Lecture 6 – Synaptic Transmission I -- Siegelbaum

Postsynaptic Mechanisms

1. Stretch receptor reflex as a model of neuronal signaling
   How does an impulse get transmitted from one cell to the next?

2. Two major forms of synaptic transmission
   a. Electrical – fast, bidirectional (usually), no amplification. Mediated by gap junctions.
   b. Chemical – slower, unidirectional, amplification. mediated by presynaptic terminals & postsynaptic receptors.

3. Gap junctions – consist of pairs of channels that span pre and postsynaptic membranes.
   protein subunits called connexin. Six subunits make one hemi-channel, called a connexon.

4. Chemical synapses – two major types of postsynaptic receptors
   a. Ionotropic receptors – receptor and ion channel in same macromolecule. Transmitter binding opens a channel.
b. Metabotropic receptors – coupled to G proteins and second messengers. Indirectly influence ion channels.

5. Neuromuscular junction – Action potential in presynaptic terminals causes calcium influx via voltage-gated calcium channels → release of transmitter acetylcholine (ACh) → ACh diffusion across synaptic cleft to postsynaptic membrane → ACh binds to and opens nicotinic ACh receptor (nAChR), a ligand-gated ion channel → leads to Na^+ influx into muscle cell → large, suprathreshold fast excitatory post-synaptic potential (EPSP) in postsynaptic muscle at end-plate. Reduce size of EPSP with curare so that it is subthreshold. See passive decay of EPSP amplitude away from endplate.

6. Nicotinic ACh receptor – a pentamer composed of four types of homologous subunits (two α subunits, and one β,γ and δ subunit). Each subunit contains a large external domain, four transmembrane domains, termed m1-m4, and a short external C terminus. Two molecules of ACh bind to the receptor. The two ACh binding sites are formed by the two α subunits together with either a γ or δ subunit. The m2 segment lines the ion-conducting pore.

7. The ionic current that generates the EPSP is called the end-plate current (epc). This current can be studied with the voltage clamp. It shows a rapid rise (<1 msec) and a slower decay, lasting a few msec.

8. Which ions flow through nAChR to generate epc? Measure reversal potential (Erev) , voltage at which current changes from inward (positive charge moving into cell) to outward (positive charge moving out of cell). For voltage-gated sodium and potassium channels, Erev = +55 mV (E_{Na}) and –80 mV (E_K), respectively. For, end-plate current, Erev = 0 mV. E_{rev} is average of E_K and E_{Na}. Conclusion: nAChR is permeable both to Na^+ and K^+. When membrane voltage= Erev, the influx of Na down its electrochemical gradient through the nAChR is exactly balanced by

efflux of K through the nAChR. nAChR channel pore is much wider than that of voltage-gated Na^+ and K^+ channels, even lets calcium permeate.

9. Patch clamp recordings show all-or-none square opening of single nAChR channels.
   Binding of two ACh to receptor → channel opens. Channel carries constant unitary current at fixed membrane potential. At –90 mV, current is 2.7×10^{-12} amperes (2 pA). Small current corresponds to very large ion flux of 20 million ions per second. Channels stay open for an average of a few msec before closing.
   Congenital myasthenic syndrome. Inherited genetic disease, mutation in m2 membrane domain of one subunit prolongs channel open times. Causes excess calcium influx, end-plate degeneration.

Relevant reading: chapters 10 and 11 in "Principles"