The sequence of steps in synaptic transmission:

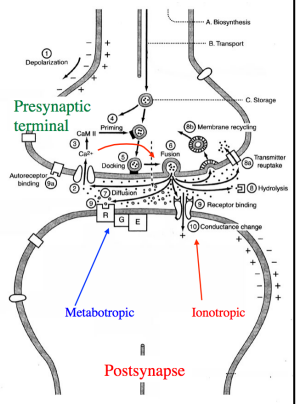
1. Depolarization of the presynapse
2. Calcium entry through V-gated calcium channels

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. Changes in the postsynaptic cell

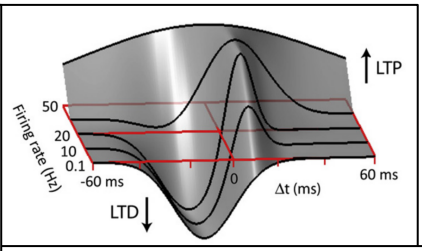
11. To terminate the synaptic action, the transmitter is metabolized (8) or removed from the cleft by reuptake (8a, 8b) in the neuron itself or in adjacent glia.

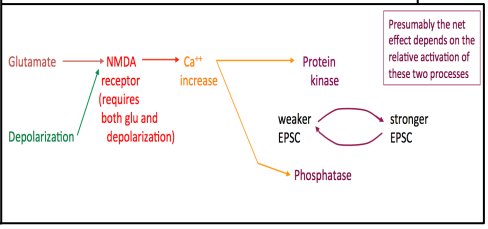
Some synaptic vesicles are synthesized in the cell body (A) and transported to the terminal (B), where they are filled with transmitter, primed (4) and docked (5) in preparation for release. Others are synthesized in the terminal; after release (6) the vesicle membrane is recycled by uptake (8b) and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



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^{++} 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^+ channels can change the EPSP or IPSP produced by the synapse.





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 (discussed later). 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.

Early studies showed that LTP displays the following properties:

Cooperativity – induced by co-incident activation of a number of synapses

Associativity – a weak input can be strengthened if activated in association with a strong one

Input specificity – only the activated synapses are strengthened, not adjacent synapses.

Types of synaptic plasticity, according to time scale:

1. Facilitation and depression of synaptic strength in a pulse pair or pulse train. Can be caused by accumulation of presynaptic Ca^{++} (facil.) or depletion of neurotransmitter (depress.).

2. Longer lasting facilitation and depression can be produced by neuromodulation, in which pre- or postsynaptic receptors change the properties of ion channels (and neural excitability) through a 2nd-messenger system.

3. Long-term plasticity (long-term potentiation LTP or depression LTD) can change the strength of synapses for hours and is thought to underlie memory formation. It depends on changing properties of the synapse, like the number of AMPA receptors in the postsynaptic membrane.