Systems Biology II: Neural Systems (580.422)

Lecture 7, Synaptic Transmission

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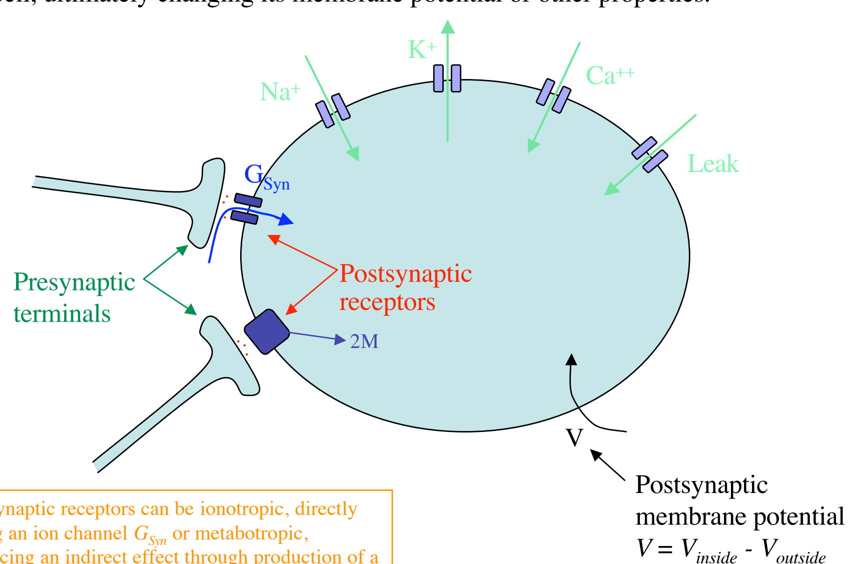
Reading (one of the following):

D. Johnston and S.M. Wu *Foundations of Cellular Neurophysiology* (MIT Press, 1995). Chapters 12, 13.

I.M. Levitan & L.K. Kaczmarek *The Neuron* (Oxford Univ. Press). Chapters 8-13, especially 9, 11, and 12.

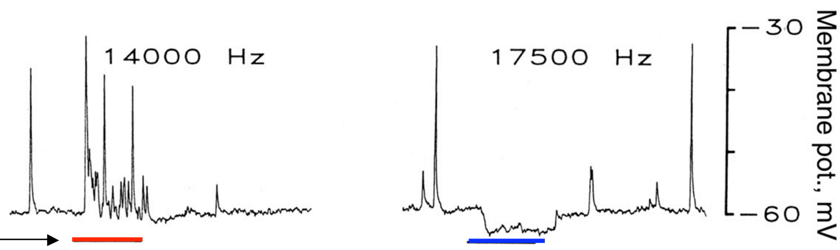
J.G. Nicholls et al. *From Neuron to Brain* (Sinauer Press). Chapters 9-14, especially 9-11.

The inputs to neurons are synapses. Mostly these are chemical synapses, shown below, at which neurotransmitter is released from the presynaptic terminal, binding to a postsynaptic receptor. The result is some effect on the postsynaptic cell, ultimately changing its membrane potential or other properties.



Postsynaptic receptors can be ionotropic, directly gating an ion channel G_{Syn} or metabotropic, producing an indirect effect through production of a second messenger *2M*.

Excitation and *inhibition* correspond to depolarization and hyperpolarization of the postsynaptic membrane



stimulus (25 ms)

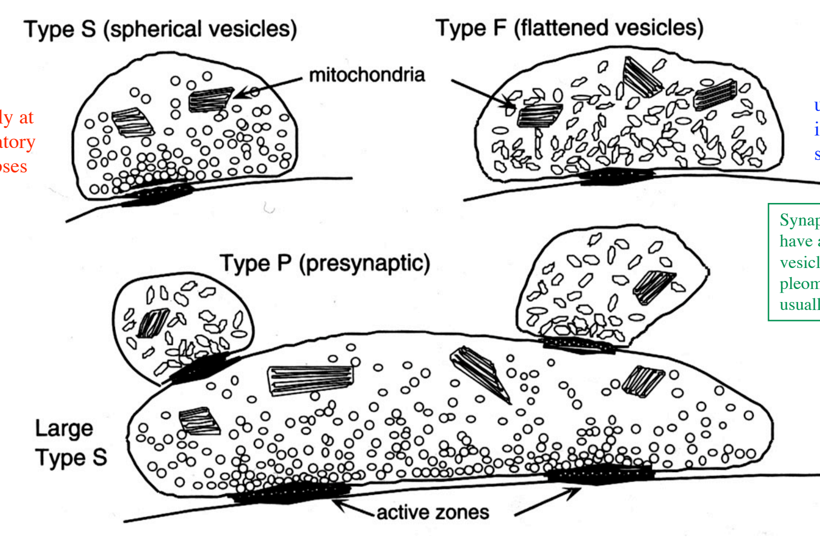
Excitation:
depolarization
EPSPs (excitatory post-synaptic potentials)
Increased spike rate

Inhibition:
hyperpolarization
IPSPs (inhibitory post-synaptic potentials)
Decreased spike rate

Smith and Rhode, 1987

Synapses consist of a presynaptic terminal contacting a postsynaptic cell at a specialized region, the active zone. The presynaptic terminal contains vesicles and the synaptic contact shows thickening of the membranes, presumably containing the molecules that release vesicles and that bind neurotransmitter. In some parts of the brain, synaptic terminals receive other synaptic terminals, producing *presynaptic inhibition*.

usually at excitatory synapses



usually at inhibitory synapses

Synapses can also have an intermediate vesicle type, called pleomorphic, also usually inhibitory.

Shepherd, 2004

The sequence of steps in synaptic transmission:

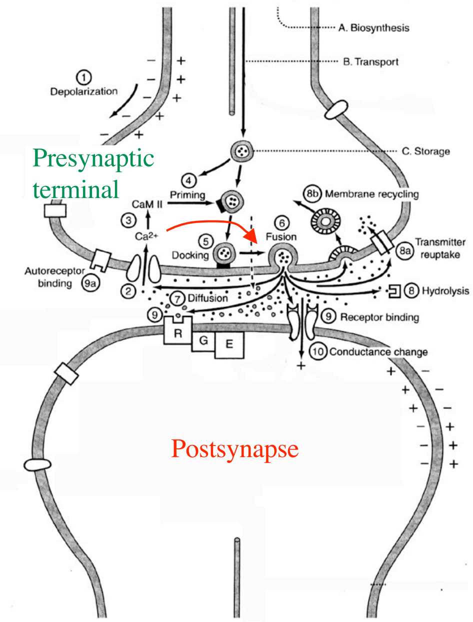
1. Depolarization of the presynapse
2. Calcium entry through V-gated calcium channels

3-5. Transfer of synaptic vesicles to the membrane.

6. Fusion of the vesicle with the membrane, releasing neurotransmitter.
7. Diffusion of the neurotransmitter across the synaptic cleft
9. Binding of transmitter to the postsynaptic receptor.
10. Change in the postsynaptic cell (later)

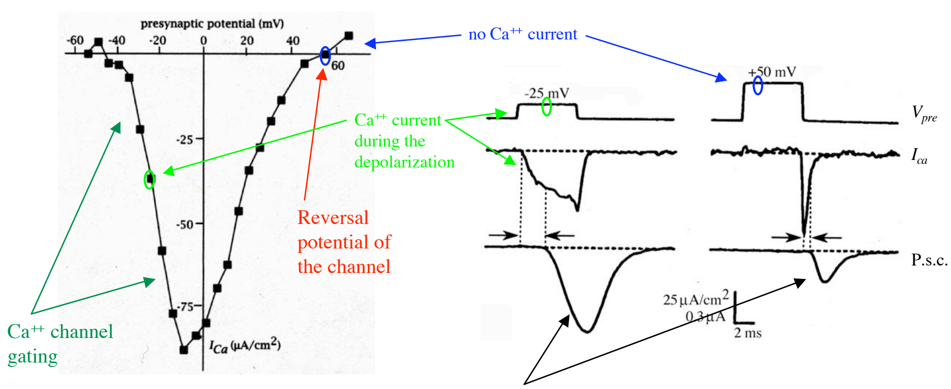
11. To terminate the synaptic action, the transmitter is metabolized (8) or removed from the cleft by reuptake (8a).

Synaptic vesicles are synthesized in the cell body (A) and transported to the terminal (B), where they are filled with transmitter, primed (4) and docked (5) in preparation for release. After neurotransmitter release (6), the vesicle membrane is recycled by uptake (8b) and refilled with transmitter.



Modified from Shepherd, 2004.

Transmitter release is triggered by the rise in calcium that follows the presynaptic action potential. The data shown below demonstrate that it is the calcium entry to the presynaptic terminal, and not the depolarization of the terminal, that releases the transmitter.

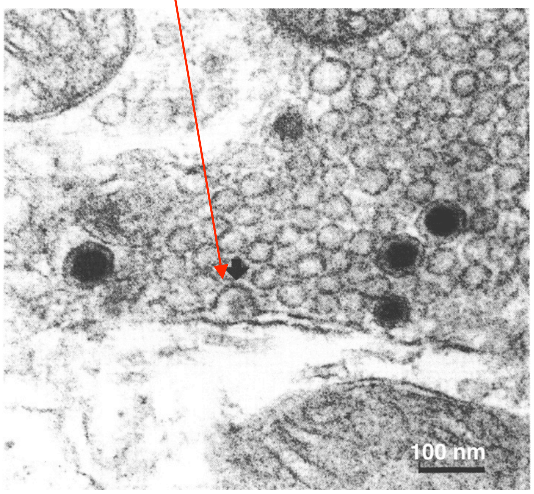


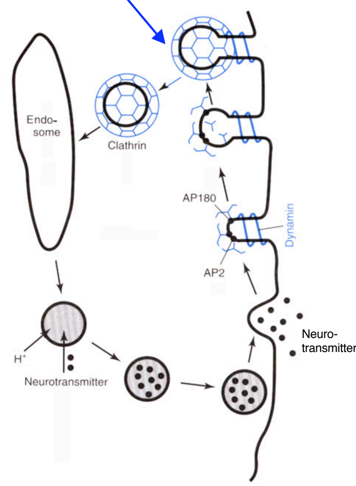
Presynaptic Ca^{++} current versus membrane potential in voltage clamp. Current is 0 at negative potentials because the Ca^{++} channels are gated off. Current approaches 0 at positive potentials near E_{Ca}.

Postsynaptic current *P.s.c.* occurs in response to Ca^{++}, given by I_{ca} and not in response to presynaptic membrane potential, V_{pre}.

Augustine et al. 1985

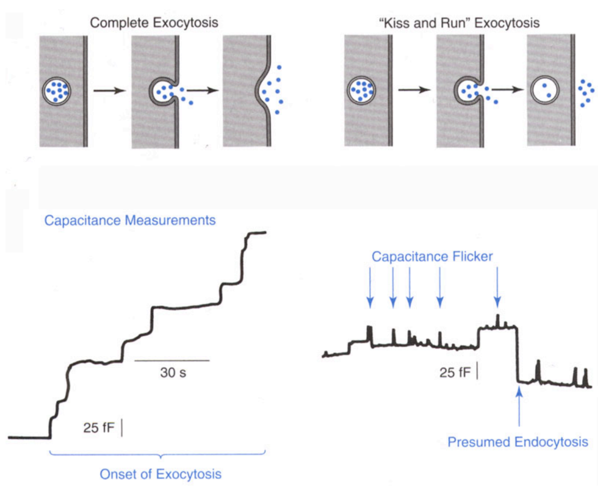
Evidence for the synaptic vesicle hypothesis includes the fact that vesicles have been caught in the act and that vesicle membrane is recycled. The steps in recycling have been demonstrated by placing a fluorescent dye outside the terminal and showing that it is internalized on synaptic vesicles when the synapse is stimulated.





Levitan & Kaczmarek, 2002

More evidence for vesicle cycling is provided by measuring the capacitance of the membrane of a synaptic terminal. The capacitance of a terminal is proportional to the membrane area (1 µFd/cm^2). When vesicles release transmitter, the area and capacitance should increase and when vesicles are recycled, area and capacitance should decrease. Events of this kind are observed.

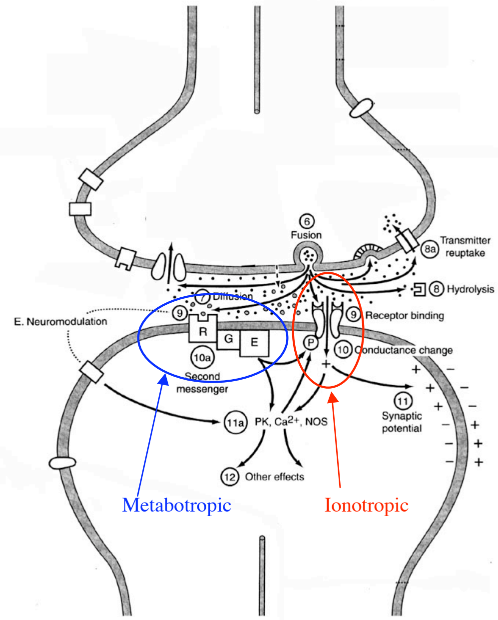


Notice the capacitance scale, 25 f Fd (f Fd = 10^{-15} Fd)! How many vesicles are required to produce a 25 fFd change in capacitance? The data at right were obtained from mast cells, which release secretory vesicles that are larger than typical neurotransmitter vesicles.

Levitan & Kaczmarek, 2002

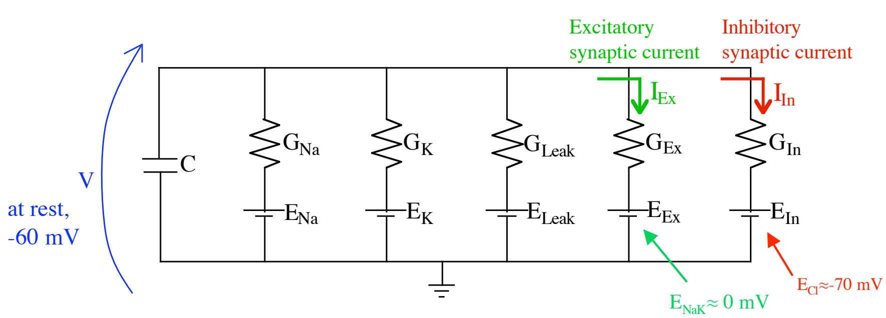
On the postsynaptic side, neurotransmitter binds to a receptor (9). Ionotropic receptors open an ion channel (10) for some ion, allowing a current to flow. The effect of the synapse depends on which ion the channel conducts.

Metabotropic receptors are coupled to G-proteins and/or kinases which produce second messengers (10a, 11a) in the cell. Their effects often include changing the membrane potential, but they also have other effects, ranging from modulating ion channels to causing the production of new channels or receptors in the cell (12).



Modified from Shepherd, 2004

To model postsynaptic <u>ionotropic</u> effects, excitatory and inhibitory synaptic conductances are added to the membrane model.



$$I_{Cap} = -[I_{Na} + I_K + I_{Leak} + I_{Ex} + I_{In}]$$

$$C\frac{dV}{dt} = -[G_{Na}(V-E_{Na}) + G_K(V-E_K) + G_{Leak}(V-E_{Leak}) + \underline{G_{Ex}(V-E_{Ex})} + \underline{G_{In}(V-E_{In})}]$$

The battery-resistor model is very accurate for the ion channels of ionotropic neurotransmitter receptors. When open, these channels show no rectification.

Synaptic conductances G_{Ex} and G_{In} can be simulated by kinetic models like the one below.

$$T + R \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} TR \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} TR^* \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} D$$

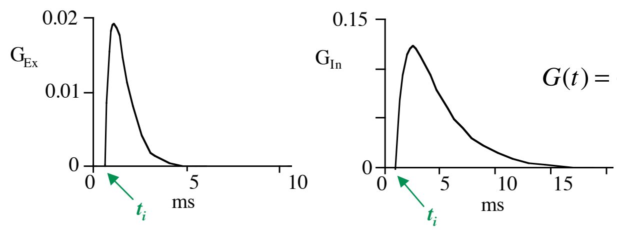
$$G = (const)\, TR^*$$

the channel conductance

T is the transmitter, *R* is the receptor, *TR* is the bound receptor, *TR** is the receptor in the open-channel state, and *D* is a desensitized state from which the channel exits slowly. This is a simplification; usually more than one *T* must bind and there are additional *TR* and *D* states.

Activation of the receptor is modeled by letting *T* be a short pulse and beginning the simulation with all the receptor in the *R* state.

The solutions for *TR**(*t*) or *G*t) are similar to the functions below. In fact, these are approximations, called α functions, with duration parameter τ.



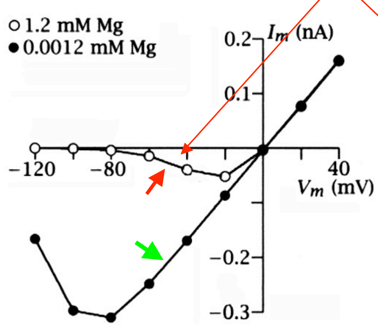
$$G(t) = (const)(t - t_i)e^{-(t-t_i)/\tau}$$

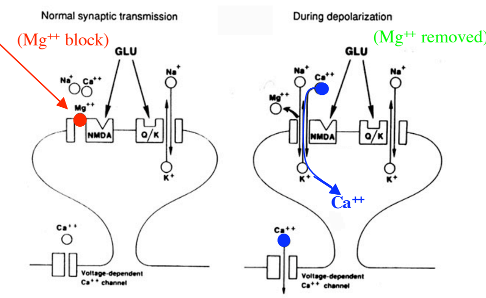
As with ion channels, the effect, excitatory or inhibitory, of a particular synaptic channel is determined by the ions that pass through the channel. For ionotropic channels in the brain, the following transmitters and ion channels are seen:

Transmitter	Receptor	Ions	Effect
Glutamate	AMPA, kainate	Na, K, (some Ca)	Excitatory
	NMDA	Na, K, Ca	Excitatory
GABA	A	Cl	Inhibitory
Glycine		Cl	Inhibitory
Acetylcholine	Nicotinic	Na, K, Ca	Excitatory
Serotonin (5-HT)	5-HT_3	Na, K	Excitatory
ATP	Purine P1	Na, K	Excitatory

The main synaptic systems in the brain

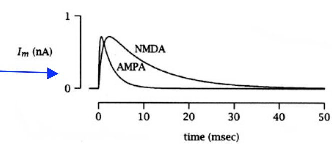
Glutamate receptors require further comment. NMDA-type glutamate receptors are conditionally activated, depending on the presence of glutamate AND depolarization of the postsynaptic terminal. The depolarization is necessary to relieve a block of the NMDA receptor channel by Mg++ ions.





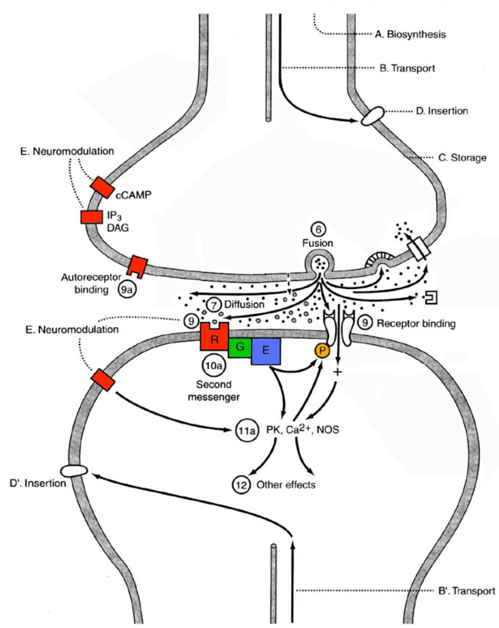
NMDA channels show two additional differences from other types of glutamate channels (AMPA or kainate):

1. NMDA currents last longer
2. NMDA channels admit Ca^{++}, which other types may or may not do. These Ca^{++} signals will be important later.



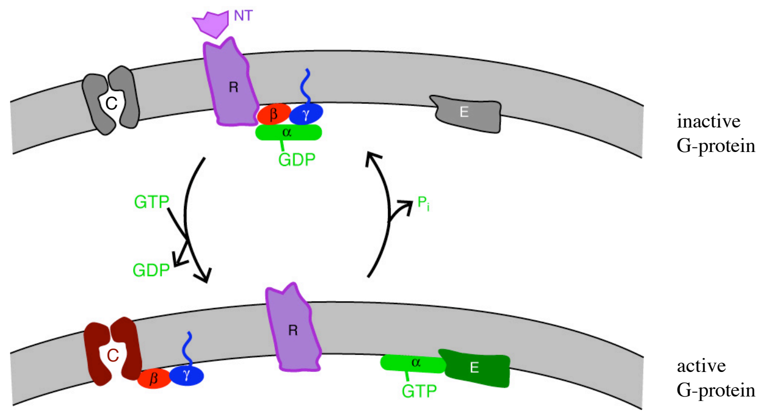
Johnstone and Wu, 1995

Metabotropic receptors are ones that do not couple directly to an ion channel; rather they couple to effector proteins that indirectly cause some change in the cell, often through phosphorylation of a protein. While this may result in opening or closing of ion channels, the connection is indirect and often can be quite indirect. Virtually all aspects of neuron physiology can be affected by neuromodulation.

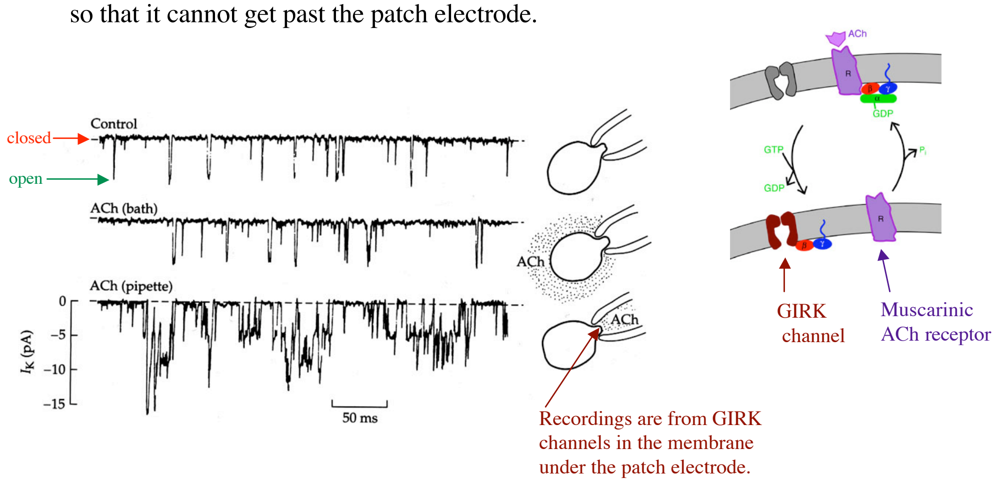


Modified from Shepherd, 2004

The best understood metabotropic effects occur through activation of G-proteins. The general scheme of G-protein activation is shown below. When the receptor (*R*) binds a transmitter (*NT*), the G-protein complex exchanges its GDP moiety for a GTP and cleaves into an α-subunit-GTP part and a β–γ subunit part. These diffuse in the membrane and both can activate other proteins, either enzymes (*E*) or ion channels (*C*). The G-protein is inactivated when the α-subunit cleaves its GTP to GDP + P_i and the subunits recombine.

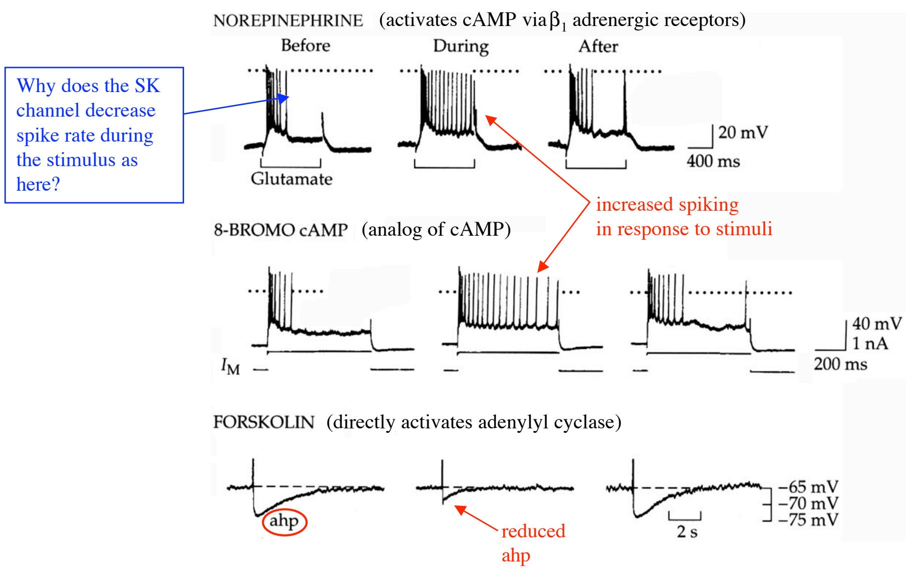


An example is provided by the GIRK channel, which open when ACh is applied to a membrane patch. This is evident in the records below by increased "open" conductance states. The increase in open states occurs if the ACh is applied locally in the patch pipette (third trace) and not if ACh is applied to the whole cell (second trace). This is interpreted to mean that the βγ subunit is constrained in its diffusion, so that it cannot get past the patch electrode.



Hille, 2001

Examples of changes in the response properties of neurons in the hippocampus due to cAMP modulation. The effect occurs by reducing the conductance of SK type K(Ca) channels. These channels are gated by Ca^{++} and produce the afterhyperpolarization (ahp) that follows one or more action potentials, as in the third trace below.



Hille, 2001

A partial summary of ionotropic and mebotropic neurotransmitters in the brain, listed by effect on ion channels.

Response	Neurotransmitter	Receptor	
$\uparrow I_{Na}$, $\uparrow I_K$	Glutamate	Quisqualate/kainate	Ionotropic
$\uparrow I_{Na}$, $\uparrow I_K$, $\uparrow I_{Ca}$	Glutamate	*N*-Methyl-D-aspartate (NMDA)	
	Acetylcholine	Nicotinic	
$\uparrow I_{Cl}$	γ-Aminobutryic acid	$GABA_A$	
	Glycine		
$\uparrow I_{K,IR}$	Acetylcholine	M_2	Metabotropic
	Norepinephrine	α_2	
	Serotonin (5-hydroxytryptamine [5-HT])	$5\text{-}HT_1$	
	GABA	$GABA_B$	
	Dopamine	D_2	
	Adenosine	A_1	
	Somatostatin	SST_5	
	Enkephalins	μ, δ	
$\downarrow I_{AHP}$	Acetylcholine	Muscarinic	
	Norepinephrine	β_1	
	Serotonin	$5\text{-}HT_7$	
	Histamine	H_2	
	Glutamate	Glutamate metabotropic	
$\downarrow I_{K,leak}$	Acetylcholine	Muscarinic	
	Norepinephrine	α_1	
	Serotonin	$5\text{-}HT_2$	
	Glutamate	Glutamate metabotropic	
$\downarrow I_{Ca}$	Multiple transmitters		

Johnstone and Wu, 1995

Several of the major neuromodulatory transmitters in the brain are associated with compact nuclei containing mainly neurons using one transmitter. These are shown schematically below. The projections of the nuclei are usually very diverse and often include practically the whole brain.

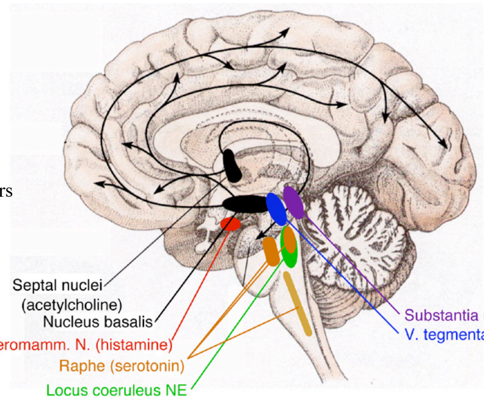
Acetylcholine - learning, memory, cognition.

Norepinephrine - ascending reticular activation, increase excitability

Serotonin (5-HT) - modulation of pain, sleep-wake cycle, complex social behaviors

Histamine - allergic reactions, gastric secretion, increase excitability, arousal

Dopamine - enabling motor function in the basal ganglion (Parkinson's disease), control of mood



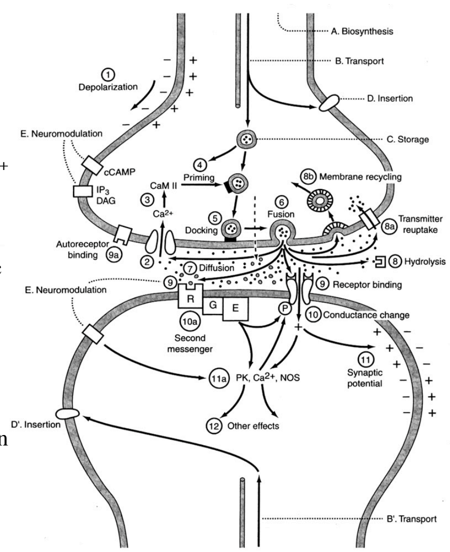
Other neuromodulators are also widely distributed, in terms of the loci of their terminals, but have diffusely localized cell bodies. These include GABA acting at $GABA_B$ receptors, often a transmitter at presynaptic inhibitory terminals that acts by decreasing presynaptic Ca currents; glutamate; adenosine; and peptides. Among the peptides, opioids (enkephalins) are important in pain and analgesia.

Nicholls et al., 2001

What is the strength of a synapse? This question will be central to the lectures on network theory later in the course.

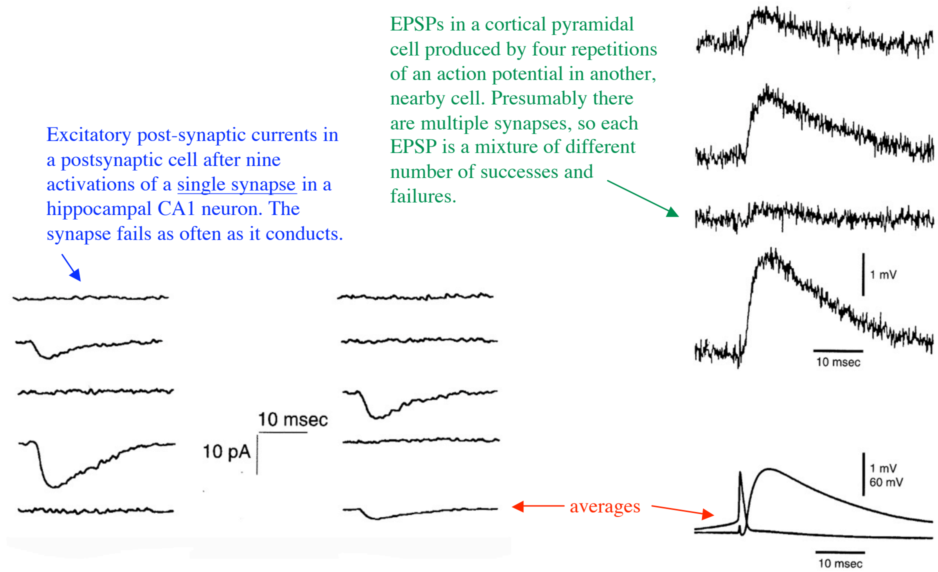
Synaptic strength is determined by a number of factors:

1. The size of the neurotransmitter release can be varied by presynaptic inhibition, often through metabotropic mechanisms.
2. Synaptic facilitation, due to accumulation of Ca^{++} in the presynaptic terminal, can increase transmitter release.
3. Synaptic depression, due to depletion of synaptic vesicles, can decrease release.
4. Synaptic depression due to desensitization of receptors (similar to inactivation, see slide 11).
5. Number of receptors. The postsynaptic effect of NT release depends on the number of receptors in the postsynaptic membrane.
6. Postsynaptic electrical processing. Changes in potassium currents through modulation of K^+ channels can change the EPSP or IPSP produced by the synapse.



Shepherd, 2004

Synaptic strength is variable, due to randomness in the release of neurotransmitter. Two examples are shown below.



Wang and Stevens, unpub. and Mason et al. 1991, reproduced in Koch, 1999.

Summary of neurotransmitters and synaptic actions:

Synaptic actions in the brain can be roughly grouped into three categories, based on the nature of the postsynaptic pathway evoked:

1. Direct ionotropic mechanisms. The receptor is coupled directly to the ion channel. The effects are immediate (latency <1 ms) and relatively short-lasting (<10 ms). The most common transmitters are glutamate (excitatory), GABA (inhibitory), and glycine (inhibitory). Most signal processing in the brain involves ionotropic mechanisms.

2. Short-pathway metabotropic mechanisms. The receptor is coupled to a second messenger, such as a G-protein, which has a direct effect on an effector, such as opening an ion channel or releasing vesicles at a synapse.

3. Long-pathway metabotropic mechanisms. The receptor is coupled to a second messenger cascade which leads to several effects or to a complex and long-lasting change in the cell's properties. For example, long-term plasticity (LTP) at synapses occurs with calcium acting as a messenger that initiates a cascade ultimately resulting in the production of new ionotropic glutamate receptors in the post-synaptic membrane, increasing the strength of the synapse.