

## Systems Biology II: Neural Systems (580.422)

### Lecture 7, Synaptic Transmission

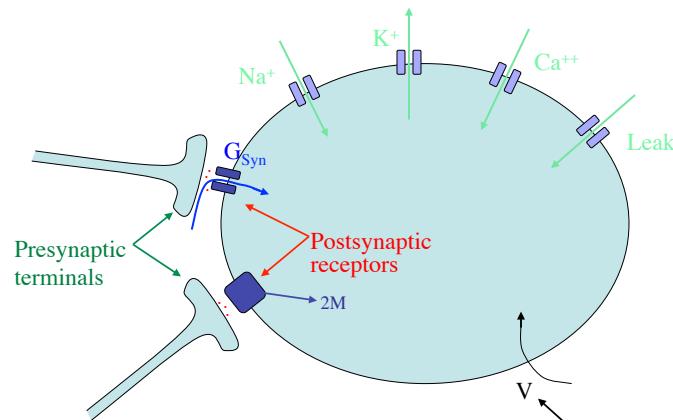
Eric Young 5-3164 [eyoung@jhu.edu](mailto:eyoung@jhu.edu)

Reading:

D. Purves et al. *Neuroscience* (Sinauer Assoc.) Chapters 5, 6, 7.

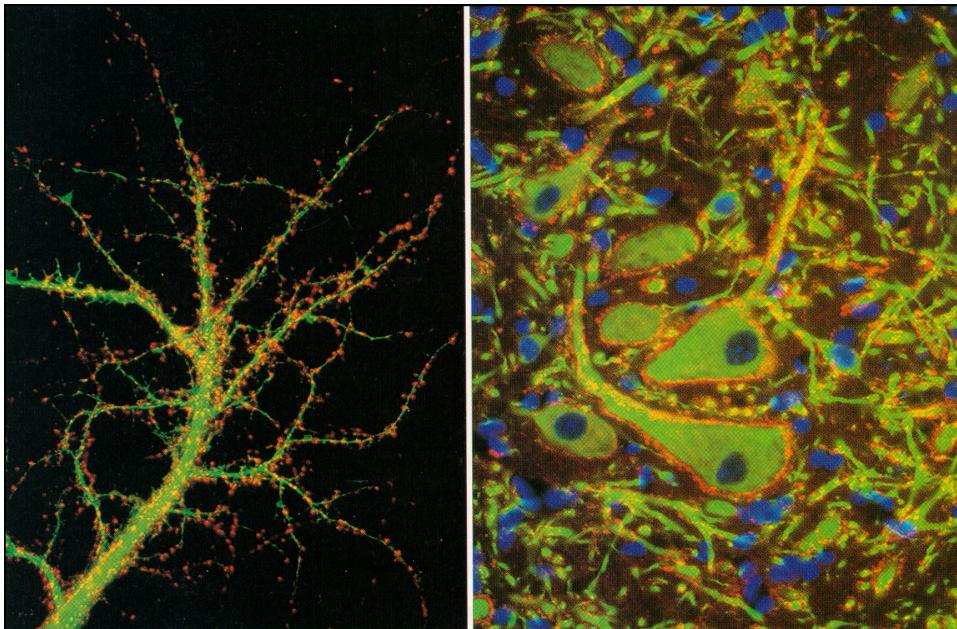
J.G. Nicholls et al. *From Neuron to Brain* (Sinauer Press). Chapters 9-14, especially 9-11.

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  $2M$ .

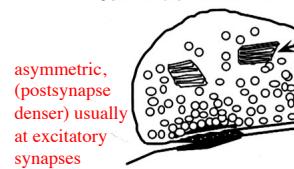
Postsynaptic membrane potential  
 $V = V_{inside} - V_{outside}$



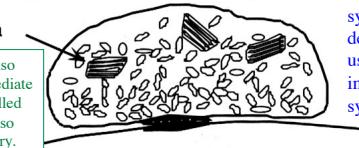
Special stains for synapses (red) show their high density on dendrites and somas on CNS neurons.

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 the molecules that release vesicles and bind neurotransmitter. In some parts of the brain, synaptic terminals receive other synaptic terminals, producing *presynaptic inhibition*.

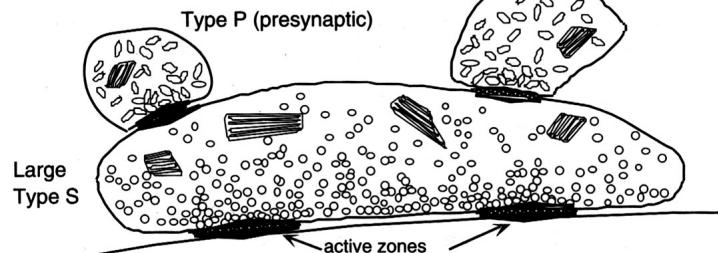
Type S (spherical vesicles)



Type F (flattened vesicles)



Type P (presynaptic)

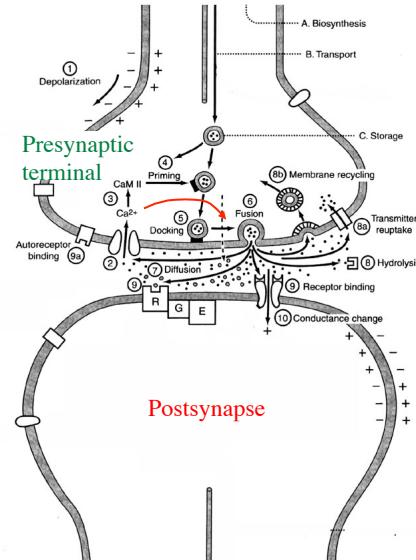


Shepherd, 2004

The sequence of steps in synaptic transmission:

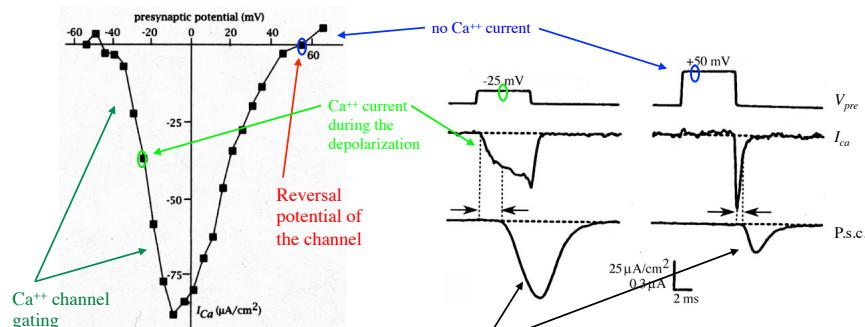
1. Depolarization of the presynapse
2. Calcium entry through V-gated calcium channels opened by depolarization
- 3-5. Transfer of synaptic vesicles to the membrane.
6. Fusion of the vesicle with the membrane, releasing neurotransmitter.
7. Diffusion of the neurotransmitter across the synaptic cleft
9. 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, 8b) in the neuron itself or in adjacent glia.

Some 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. Others are synthesized in the terminal; after 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  $\text{Ca}^{++}$  current versus membrane potential in voltage clamp. Current is 0 at negative potentials because the  $\text{Ca}^{++}$  channels are gated off. Current approaches 0 at positive potentials near  $E_{\text{Ca}}$ .

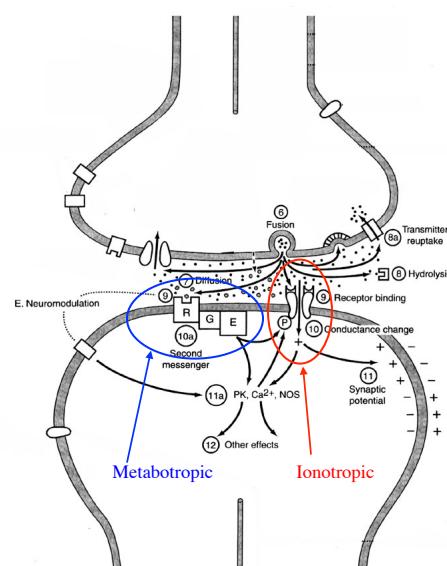
Postsynaptic current  $P.s.c.$  occurs in response to  $\text{Ca}^{++}$ , given by  $I_{\text{ca}}$  and not in response to presynaptic membrane potential,  $V_{\text{pre}}$ .

Augustine et al. 1985

Much more is known about vesicles and vesicle release. See chapter 5 in Purves for more information about the mechanisms involved in release and for other kinds of evidence about the vesicular nature of release.

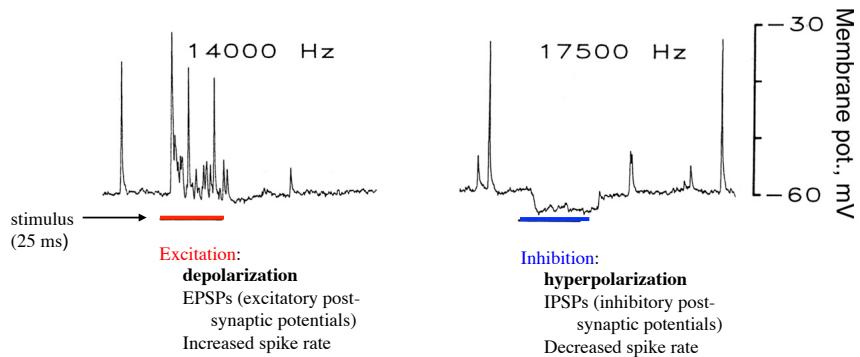
On the postsynaptic side, neurotransmitter binds to a receptor (9). **Ionotropic** receptors open an ion channel (10) for some ion or mixture of ions, allowing a current to flow. The effect of the synapse depends on which ion the channel conducts.

**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).



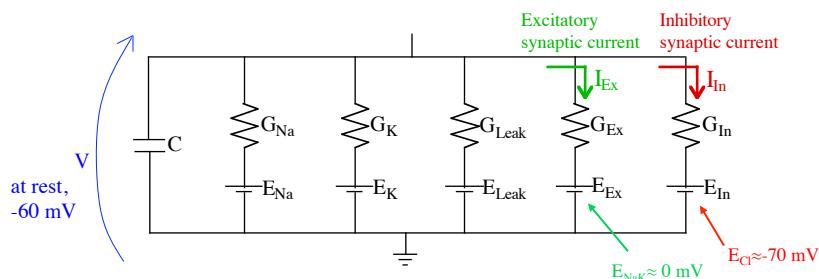
Modified from Shepherd, 2004

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



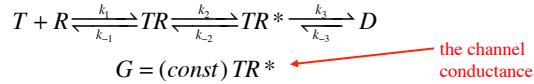
Smith and Rhode, 1987

To model postsynaptic **ionotropic** effects, **excitatory** and **inhibitory** synaptic conductances are added to the membrane model.



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

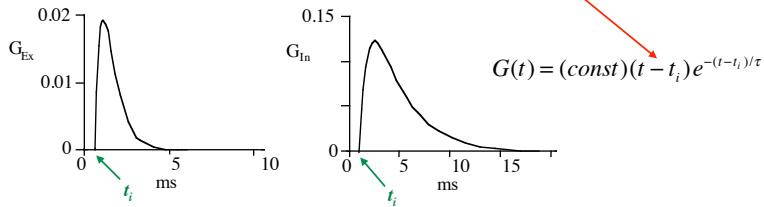
Synaptic conductances  $G_{Ex}$  and  $G_{In}$  can be simulated by kinetic models like the one below.



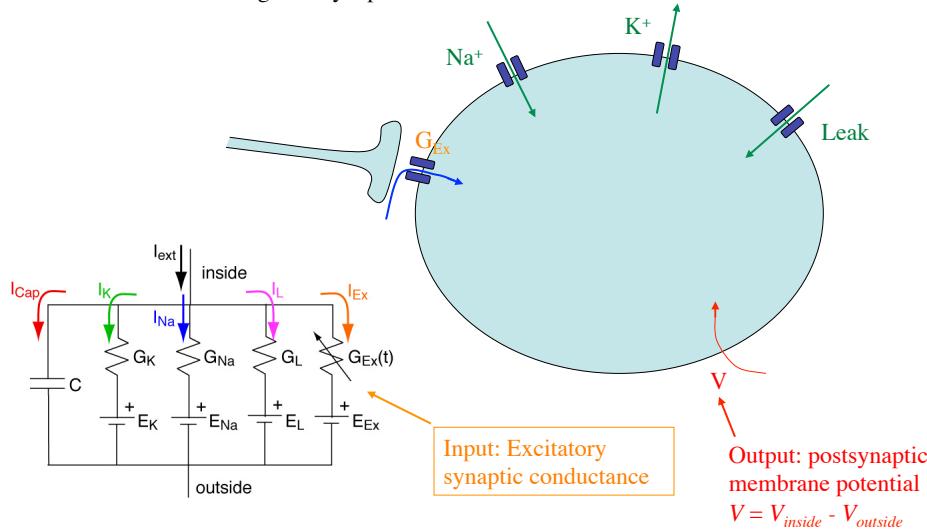
$T$  is the transmitter,  $R$  is the receptor,  $TR$  is the bound receptor,  $TR^*$  is the receptor in the open-channel state, and  $D$  is a desensitized state from which the channel exits slowly. This is a simplification; usually more than one  $T$  must bind and there are additional  $TR$  and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

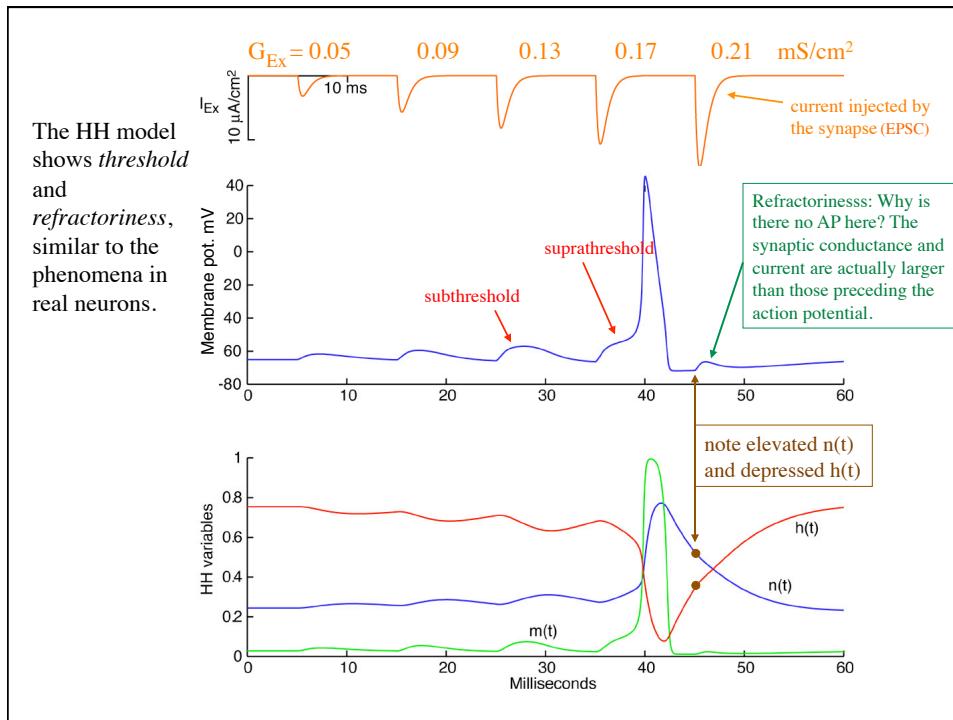
Activation of the receptor is modeled by letting  $T$  be a short pulse and beginning the simulation with all the receptor in the  $R$  state.

The solutions for  $TR^*(t)$  or  $G(t)$  are similar to the functions below. In fact, these are approximations, called  $\alpha$  functions, with duration parameter  $\tau$ .



Consider a cell with HH-style channels in its membrane and an **excitatory synaptic input**,  $G_{Ex}$ . The synapse injects depolarizing current by increasing its conductance to excite the neuron. When the conductance increases, an inward current flows through the synaptic channel.

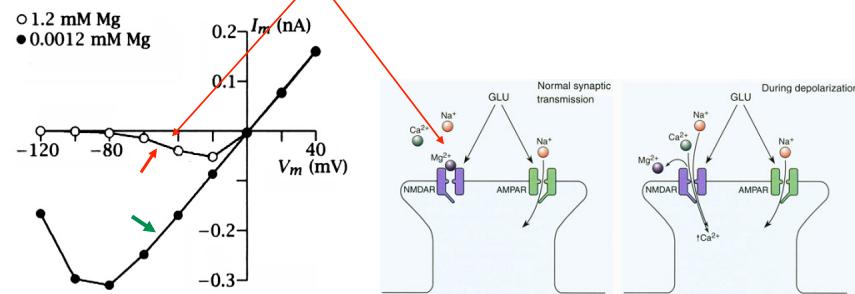




As with ion channels, the effect, **excitatory** or **inhibitory**, of a particular synaptic channel is determined by the ions that pass through the channel. For ionotropic channels in the brain, the following transmitters and ion channels are seen:

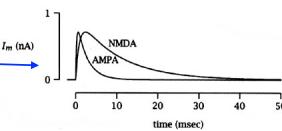
Transmitter	Receptor	Ions	Effect	
Glutamate	AMPA, kainate NMDA	Na, K, (some Ca) Na, K, Ca	Excitatory Excitatory	
GABA Glycine	A	Cl	Inhibitory Inhibitory	The main synaptic systems in the brain
Acetylcholine Serotonin (5-HT) ATP	Nicotinic 5-HT <sub>3</sub> Purine P1	Na, K, Ca Na, K Na, K	Excitatory Excitatory Excitatory	

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<sup>++</sup> ions.



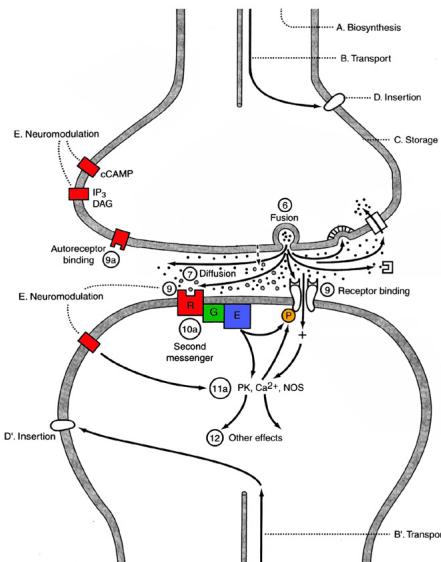
NMDA channels show two additional differences from other types of glutamate channels (AMPA or kainate):

1. NMDA currents last longer
2. NMDA channels admit Ca<sup>2+</sup>, which other types may or may not do. These Ca<sup>2+</sup> signals will be important later.



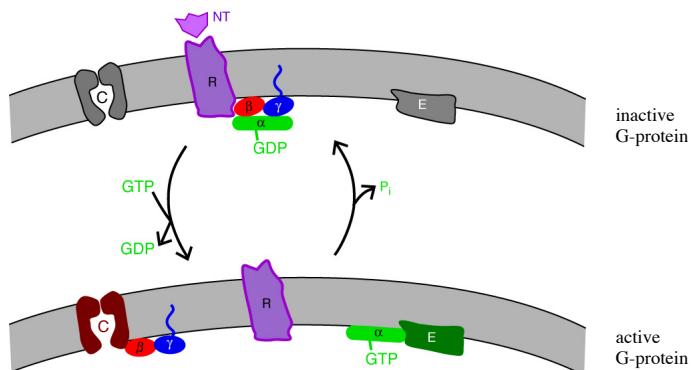
Malenka and Siegelbaum 2001 Johnstone and Wu, 1995

**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.

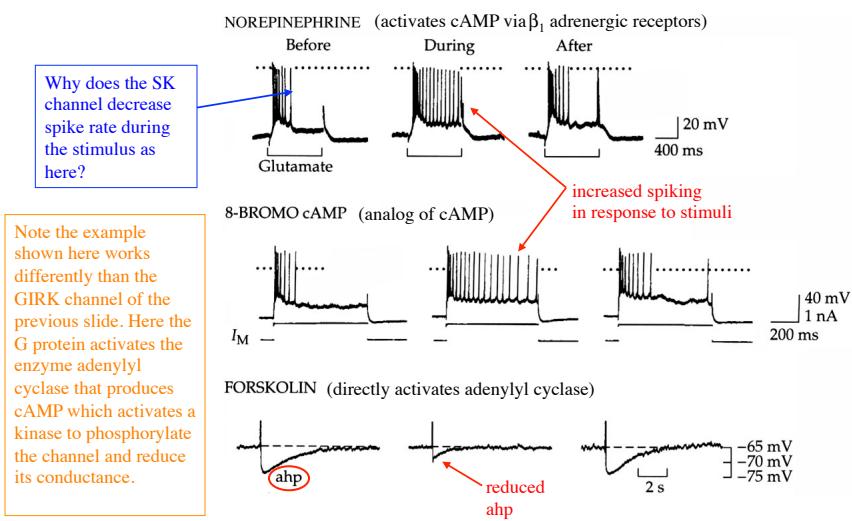


Modified from Shepherd, 2004

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  $\alpha$ -subunit-GTP part and a  $\beta-\gamma$  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  $\alpha$ -subunit cleaves its GTP to GDP +  $P_i$  and the subunits recombine.



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

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.

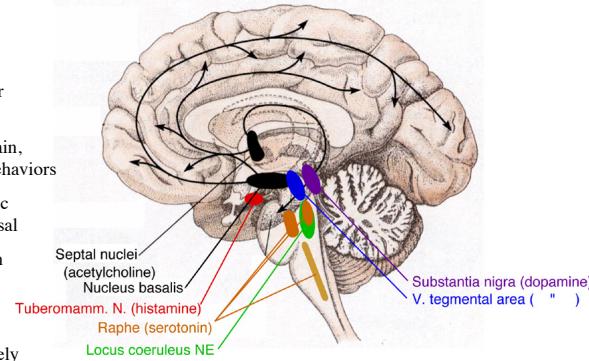
Acetylcholine - learning, memory, cognition.

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

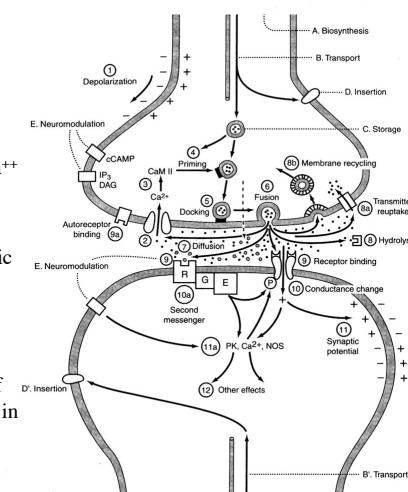
terminals, but have diffusely localized cell bodies. These include **GABA** acting at **GABA<sub>A</sub>** receptors, often a transmitter at presynaptic inhibitory terminals that acts by decreasing presynaptic Ca currents; **glutamate**; **adenosine**; **peptides** including compounds related to heroin and morphine; **cannabinoids**; and **NO** (nitric oxide). Among the peptides, opioids (enkephalins) are important in pain and analgesia. Cannabinoids and NO are often produced in the postsynaptic cell and diffuse to the presynaptic terminal.

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:

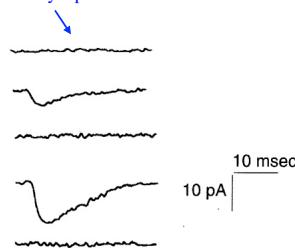
1. The size of the neurotransmitter release can be varied by **presynaptic inhibition**, often through metabotropic mechanisms (e.g. decreasing Ca currents in the presynaptic terminal).
2. **Synaptic facilitation**, due to accumulation of Ca<sup>++</sup> in the presynaptic terminal, can increase transmitter 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, especially AMPA receptors. Important for long-term plasticity.
6. **Postsynaptic electrical processing**. Changes in potassium currents through modulation of K<sup>+</sup> channels can change the EPSP or IPSP produced by the synapse.



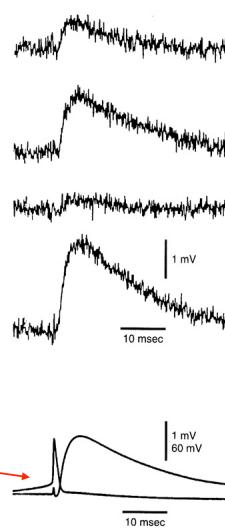
Shepherd, 2004

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

Excitatory post-synaptic currents in a postsynaptic cell after nine activations of a single synapse in a hippocampal CA1 neuron. The synapse fails as often as it conducts.



EPSPs in a cortical pyramidal cell produced by four repetitions of an action potential in another, nearby cell. Presumably there are multiple synapses, so each EPSP is a mixture of different numbers of successes and failures.



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

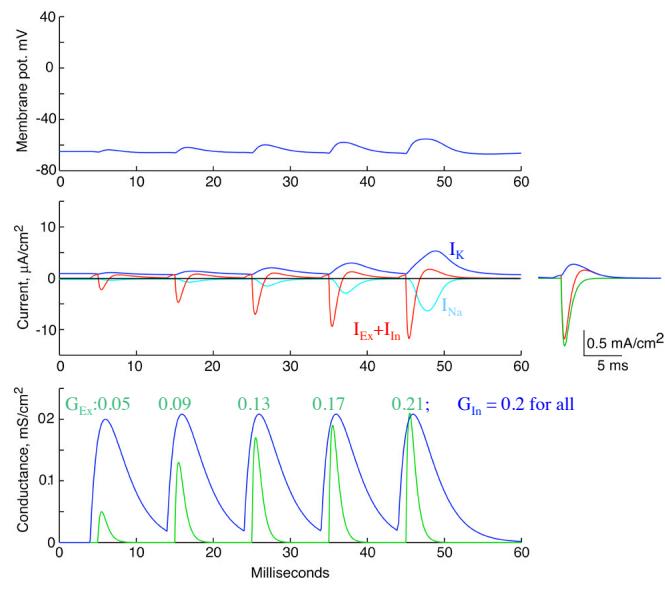
#### Summary of neurotransmitters and synaptic actions:

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 multiple 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 placement of new ionotropic glutamate receptors in the post-synaptic membrane, increasing the strength of the synapse.

end lect 7

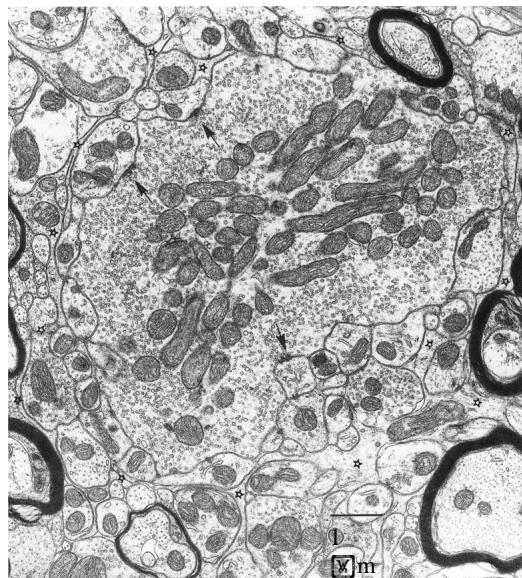
Addition of an inhibitory conductance blocks spiking. Recall that the model spiked at  $0.17 \text{ mS/cm}^2$  previously.



EM cross section of a specialized synapse in cerebellum that contains many synaptic connections.

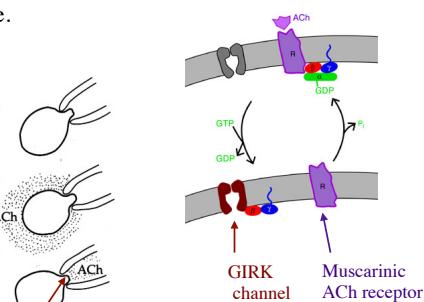
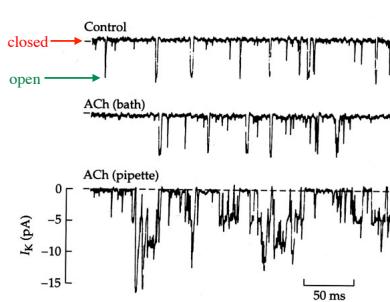
The large vesicle-filled structure in the center is the presynaptic terminal.

The arrows point to synaptic densities. The stars are astrocytic processes that surround the synapses.



De Camilli et al. 2001

An example is provided by the GIRK channel, which opens 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 bg subunit is constrained in its diffusion, so that it cannot get past the patch electrode.



Recordings are from GIRK channels in the membrane under the patch electrode.

(Pharmacological evidence shows that a G-protein is an essential part of the process.)

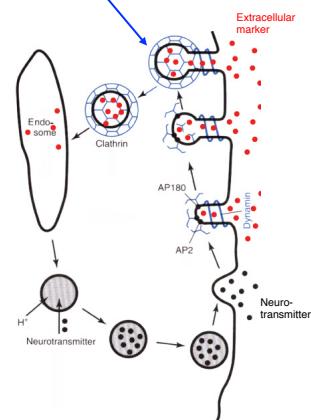
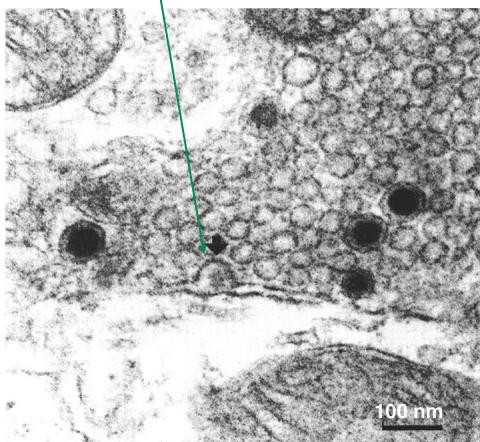
Hille, 2001

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

Response	Neurotransmitter	Receptor
$\uparrow I_{Na}$ , $\uparrow I_K$	Glutamate	Quisqualate/kainate
$\uparrow I_{Na}$ , $\uparrow I_K$ , $\uparrow I_{Ca}$	Glutamate	<i>N</i> -Methyl-D-aspartate (NMDA)
$\uparrow I_{Cl}$	Acetylcholine $\gamma$ -Aminobutyric acid Glycine	Nicotinic GABA <sub>A</sub>
$\uparrow I_{K,IR}$	Acetylcholine Norepinephrine Serotonin (5-hydroxytryptamine [5-HT]) GABA	M <sub>2</sub> $\alpha_2$ 5-HT <sub>1</sub> GABA <sub>B</sub>
	Dopamine Adenosine Somatostatin Enkephalins	D <sub>2</sub> A <sub>1</sub> SST <sub>5</sub> $\mu$ , $\delta$
$\downarrow I_{AHP}$	Acetylcholine Norepinephrine Serotonin Histamine Glutamate	Muscarinic $\beta_1$ 5-HT <sub>7</sub> H <sub>2</sub> Glutamate metabotropic
$\downarrow I_{K,leak}$	Acetylcholine Norepinephrine Serotonin Glutamate	Muscarinic $\alpha_1$ 5-HT <sub>2</sub> Glutamate metabotropic
$\downarrow I_{Ca}$	Multiple transmitters	

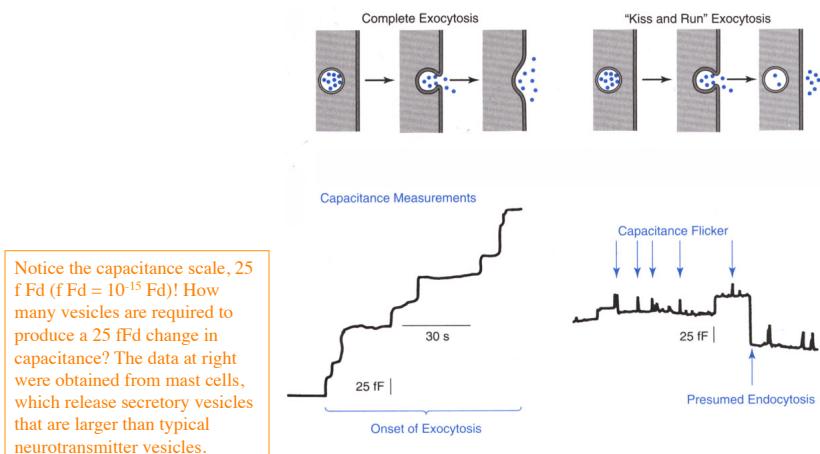
Johnstone and Wu, 1995

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 ( $1 \text{ mFd/cm}^2$ ). 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.



Levitin & Kaczmarek, 2002