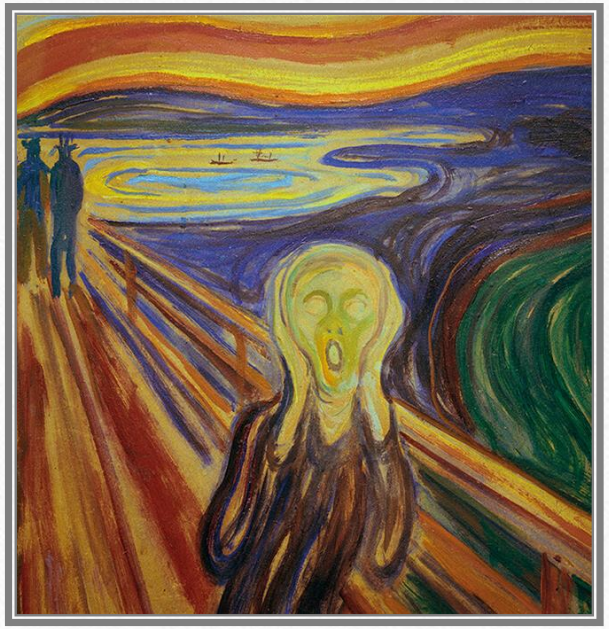
  1. The first explanation is that the nature of chemical synapses allows for the modification of information, for example, by amplifying an existing signal. Because neurotransmission based on chemical transmitters permits the protein molecules expressed on neural cell membranes to function as, for example, active amplifiers, the nature of a single chemical synapse is not strongly dictated by the electrical properties of the neurons participating in it. In contrast, electrical synapses only allow for signal attenuation, never amplification.

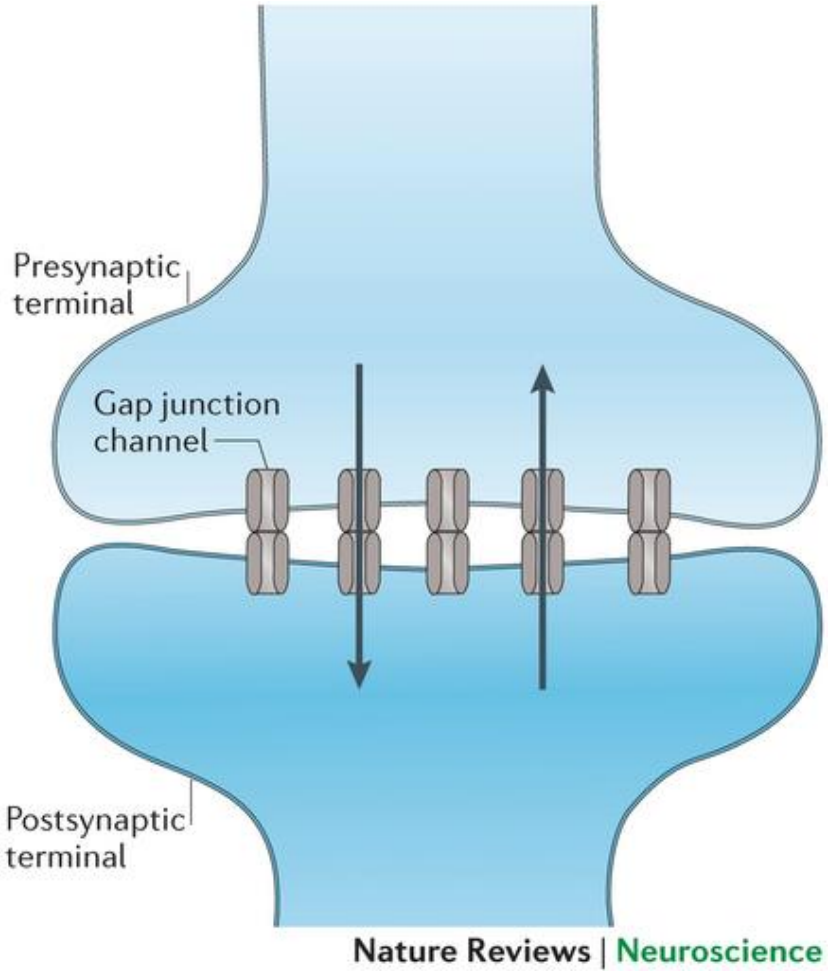
  2. Another viewpoint is related to the properties of the neurotransmitters present in the synapses (excitatory vs. inhibitory). Chemical synapses allow for the per-synapse selective inhibition or excitation of post-synaptic cells. Electrical synapses cannot be classified as excitatory or inhibitory, with the effect of synaptic transmission instead depenging on a larger number of factors. It is now known that electrical synapses are also subject to regulation, but apparently on a much more limited basis than chemical ones.

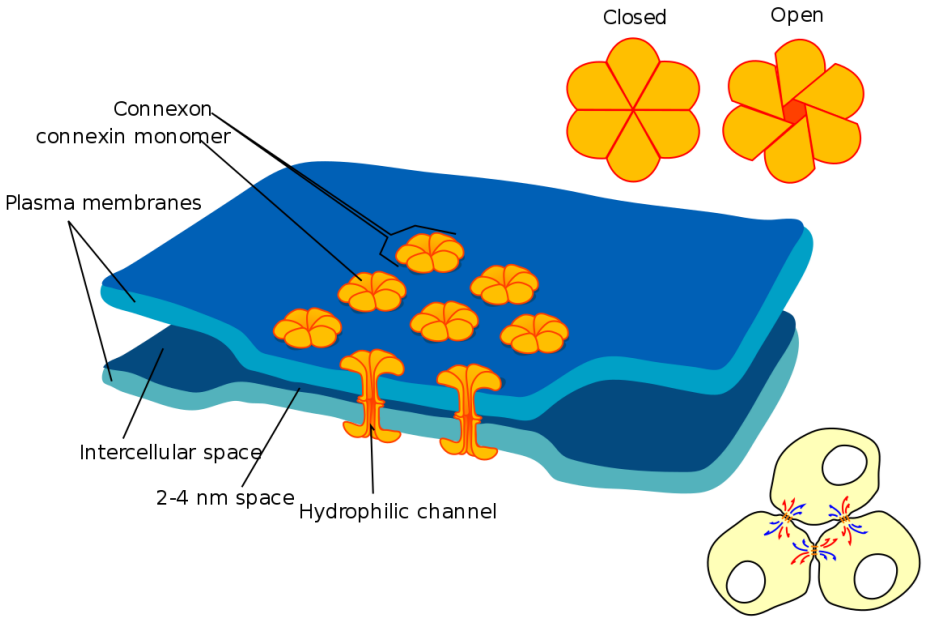
  3. A third viewpoint is related to the temporal properties of the physiologic responses triggered by chemical synapse function: in chemical synapses, the duration and time course of the responses may vary from milliseconds to hours or even longer periods. In electrical synapses, the effects of synaptic transmission usually do not outlast the synaptic event itself.

  4. The fourth viewpoint is related to plasticity, as recent neural activity can affect the strength of synapses, and as such they are better "platform" for processes such as learning and memory.

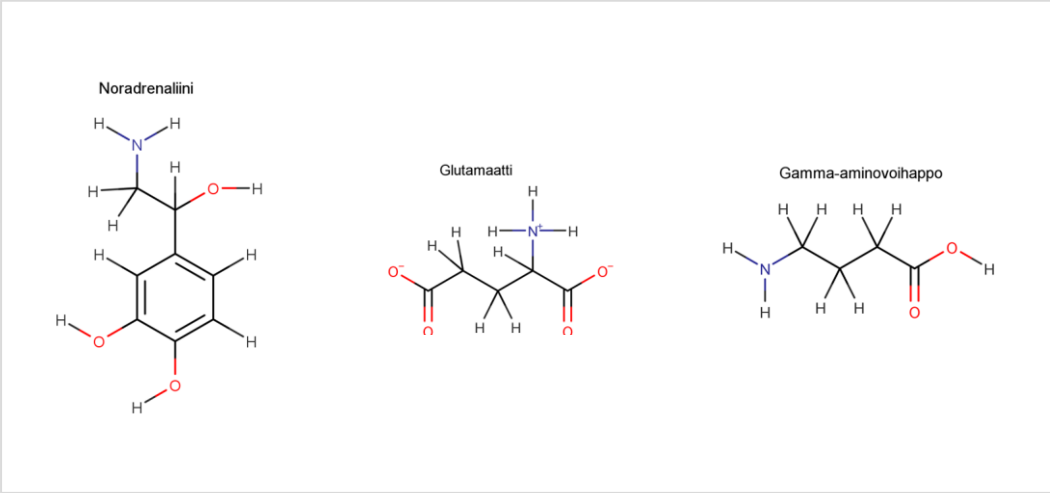
- The perceived advantages of electrical synapses may in some cases be more apparent than real. Bidirectionality may not be useful in many neural circuits, and the difference in transmission speed may not be that important either. Electrical synapses may be mostly useful in neural networks that must react first and that mediate *stereotypic* responses. In line with this, electrical synapses have been discovered in quick escape systems forming parts of fear response in neural networks, Neural networks coordinating rapid eye movements, or where rhythmic neural activity is required.




Presynaptic terminal
Gap junction channel
Postsynaptic terminal
Nature Reviews | Neuroscience

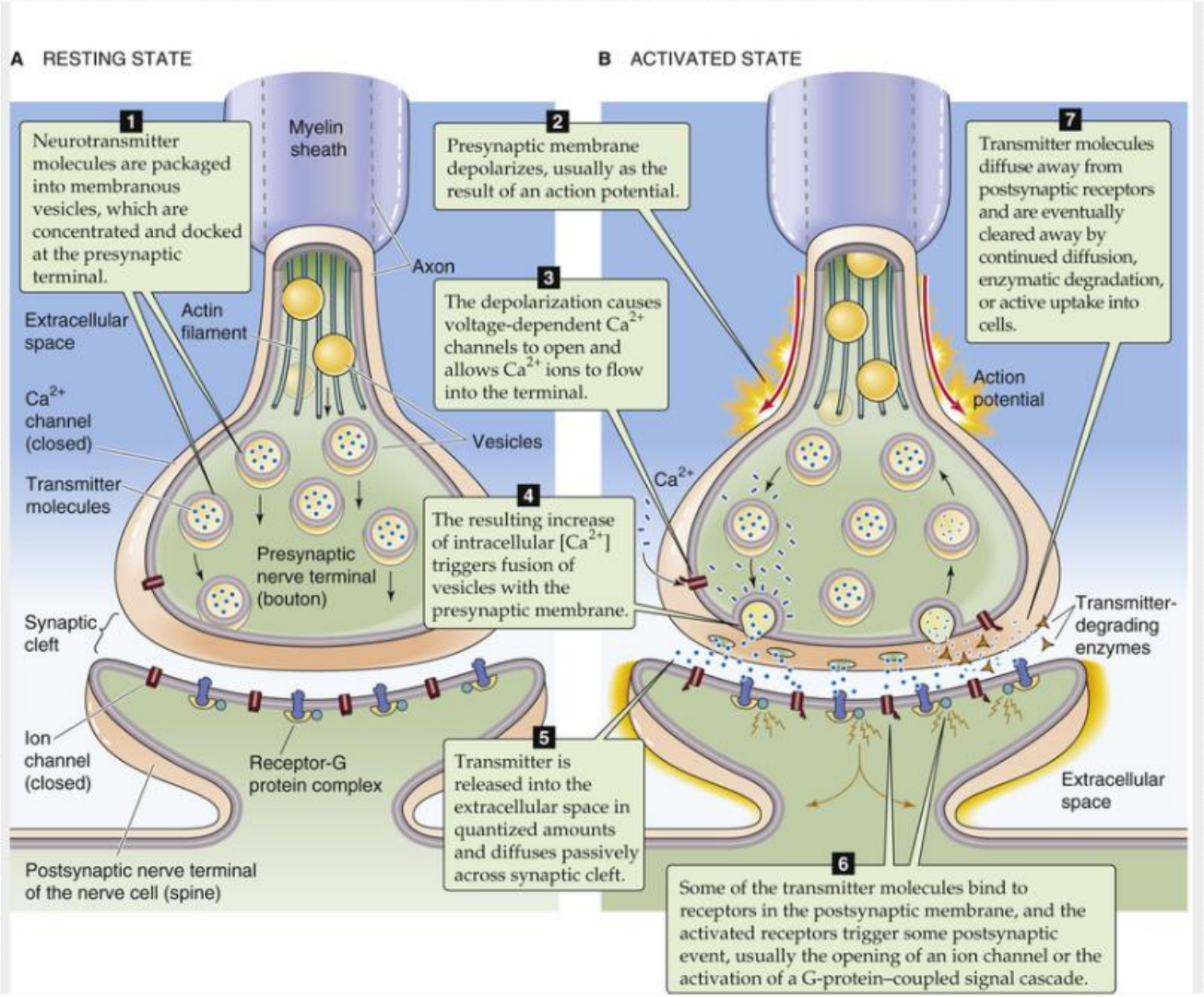

Closed
Open
Connexon
connexin monomer
Plasma membranes
Intercellular space
2-4 nm space
Hydrophilic channel

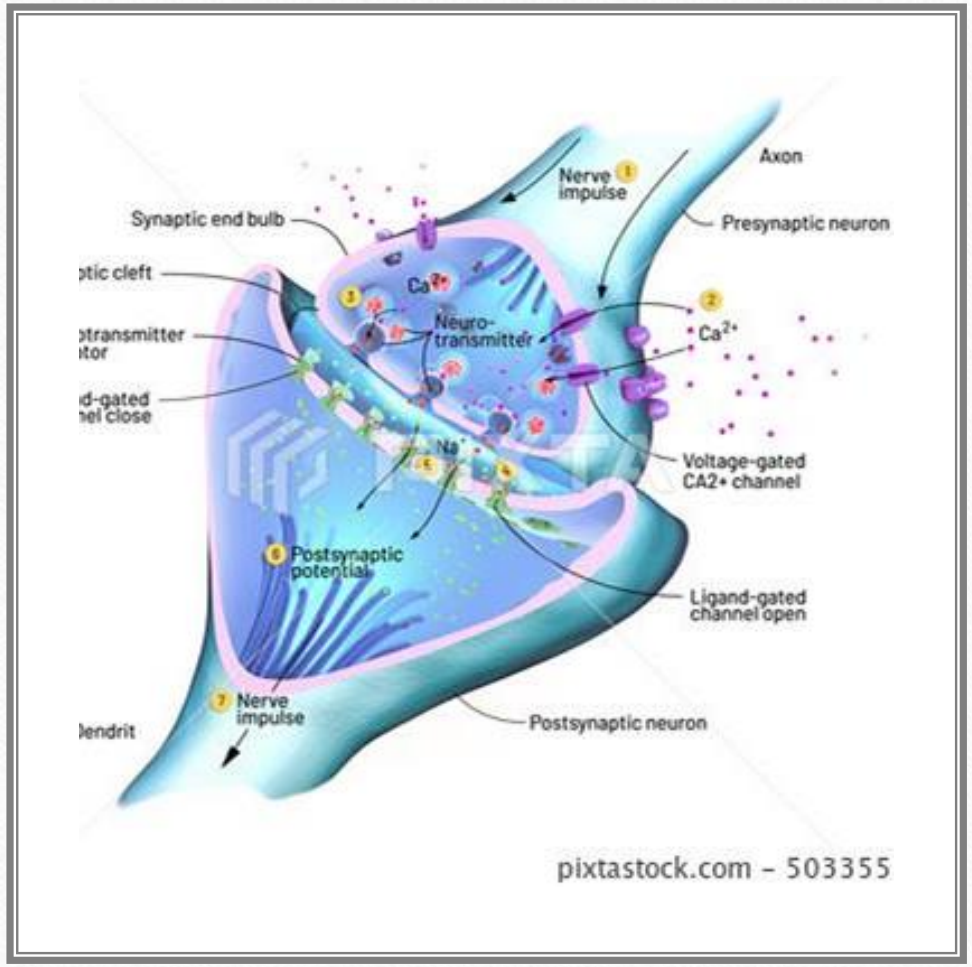
Chemical synaptic function is based on neurotransmitters



- Chemical synapses are mostly unidirectional, although exceptions have more recently been discovered. The direction of current flow is from the presynaptic cell to post-synaptic cell (which contains the neurotransmitter receptor). Transmitter secretion is a characteristic feature of chemical neurotransmission. Neurotransmitters include:

  - Small organic molecules (carbon-containing molecules present in living tissues): amino acids (including glutamate, aspartate,gamma-aminobutyric acid or GABA, and glycine), amines (acetylcholine, serotonin, histamine, dopamine, epinephrine and norepinephrine)
  - Peptides (small protein molecules such as endorphins and enkephalins, which are *endogenous opioids*; also called large molecule neurotransmitters, because they are large for neurotransmitter molecules but small for proteins). Opioids are a collective term for substances whose effect resembles that of the opium poppy (*Papaver somniferum*).
  - Gases (such as nitric oxide)
  - Endocannabinoids (fat soluble molecules, whose effects resemble those of THC as found in *Cannabis sativa*; such as anandamide and 2-arachidonoylglycerol (2-AG).
  - The list of known transmitters comprises about twelve non-peptides and at least 100 peptides, but the list is constantly growing.
  - We mentioned previously that a single synapse may secrete more than one neurotransmitter. Usually this phenomenon, known as *cotransmission*, involves the simultaneous release of a small molecule and a large molecule transmitter, such as secretory granules containing enkephalin alongside acetylcholine vesicles. Both types of secretory bodies also contain adenosine triphosphate or ATP. Although the detailed mechanism is unknown, it appears that the secretion is controlled by the action potential frequency: it appears that, for example, in the case above, the simultaneous release of acetylcholine and enkephalin requires a higher stimulation frequency than does that of the primary transmitter, acetylcholine, alone. Therefore, if the frequency goes below a certain threshold, enkephalin secretion will cease, but acetylcholine secretion will continue.


A RESTING STATE
B ACTIVATED STATE
1
Neurotransmitter molecules are packaged into membranous vesicles, which are concentrated and docked at the presynaptic terminal.
Myelin sheath
Axon
2
Presynaptic membrane depolarizes, usually as the result of an action potential.
3
The depolarization causes voltage-dependent Ca^{2+} channels to open and allows Ca^{2+} ions to flow into the terminal.
7
Transmitter molecules diffuse away from postsynaptic receptors and are eventually cleared away by continued diffusion, enzymatic degradation, or active uptake into cells.
Extracellular space
Actin filament
Action potential
Ca^{2+} channel (closed)
Vesicles
Ca^{2+}
Transmitter molecules
4
The resulting increase of intracellular $[Ca^{2+}]$ triggers fusion of vesicles with the presynaptic membrane.
Presynaptic nerve terminal (bouton)
Transmitter-degrading enzymes
Synaptic cleft
Ion channel (closed)
Receptor-G protein complex
5
Transmitter is released into the extracellular space in quantized amounts and diffuses passively across synaptic cleft.
Extracellular space
Postsynaptic nerve terminal of the nerve cell (spine)
6
Some of the transmitter molecules bind to receptors in the postsynaptic membrane, and the activated receptors trigger some postsynaptic event, usually the opening of an ion channel or the activation of a G-protein–coupled signal cascade.

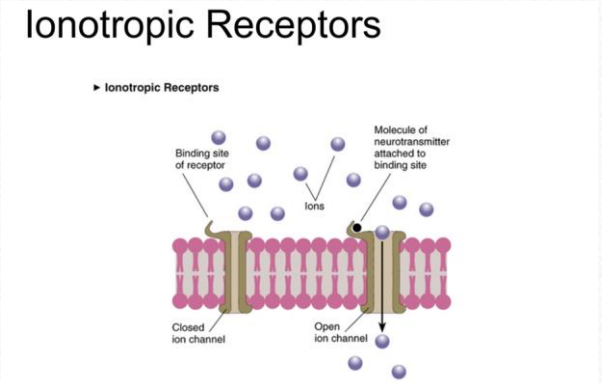


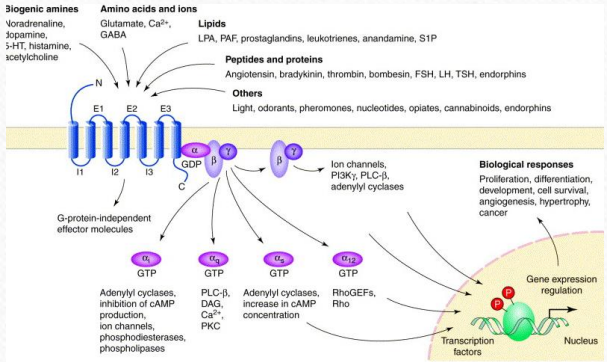
Synapses are diverse

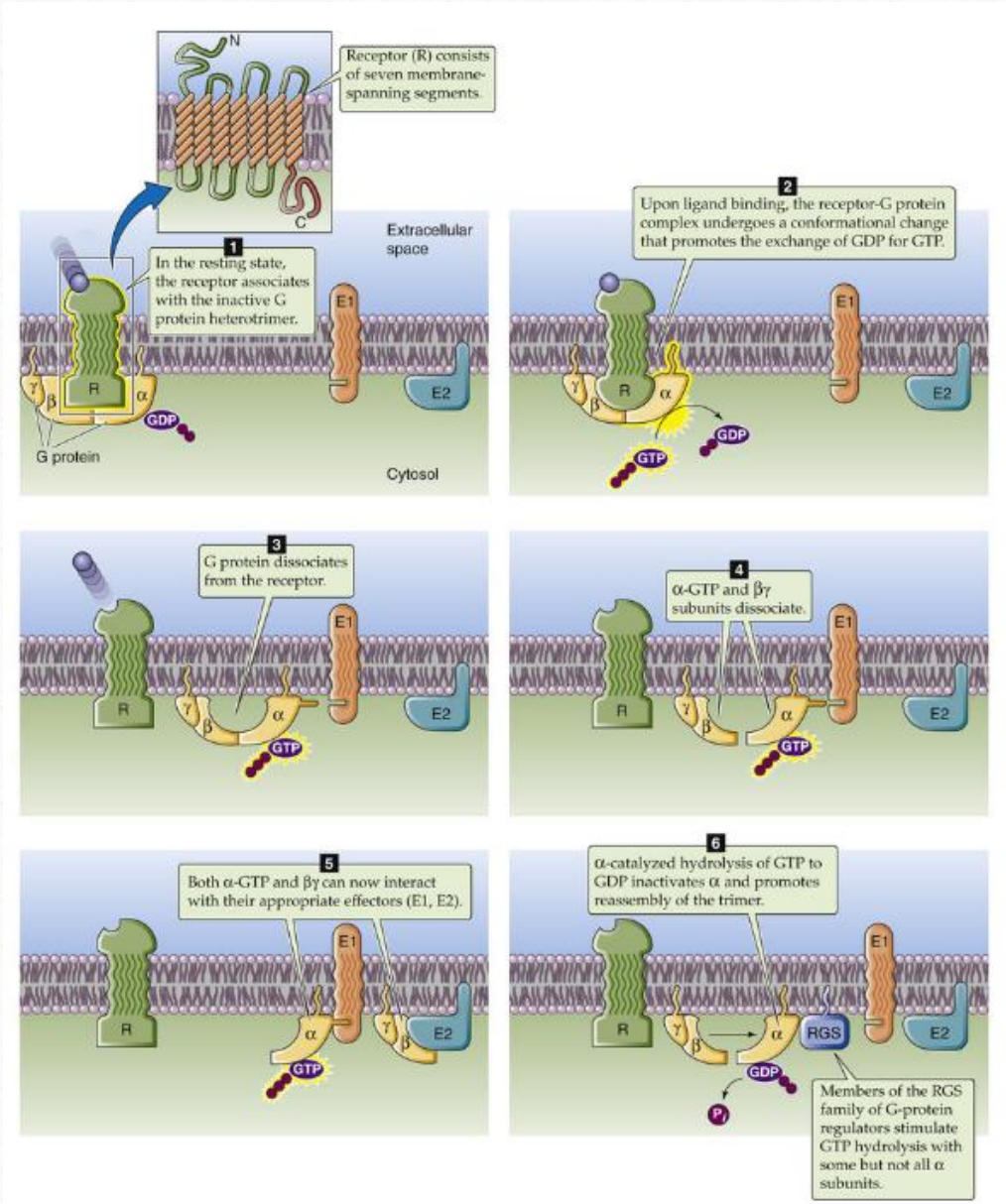
- Chemical synapses differ in many way:
  - Transmitters
  - Receptors
  - Post-synaptic events

Neurotransmitter receptors may be divided into two main classes

- Certain receptors contain an ion channel in their 3D structure. These are known as *ionotropic* receptors.
- Signal transmission in other receptors is associated with complex "metabolic" events, which is why these receptors are known as *metabotropic*. The activation of many metabotropic receptors is associated with a signaling cascade that leads to the activation of a so-called G-protein, giving them the name G-protein coupled receptors. G-proteins are large molecules that traverse the membrane seven times (also known as 7TM molecules). Receptor activation causes intracellular release of parts of the G-protein, which in turn may affect other biomolecules inside the cell. Upon termination of signaling, the structure of the G-protein reverts to its stable configuration.







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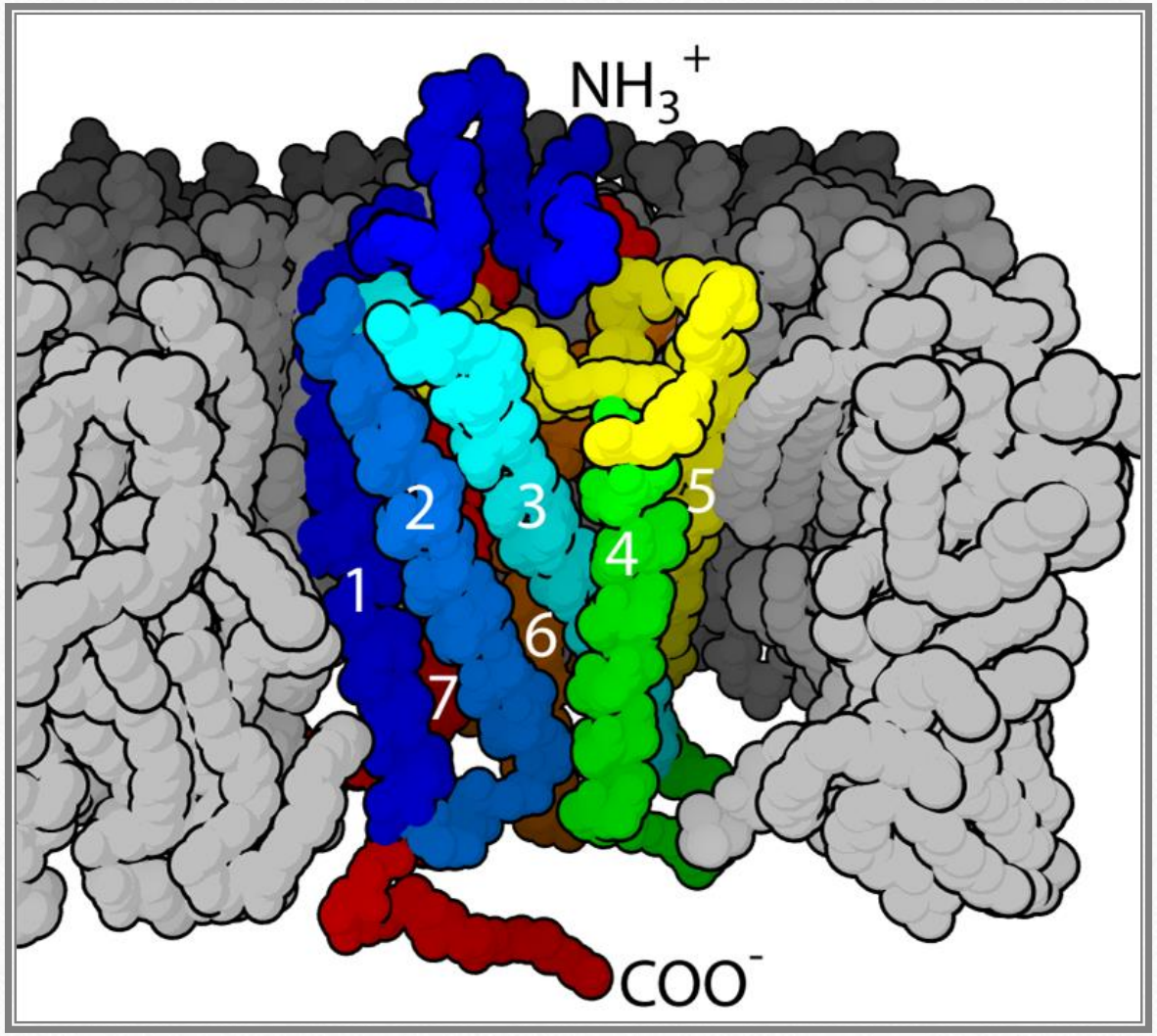
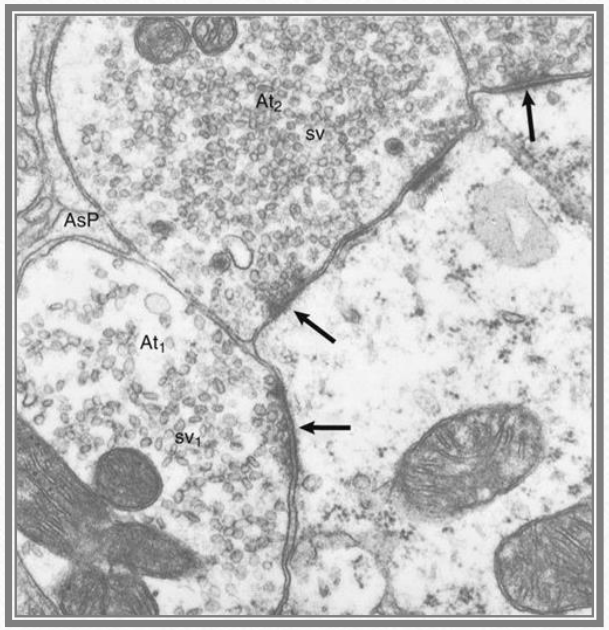
Synaptic diversity emerges as a combination of diversity in both neuotransmittors and their receptors

- As an example, acetylcholine has both ionotropic and metabotropic receptors: ionotropic or *nicotinic* acetylcholine receptors (further divided into classes Nm and Nn) are found in, for example, skeletal muscle, where attachment of neurotransmitter to the receptor opens sodium and potassium channels, triggering a small voltage change that activates the muscle fibre (causing the muscle to contract).
- Metabotropic or muscarinic acetylholine receptors are found in, for example, the heart (classes 1-5, of which class 2 is the most important in cardiac muscle). In these receptors, G-protein activations opens a separate potassium channel (there are none in the receptor itself).
- The names nicotinic and muscarinic are pharmacologic terms that are based upon the chemical substance (exogenous ligand) that causes them to activate. In some cases, some rather surprising compounds can act as exogenous ligands: for example, the active substance, *capsaicin*, in chili peppers (*Capsicum annuum*, *Capsicum chinense*) is an exogenous ligand of the TRPV1 pain receptor, which explains its effect. Similarly, the apparent cooling effect of menthol occurs because it activates several cold receptors (there is limited evidence that menthol may have mild actual cooling effects due to secondary effects of the substance).



Synaptic diversity is especially great in the central nervous system

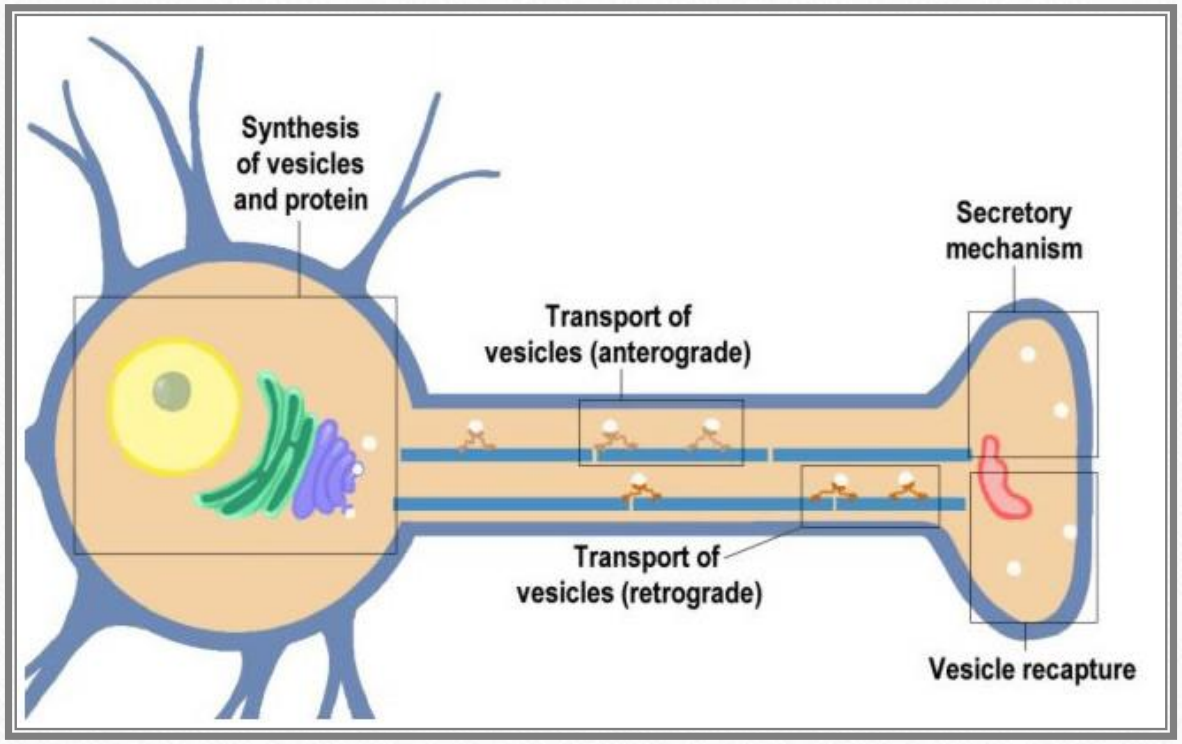
- All the components of the chemical synaptic transmission machinery appear in non-neuronal cells in some form. On the other hand, the CNS exhibits particularly great variety both in terms of transmitters and receptors. A good example is the temporal duration of the transmitter effect, which can vary from milliseconds to more than a week. As an example, the effects of some of the peptides associated with the brain's pain perception system can last for up to ten days, which explains the sensitisation of pain responses in conjunction with tissue damage.
- Synapses may be anatomically classified according to the structures between which they form: the CNS contains axoaxonic, axodendritic and axosomatic synapses, among others. The most excitatory synapses occur between axons and dendritic spines. Dendritic spines are known to be very important for carious learning-associated neural events (studied at the University of Helsinki; Pirta Hotulainen). The formation of dendritic spines is associated with changes in the shape of the neural cytoskeleton, which may be controlled by proteins which in turn are controlled by synaptic messaging cascades.
- As we saw previously, secretory granules occur in addition to transmitter vesicles in some synapses, that as an example may contain neuropeptides important for normal function of the pain system. Many of the compounds present in secretory granules, such as ACTH and cholecystokinin can also be found outside the nervous system.

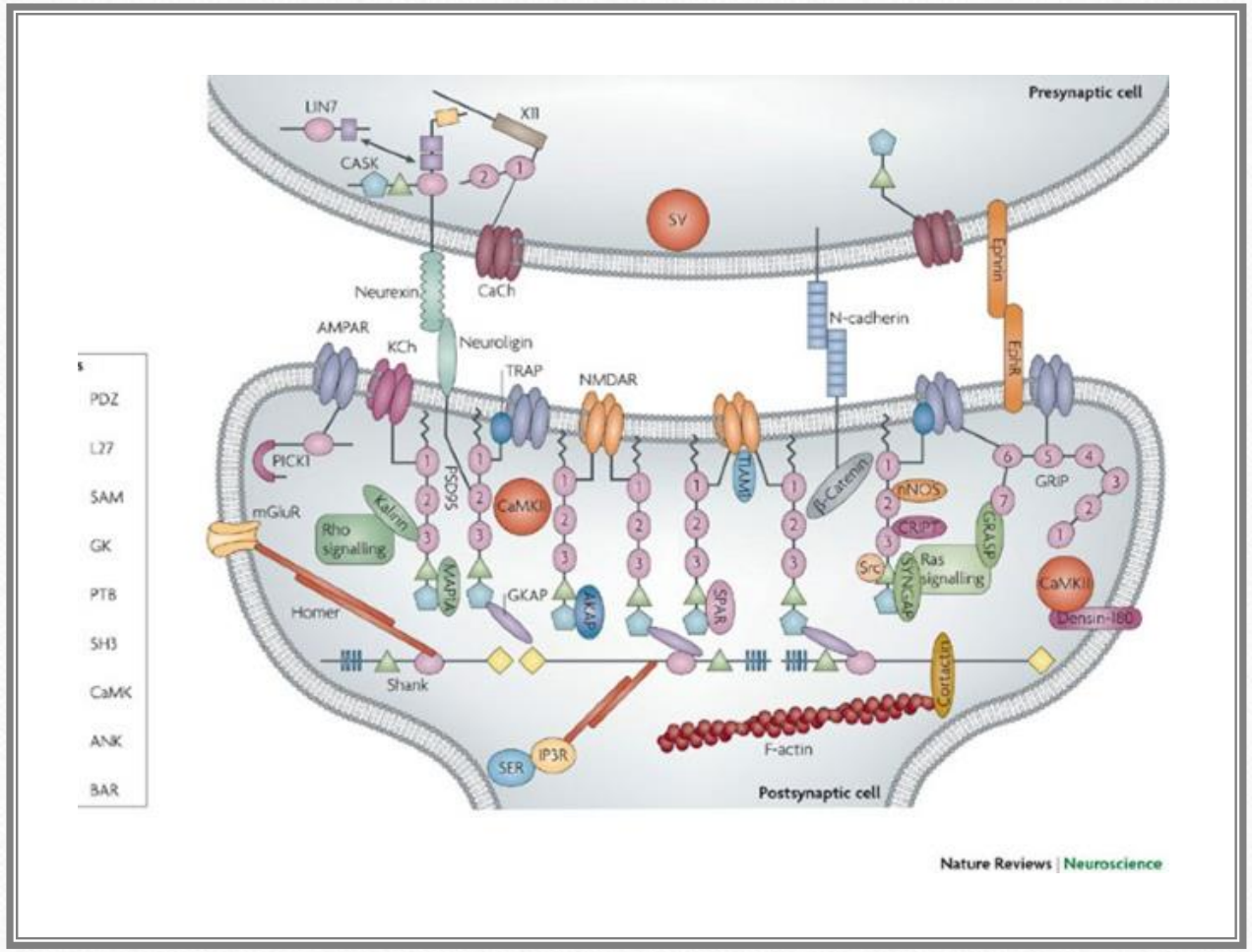


Synapses in the cochlear nucleus of the auditory pathway. The image shows three presynaptic terminals, in addition to postsynaptic densities that consists of protein. The areas marked with arrows are active zones of neurotransmitter release.

Transmitter release is tightly regulated

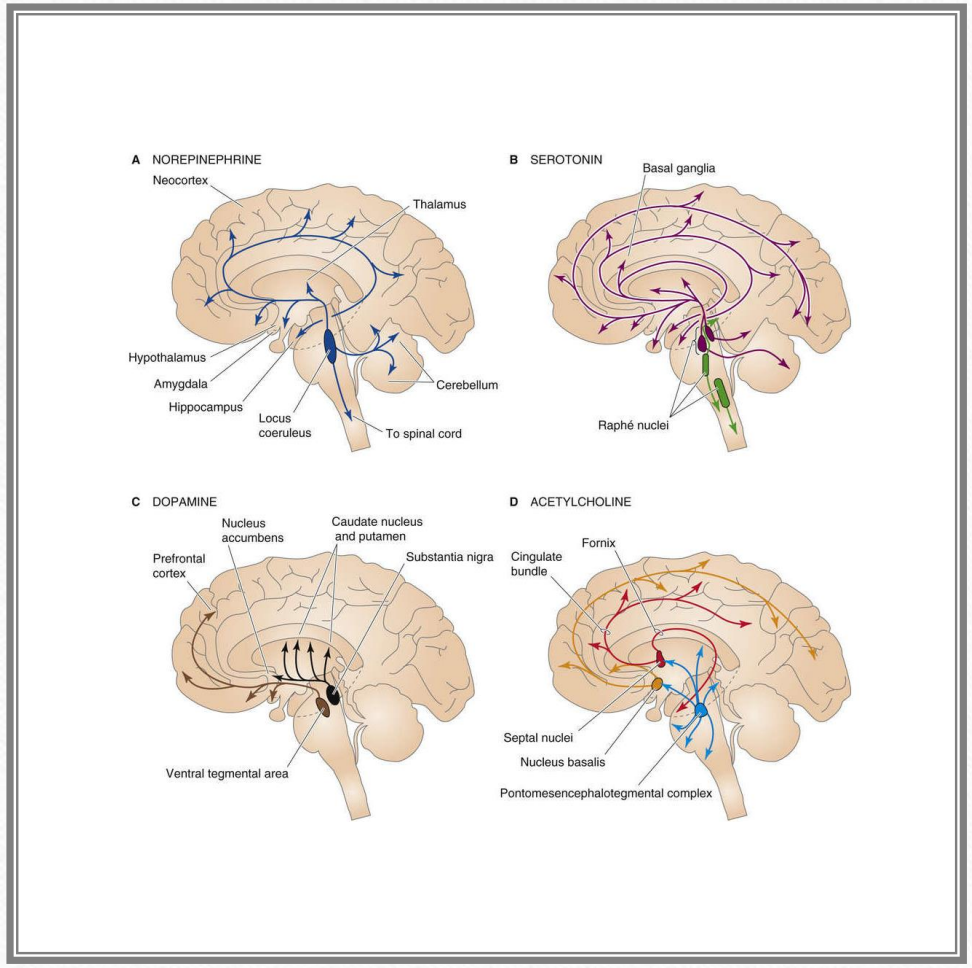
- The neural cytoskeletal attaches the transmitter vesicles (not the secretory granules) to special regions in the presynaptic terminal called *active zones* that also constitute zones of transmitter release. The number of active zones varies greatly per synapse.
- The secretory granules, containing neuropeptides, are instead randomly situated within the presynaptic terminal, and they are not associated with any active zones. The mechanisms regulating release from secretory granules are poorly understood.





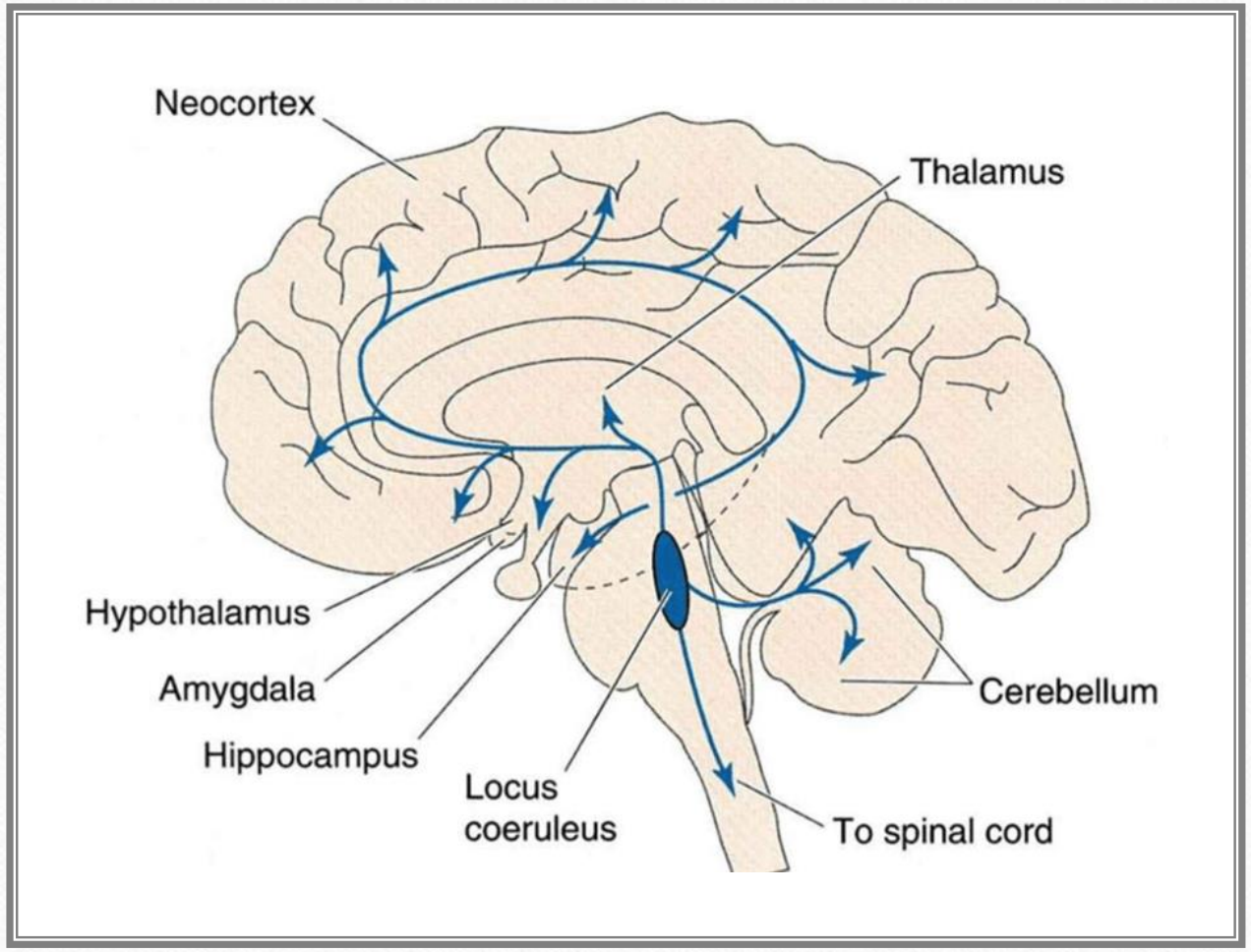
The post-synaptic membrane contains receptors and ancillary proteins

- The two membranes that comprise the synapse have the same orientation, and in chemical synapses are separated by a synaptic cleft of approx. 30 nanometers. The transmitter molecules must diffuse across this cleft in order to be able to initiate a response.
- In nearly all CNS synapses there is a dendritic spine on the post-synaptic side. A post-synaptic density, consisting of receptors and other proteins may also be defined (dozens of proteins known, but the real diversity is probably much higher).



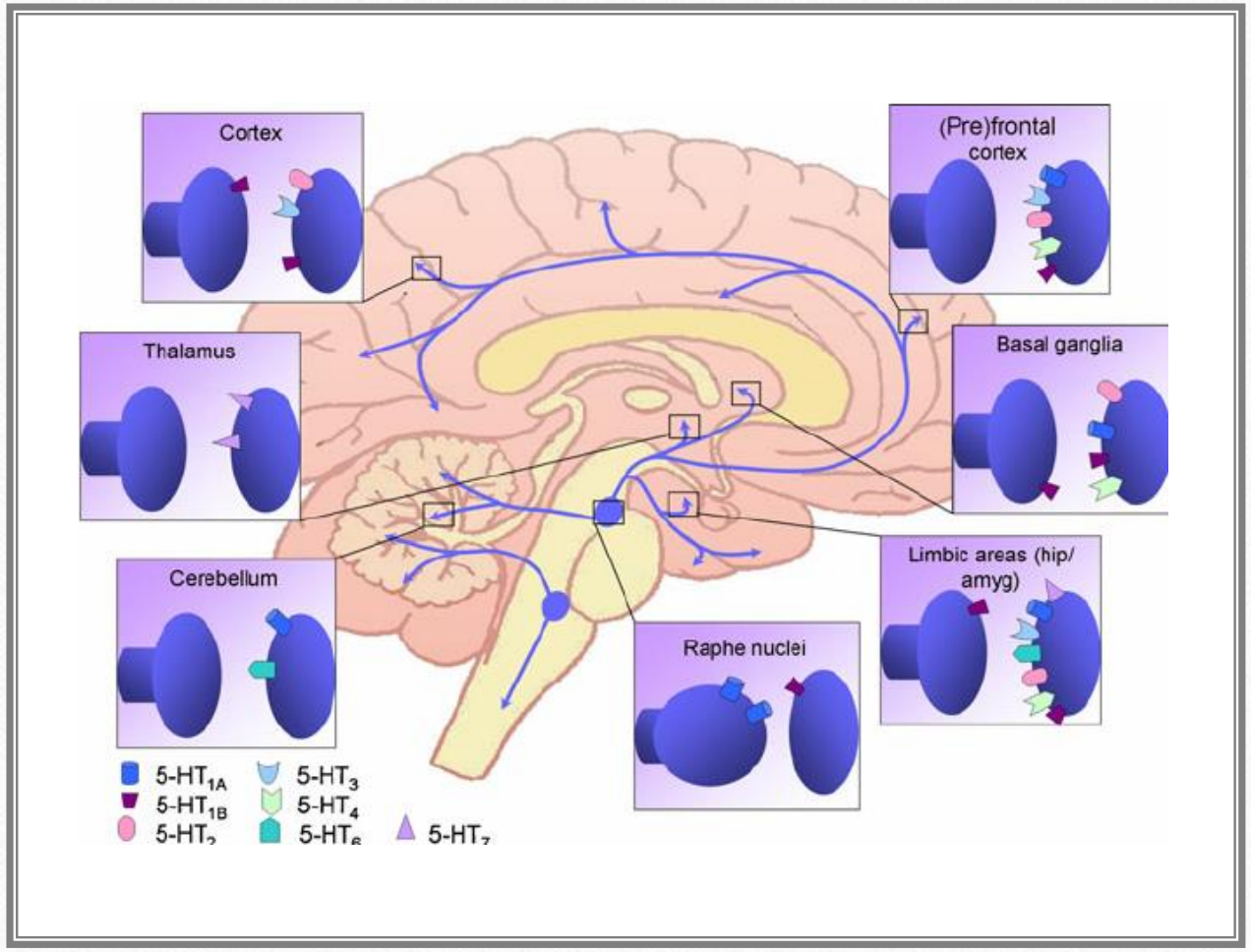
Some transmitters are released by widely distributed networks of neurons

- Normal brain function is dependent upon the coordinated activity of many complex neural networks. Many of the neural networks that control, for example, challenging motor performances are said to be *locally delimited*.
- In addition to these, widely distributed transmitter systems (diffuse networks) are also required. As an example, these networks have a role in regulating alertness. The diffuse networks are especially interesting from a psychology and psychiatry perspective, because their normal function appears to be perturbed in psychiatric and cognitive disorders, such as those affecting attention, and also because modification of their function is relatively easy to accomplish pharmacologically.
- The diffuse networks have a number of common properties: usually the network contains a central core that consists of at most a couple thousand neurons. Most central core neurons originate in evolutionarily older regions of the brain, such as the brain stem. A single central core cell axon can make tens of thousands of synapses whose post-synaptic cells are distributed throughout the brain.
- We also know that some central core cells release transmitters into the extracellular fluid in a non-specific manner, where they will be able to travel by diffusion for extended distances. Because of this, transmitter secretion in these networks is commonly not locally delimited.
- The most important diffuse networks are those containing serotonergic, dopaminergic, cholinergic and histaminergic cells. In these networks, the functionally most important receptors tend to be metabotropic, which means that the activity of these networks can have far-reaching physiologic effects, such as affecting the transcription of DNA. These effects can involve a wide variety of target cell types.



The norepinephrine system controls alertness and the sleep-wake cycle

- Noradrenergic cells are most importantly located in the *locus coeruleus*, which is a bilateral structure in the brain stem. The axons locating in the locus coeruleus distribute throughout the CNS, such as in the cerebral cortex, the thalamus and the hypothalamus, the olfactory bulb, cerebellum, midbrain structures and even the spinal cord.
- These cells are apparently involved in regulating attention, alertness and the sleep-wake cycle, and are of central importance in learning and long-term memory. Their abnormal function appears to play a role in the genesis of anxiety disorders, and they also regulate mood and are important for the basal metabolism of the brain.
- Single-cell recordings show that neurons in the locus coeruleus (at least in the feline) signal at highest intensity in response to novel and surprising but painless stimuli. They exhibit minimum activity in sleep, and, for example, after meals (known as the *postprandial state*).

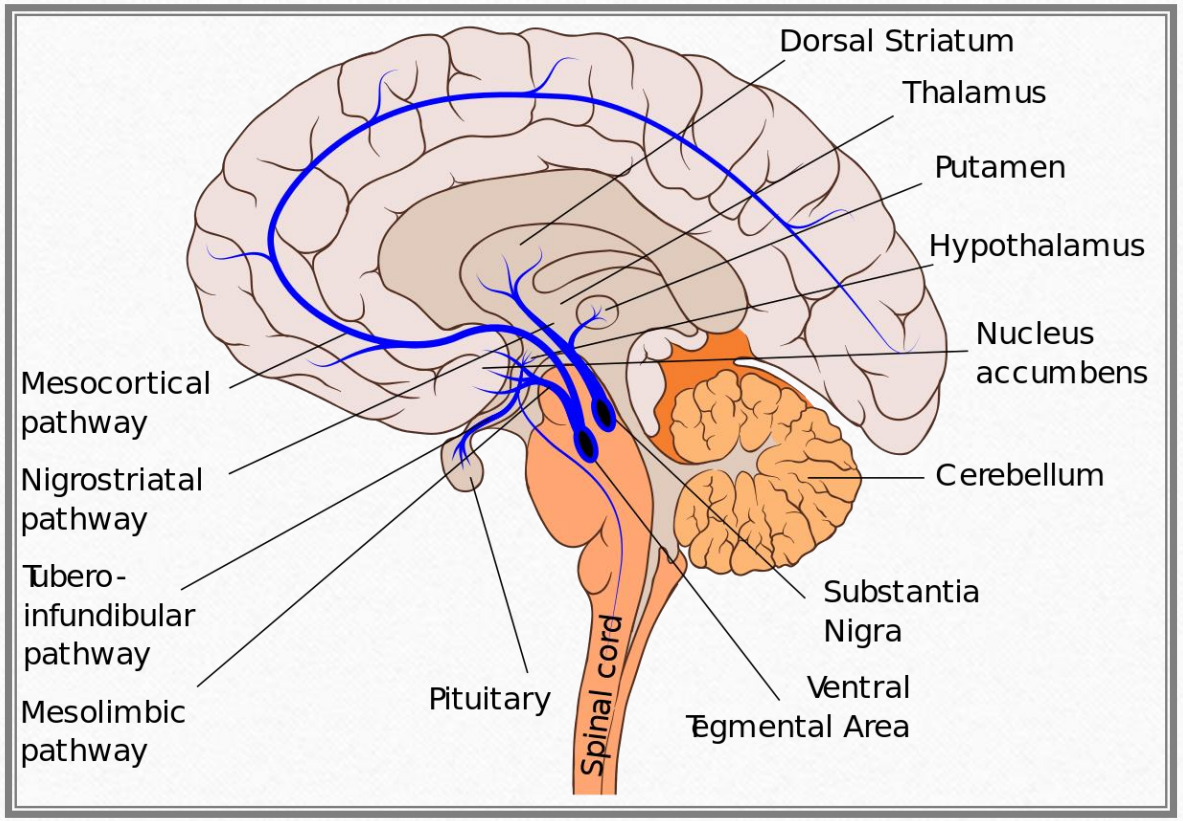


The serotonin system regulates mood partly by regulating alertness

- The serotonergic cells, also located bilaterally in the so called raphe nuclei, seemingly behave very similarly to those in the locus coeruleus: they also project highly diffusely and to much the same regions as the noradrenergic cells, and their activity reaches a peak during states of activity. However, based on studies of the mechanisms of action of antidepressant and hallucinogenic drugs (that have serotonergic effects), it has been surmised that these systems differ functionally: serotonin appears to have strong effects upon mood and affective reactivity. The serotonin hypothesis of depression has occupied a central position in the high school curriculi of several countries. However, it is now known with high certainty that the antidepressant effects of serotonergic drugs are not directly related to changes in serotonin metabolism, but involve neuroplasticity phenomena mediated by neural growth factor receptors. This explains why the onset of effect is much slower than the increase in effective serotonin concentration, which is almost immediate.

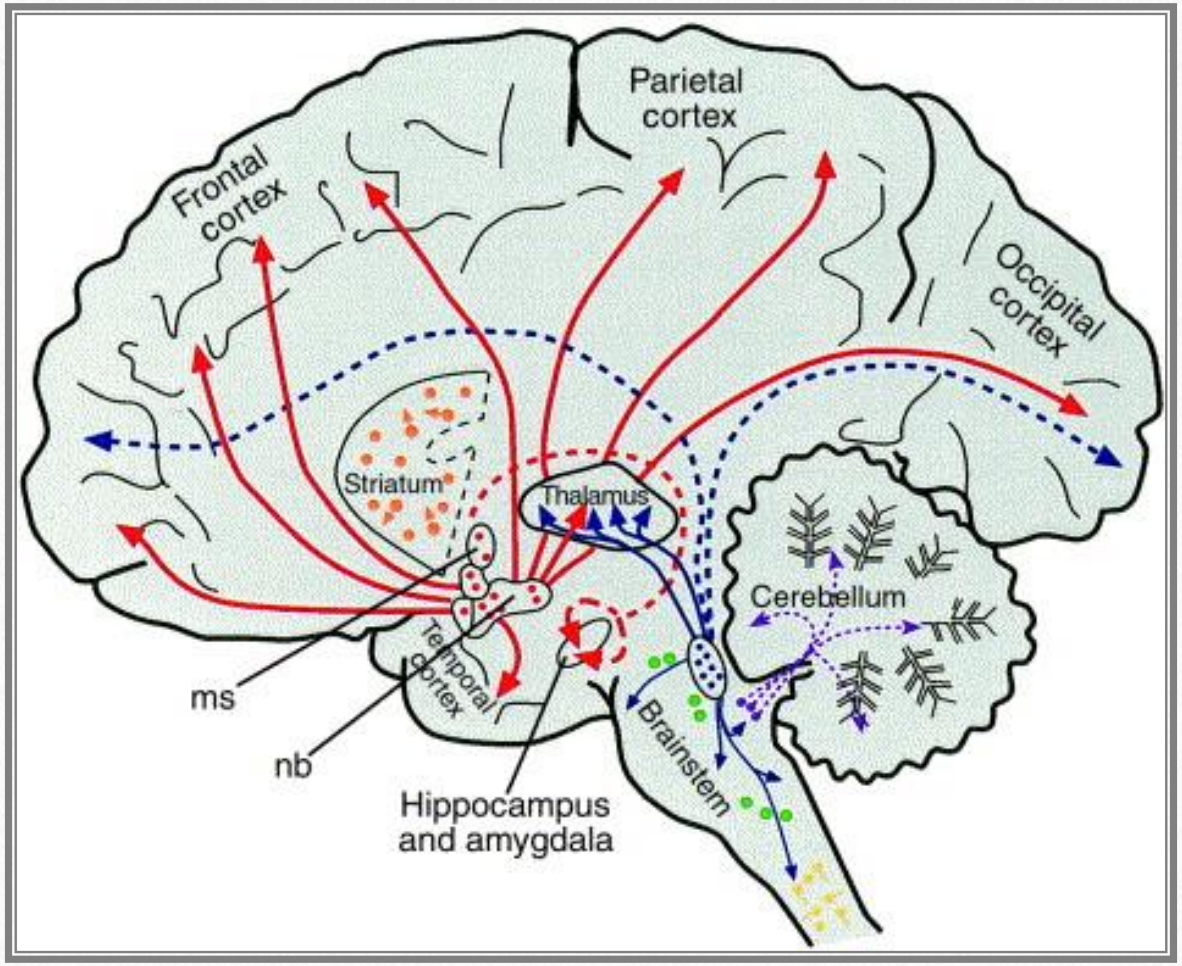
The dopamine system controls movement and behaviour

- Dopaminergic cells can be found throughout the CNS, but are regulated by at least two structures: the substantia nigra, whose cells project to the striatum, which, among other structures, contains the basal ganglia. The progression of Parkinson's disease is largely due to death of dopaminergic cells in the substantia nigra.
- Another important concentration of dopaminergic cells is located in the ventral tegmental area of the midbrain (formerly known as the ventral tegmental nucleus). This area has projections to the prefrontal lobes and the areas previously referred to as the limbic system. Cells in the VTA apparently produce teaching signals that shape neural connections in the basal ganglia. The net effect is integration of affective stimuli into motor behaviour. Due to plasticity in the basal ganglia, the relative probabilities of various behaviours are altered, as they directly modulate the motor system. This appears to be the neural basis of behavioural alterations caused by addictive stimuli.



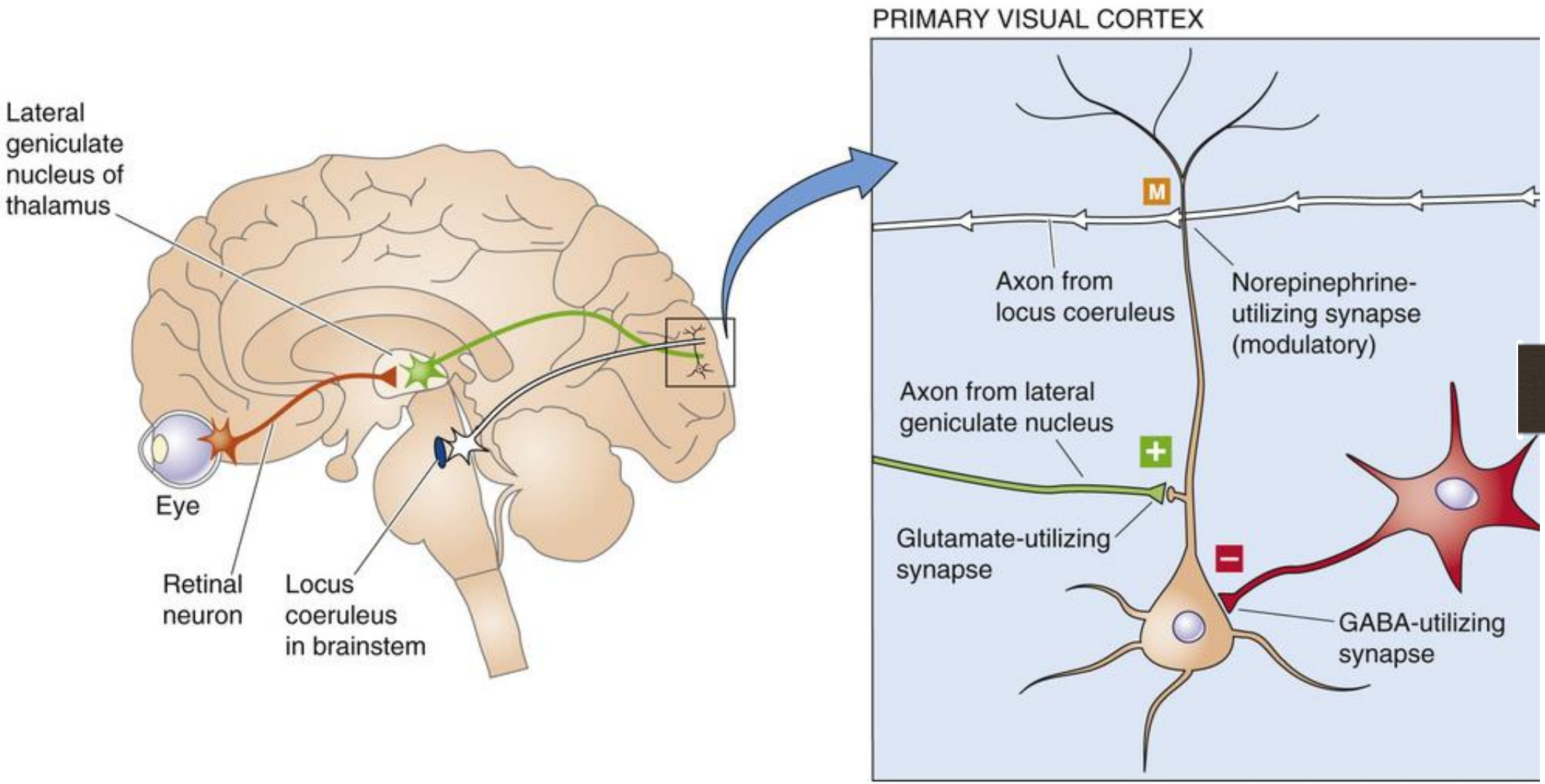
The cholinergic system is important for functions including sleep

- Although acetylcholine is perhaps best known as the neurotransmitter of the neuromuscular junction, it also subserves important functions in the CNS. The central core cells of the cholinergic system are located in two places: the basal forebrain (which accumulates adenosine during wakefulness), connected to the hippocampus and cortex, and the pontine-midbrain cholinergic system, connected to the thalamus and parts of the forebrain. It is known that in sleep, the glutamatergic networks largely responsible for excitatory signaling in the brain is almost totally inhibited, while the cholinergic networks are strongly activated.



Neurons form circuits that comprise excitatory, inhibitory and modulatory connections

- Information processing in the CNS is much more diverse and flexible than, for example, in the simple connection of the neuromuscular junction, in which transmission is reliable, but also static: a spinal motoneuron generates an action potential, causing the excitation and contraction of the muscle cell. This "bioelectromechanical" connection is is highly reliable but not much processing occurs. This differs from CNS synapses, that exist in excitatory, inhibitory and modulatory varieties. Any single synapse has a very low probability of initiating an action potential, but the neural computation inherent to the CNS is a consequence of the compound effects of different kinds of synapses in highly complex neural networks, such that the effects of different synapses converge on the same cells.
- Most of the fast excitatory synapses in the brain use the amino acid glutamate as their transmitter, making them *glutamatergic*. According to the principles of neural computation, the voltage change in the target cell triggered by a single synapse is at most a couple of millivolts, whereas in the neuromuscular junction, it usually is 40 millivolts. Therefore, in the CNS, neural computation, such as initiation of an action potential in a single target cell, requires summation of voltage changes of many presynaptic cells. If we also consider the effects of inhibitory and modulatory synapses, we quickly see that complex neural circuits have emerged in evolution, capable of demanding computation.
- In most inhibitory synapses, the transmitter is GABA or glycine. Synaptic inhibition is usually mediated by the transmitters opening ion channels that allow negatively charged ions to enter the cell, which moves the membrane voltage away from threshold. Other inhibitory mechanisms also exist.
- An example of modulatory synapses can be found in the noradrenergic cells of the locus coeruleus, that form a dense network of synapses onto cortical pyramidal cells. The modulatory effects of these cells are apparent in such a way that when the target cell is exposed to norepinephrine via the locus coeruleus, it will react more strongly to other excitatory stimuli. However, noradrenergic stimulation alone has no significant effect on the target cell. This explains why the neural networks in the locus coeruleus are well suited for functions such as the regulation of alertness. The effects are mediated via β-adrenergic receptors, similar to those blocked by some drugs used to treat panic disorder.


Lateral geniculate nucleus of thalamus
Eye
Retinal neuron
Locus coeruleus in brainstem
PRIMARY VISUAL CORTEX
M
Axon from locus coeruleus
Norepinephrine-utilizing synapse (modulatory)
Axon from lateral geniculate nucleus
+
Glutamate-utilizing synapse
−
GABA-utilizing synapse

CNS neurons are engaged in diverse computation

- Features such as those described below are typical of CNS circuits:

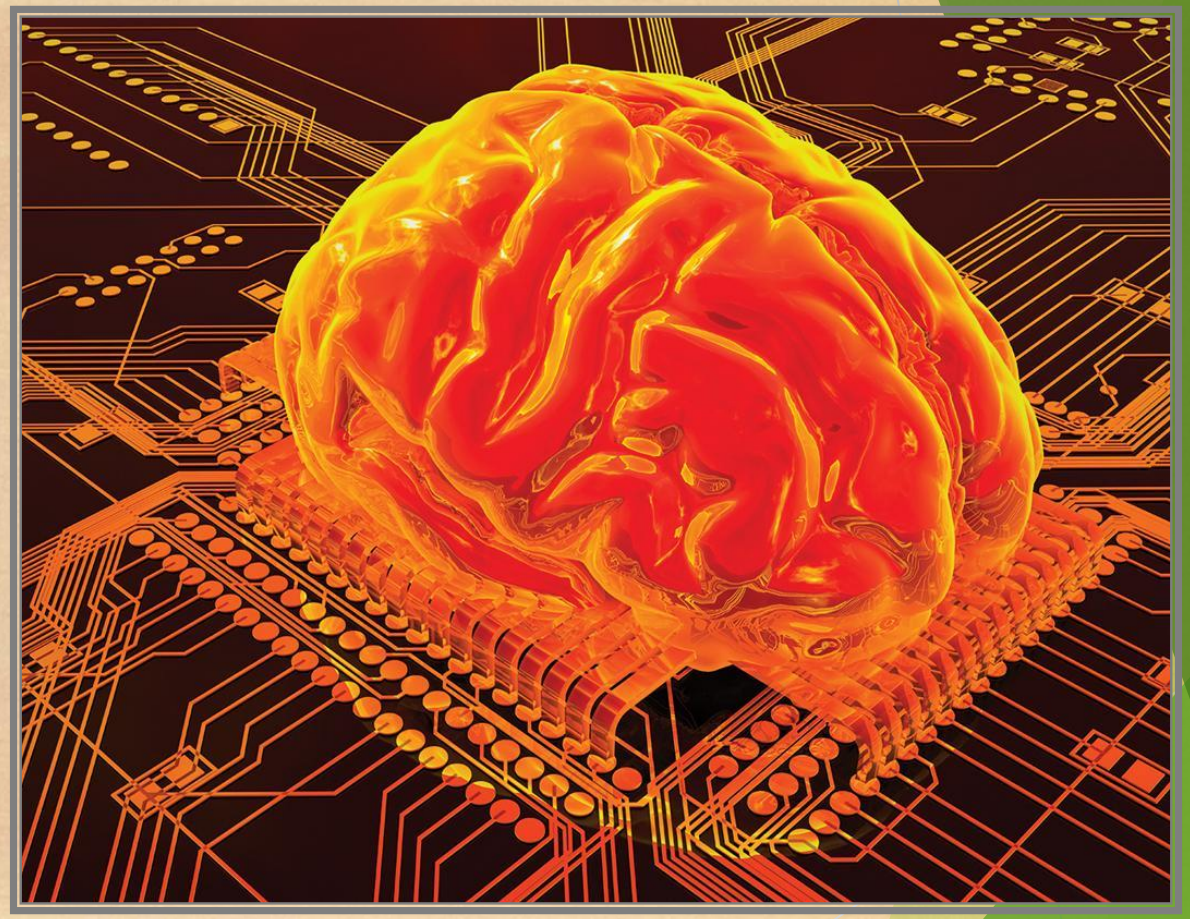
  - Signal amplification

    - A typical example of signal amplification is the aforementioned noradrenergic synapse: its receptor is a G-protein coupled receptor that indirectly affects a large number of ion channels that mediate excitatory effects. A neural singal is therefore amplified when it passes from a locus coeruleus cell to the target cell or group of cells.

  - Synaptic divergence and convergence

    - We said above that the same transmitter can affect different targets in different ways, often due to the presence of different types of receptors for the same transmitter. On the other hand, divergence can also refer to the same neural stimulus having a number of synchronous effects in the same cell. This type of messaging cascade usually involves a multistep process in which the activation of a single type of GPCR results in the generation of a number of different kinds of second messenger molecules in the target cell. Each type of second messenger can have a different effect independent of others.

    - Convergence can be viewed as the “opposite” of divergence, where a given target, such as a certain type of ion channel, is subject to the effects of, for example, multiple types of transmitters. In such a case, the effects will sum, and the response of the target molecule then depends on the compound effect. For example, an ion channel can be simultaneously influenced by signals that increase or reduce its open probability.

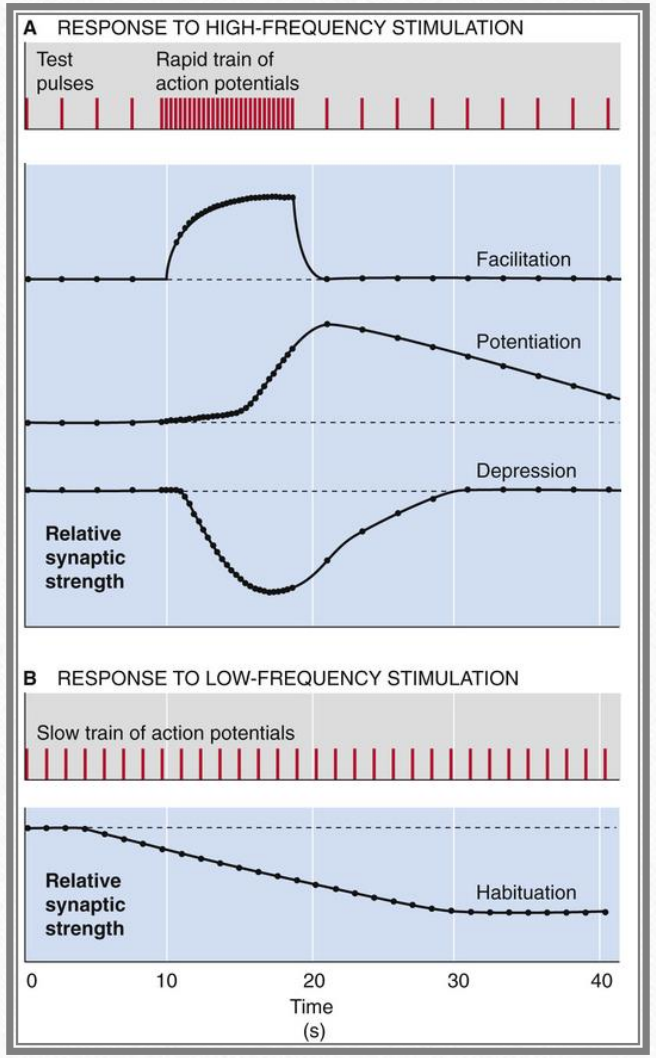


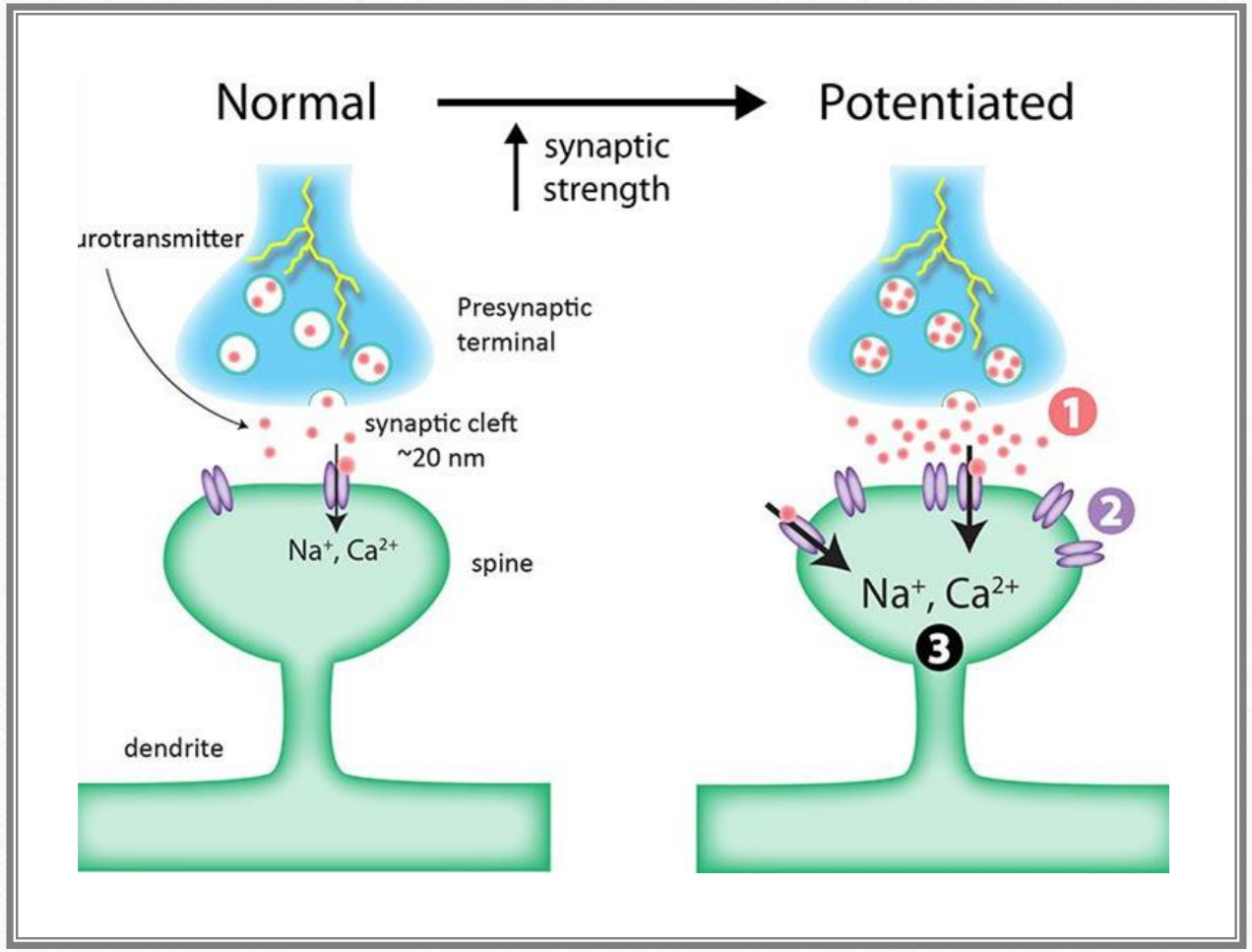
Learning and memory are dependent on synaptic plasticity

- Learning and memory have traditionally occupied an important position in high school psychology. Some authorities consider these to be the most important functions of the CNS, without which it would be very "dumb". We will now consider the most important forms of synaptic plasticity and the physiologic events that mediate them.

Plasticity phenomena in the CNS may be divided into short and long term

- The best known forms of short term synaptic plasticity require repeated stimulation. Some forms of short term facilitatory plasticity include facilitation, augmentation and potentiation, which differ only in duration: the duration of facilitation is on the millisecond scale, whereas potentiation can be maintained for several minutes, even in the absence of the potentiating stimulus.
- Some forms of short term antifacilitatory plasticity include synaptic depression, also associated with high frequency stimulation and habituation, in which the depression of synaptic strength progresses slowly, and is associated with low-frequency stimulation.





There are at least three molecular level explanations for short term increases in synaptic strength

- More transmitter may be released to in response to an action potential.
- The post-synaptic receptors may be sensitised to the transmitter, either through changes in intrinsic sensitivity or receptor number.
- The third option is that both of the above occur simultaneously. Studies show, however, that the increase in the amount of transmitter released is the more common explanation, such that each action potential releases more transmitter than before facilitation took place. Repeated stimulation apparently increases the calcium concentration in the synaptic terminal, and normalisation of the concentration takes time. In simple terms, calcium-sensitive proteins in the synaptic terminal cause the structure of the synapse to alter in response to repeated stimulation. Remember that the arrival of an action potential at the synaptic terminal will open calcium channels, causing a natural increase in the calcium concentration of the terminal. The changes in the calcium concentration that drive plastic changes are caused by the effects of a number of successive action potentials, that in turn change the function of calcium-sensitive proteins in the terminal.

Synaptic depression is usually associated with habituation phenomena

- The mechanisms of synaptic depression include the exhaustion of transmitter vesicles (in other words, the cell's rate of transmitter use exceeds the rate of manufacture) and the inactivation of calcium channels in the terminal, which weakens the propagation of the stimulus.
- The Nobelist Eric Kandel did experiments in the sea hare (*Aplysia*), in which the animal will retract its gill when stimulated electrically. When the stimulus is repeated, the retraction reflex is attenuated. Kandel and colleagues showed that this attenuation is due to a decrease in transmitter release.

Long term plasticity phenomena are associated with more permanent changes in neuronal physiology

- In 1973, Timothy Bliss and colleagues found a form of synaptic facilitation that can last for up to weeks. This phenomenon is now known as long-term potentiation.
- In this phenomenon, the strength of synapses increases when stimulated presynaptically by a series of high-frequency stimuli. Although first described in the cerebral cortex, the primary model system is now the hippocampus (which actually is part of the cerebral cortex).
- The discovery of LTP was a sensation due to it having properties that make it a possible candidate mechanism of learning and memory.
- Especially interesting was that LTP was found to behave in accordance with Hebb's law: it was observed that when the post- and presynaptic cells of a hippocampal synapse were simultaneously activated, the synapse underwent long term potentiation. It was later observed that even just high-frequency stimulation of the presynaptic cell was sufficient to induce LTP. LTP is described as input specific, which means that only the activated synapses are strengthened, and cooperative, which means that the target cell must in practice be stimulated by multiple cells in order to undergo LTP.
- LTP involves a phenomenon in which the post-synaptic calcium concentration increases due to the activation of NMDA and AMPA type glutamate receptors. The NMDA receptors only activate when both cells participating in the synapse are sufficiently stimulated via AMPA receptors. This increases the post-synapctic calcium concentration via a calcium channel located within the NMDA receptor, which initiates a messaging cascade that leads all the way to the genome and changes its activity. The NMDA receptor is therefore a coincidence detector, because it only activates when AMPA receptors are activated in both cells at the same time, or the frequency is very high.
- Pitkäkestoinen heikentyminen (long-term depression, LTD) puolestaan liittyy matalataajuisiin ärsykkeisiin. Sekin rajoittuu vain tiettyihin synapseihin, joihin aiheuttava ärsyke kohdistuu. Matala ärsyketaajuus kuitenkin saa solussa aikaan ilmiöitä, jotka heikentävät synaptista vahvuutta. Sekä vahvistuminen että heikentyminen välittyvät eräitä solun proteiinieja muokkaavien entsyymien välityksellä.
- Pitkäkestoinen heikentyminen pikkuaivoissa liittyy eräiden monimutkaisten liikesarjojen oppimiseen: tästä löytyy lisätietoa lukuisista neurotieteen oppikirjoista. LTP ja LTD ovat lyhytkestoisemmista vahvistumis- ja heikentymisilmiöistä ilmeisesti erillisiä ilmiöitä, joilla kuitenkin lienee yhteisiä vaiheita lyhytkestoisempien ”serkkujensa” kanssa.

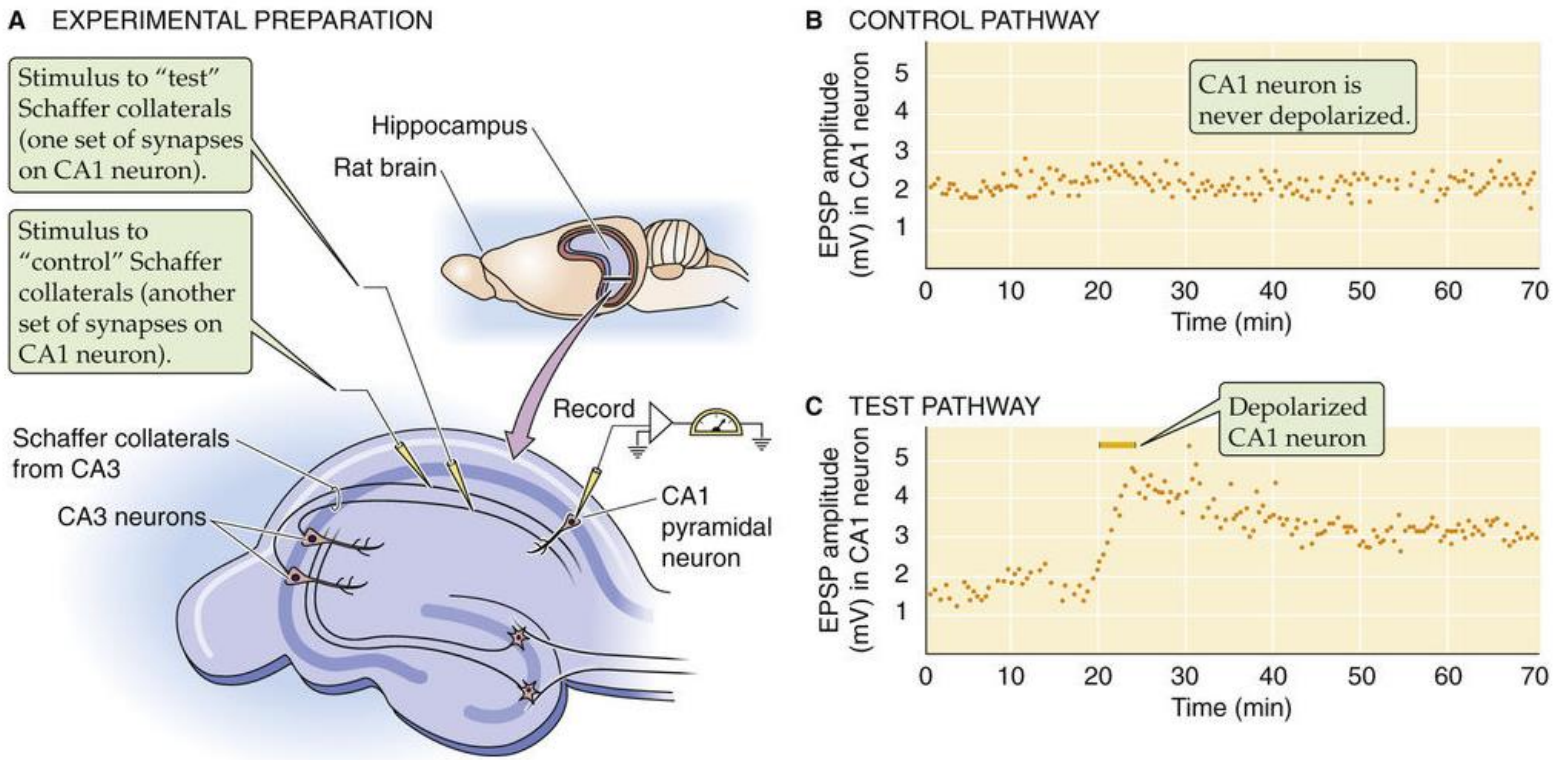


FIGURE 13-20 Causing LTP by pairing presynaptic and postsynaptic stimuli. **A,** Pyramidal CA3 neurons in the hippocampus send axons (Schaffer collaterals) to synapse on pyramidal CA1 neurons. In the case of the "control" stimulus, the stimulating electrode stimulates collaterals that activate one set of synapses on the postsynaptic CA1 neuron. In this case, the CA1 neuron receives only presynaptic stimuli. In the case of the "test" stimulus, a second electrode stimulates a different set of collaterals that activate a different set of synapses on that same CA1 neuron. However, in this case, the presynaptic stimuli will be paired with a postsynaptic depolarization that is delivered by a third microelectrode. Aside from pairing or not pairing the presynaptic stimuli with a postsynaptic stimulus, the test and control pathways are equivalent. The third microelectrode records the EPSPs from the CA1 neuron in both the test and control experiments. **B,** In this case, the control Schaffer collaterals are stimulated. Each test pulse is represented by a point on the graph. However, because the CA1 neuron is not depolarized, the amplitude of the EPSPs remains constant (i.e., there is no LTP). **C,** In this case, the test Schaffer collaterals are stimulated. When the CA1 neuron is also depolarized, the amplitude of the EPSPs greatly increases (i.e., LTP has been induced). (Data from Gustafsson B, Wigstrom H, Abraham WC, Huang YY: Long-term potentiation in the hippocampus using depolarizing current pulses as the conditioning stimulus to single-volley synaptic potentials. J Neurosci 7:774–780, 1987.)