Lecture 7 – Synaptic Transmission II -- Siegelbaum

Postsynaptic Mechanisms -- Central Nervous System

1. Consider stretch receptor reflex in CNS. Two major differences with NMJ:
    1. EPSPs are much smaller, around 1 mV. Need integration of many EPSPs to reach threshold.
    2. Also see inhibitory postsynaptic potentials (IPSPs) that hyperpolarize cell.
    3. Importance of spatial and temporal integration.

2. IPSPs due to action of inhibitory amino acid transmitters, GABA and glycine, on ionotropic receptors that contain a Cl^- channel. Influx of Cl^- makes cell membrane potential more negative. GABA and glycine receptors are pentamers similar in structure to nAChR.

3. *Hyperekplexia or familial startle disease* – inherited genetic disorder due to defect in subunit of glycine receptor.

4. Excitatory transmission in CNS due to activation by glutamate of ionotropic receptors permeable to Na^+ and K^+. There are three major families of ionotropic glutamate receptors. They were originally identified pharmacologically by three agonists that preferentially activate them: NMDA, AMPA and kainate. Hence the receptors are called NMDA receptors, AMPA receptors and kainate receptors (sometimes AMPA and kainate receptors are lumped together as non-NMDA receptors).

5. NMDA receptors are blocked by external Mg^{2+}, which binds to a site within the pore at negative resting potentials. Thus, current carried by AMPA and kainate receptors largely determines EPSP at negative resting potentials. However, during strong synaptic activity, the postsynaptic cell depolarizes, expelling Mg^{2+} from NMDA receptor channel by electrostatic repulsion. Now NMDA receptor can conduct. Importantly, NMDA receptors are also permeable to Ca^{2+}, which can act as second messenger. Triggers long-term changes in synaptic strength – long-term potentiation or long-term depression. These are potential mechanisms for learning and memory. Too much Ca^{2+} influx can kill cells – excitotoxicity. Source of cell death during cerebral ischemia (stroke).

6. Glutamate receptors constitute a separate receptor family from nAChRs. They are tetramers. Each subunit has an external N terminus, three membrane spanning segments (M1, M3 and M4) and a pore forming loop connecting M1 and M3 that dips into and out of the membrane, like P loop of voltage-gated channels – except loop is on intracellular surface of membrane. C terminus is intracellular.

7. Metabotropic receptor actions. Slower than ligand-gated channel (ionotropic receptor) actions. Often due to activation of G protein coupled receptors (GPCRs) -- family of seven transmembrane segment receptors. Leads to activation of GTP binding protein (G protein) that often leads to production of second messengers. Second messengers often activate protein kinases that then phosphorylate channels to alter neuronal excitability. All ionotropic receptor actions lead to opening of ion channels. Many metabotropic receptor actions can cause channels to close. Some actions due to closure of K^+ channels. This can depolarize resting potential, increase input

resistance, increase length and time constants, decrease the threshold for firing a spike, and increase the duration of the action potential.

8. In autonomic ganglia, ACh acts as fast transmitter at nicotonic ionotropic receptors and slow transmitter at the muscarinic class of ACh metabotropic receptors. These receptors are coupled to a G protein, which causes a decrease in the magnitude of a slow, voltage-gated delayed rectifier K^+ current called the M current (for muscarine-sensitive). Normally, in the absence of ACh, the M current plays a role in accommodation – the tendency of many neurons to decrease their rate of firing in response to a prolonged depolarizing stimulus. The reduction in the M current in response to ACh acts to decrease spike accommodation (causing more spikes to be fired during maintained depolarization).

Relevant reading : chapters 12 and 13 in Principles