Part IX: Modeling Synapse Complexity with Multiple Receptors

9a. Assemble a synapse with multiple receptors in the postsynaptic neuron following the diagram shown below. Be sure to include all of the following: voltage-gated sodium channel, voltage-gated potassium channel, dopamine, synaptic vesicle, presynaptic cell, postsynaptic cell, potassium leak channel, sodium-potassium pump, synaptic cleft, G-protein coupled receptor, calcium channel, dopamine reuptake protein, vesicular transporter, adenylyl cyclase, protein kinase, ATP, AMPA receptor, NMDA receptor, glutamate, and glycine or D-serine.
Step 1 - A nerve impulse (action potential) reaches the axon terminal of the presynaptic neuron which triggers the release of the neurotransmitter dopamine.

Step 2 - Calcium channels open in the presynaptic axon terminal. Open the calcium channels (red) and move some calcium ions to the interior of the neuron. Calcium ions bind to synaptotagmin.

Step 3 - Dopamine is released. Move the synaptic vesicle to the terminal end of the neuron. SNAP/SNARE proteins interact to bring the vesicle in position to fuse with the cell membrane.

Step 4 - Dopamine traverses the synaptic cleft to bind to the extracellular domain of the metabotropic receptor in the postsynaptic membrane. The intracellular domain of the metabotropic receptor binds to G-proteins. The G-protein has three subunits: alpha(α), beta(β), and gamma(γ).
**Step 5** - Bound dopamine activates the metabotropic receptor. The α subunit dissociates from the βγ complex.

**Step 6** - The α subunit binds to a membrane bound adenylyl cyclase setting up a signal cascade.

**Step 7** - Adenylyl cyclase converts ATP into cyclic AMP.

**Step 8** - Cyclic AMP binds to the regulatory domain of protein kinase. Four cyclic AMP’s must bind to the protein kinase in order for the regulatory domain to separate from the catalytic domain.
**Step 9** – The catalytic portion of the protein kinase phosphorylates the NMDA receptor (N-methyl-D-aspartate). NMDA also has an Mg\(^{2+}\) ion bound in the channel.

**Step 10** - The neurotransmitter, glutamate, binds to a second receptor, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. Up to four glutamate molecules may bind to the AMPA receptor to allow depolarization in the postsynaptic neuron.

**Step 11** - A slight depolarization of the postsynaptic neuron is required to cause the release of the bound Mg\(^{2+}\) from the NMDA receptor.

**Step 12** - Two glutamate and either two glycine OR two D-serine must bind to the N-methyl-D-aspartate (NMDA) receptor in order to open the channel.
Step 13 - Release of Mg$^{2+}$ opens the NMDA channel allowing the flow of Na$^+$ and Ca$^{2+}$ into the postsynaptic neuron to further depolarize the cell.

Step 14 - The effects of dopamine are terminated when dopamine is removed from the synaptic cleft by the dopamine uptake transporter. Effects of the neurotransmitters are terminated when they are removed from the synapse by specific uptake transporters.

9b. What neurotransmitters are involved in this model? 
(dopamine, glutamine, glycine or D-serine)

9c. Which receptor in this model is phosphorylated by protein kinase? 
(NMDA)

9d. Explain why phosphorylation alone does not open the receptor in this model. 
(NMDA must have all four of its ligand binding sites bound with two glutamate and 2 glycine or D-serine AND the magnesium ion must be released in order for the channel to allow the passage of sodium and calcium ions.)

9e. How is neurotransmitter binding different in the AMPA receptor as compared to the NMDA receptor? (Only glutamate binds to the AMPA receptor. The receptor is slightly responsive if only one glutamate is bound and opens more with each subsequent glutamate bound to the receptor. The NMDA receptor must have all sites bound in order to open.)
Part X: Modeling a Perturbation in the Glutamatergic Synapse

Next you will introduce two substances that perturb neural transmission in the glutamatergic synapse via the NMDA receptor. Phencyclidine (PCP) binds to the NMDA receptor in the postsynaptic membrane in a noncompetitive manner. Ketamine inhibits the NMDA receptor by blocking the open channel and reducing channel mean open time and, by an allosteric mechanism, decreasing the frequency of the channel opening.

10a. How would PCP affect nervous transmission in this synapse? (PCP opens the ionotropic NMDA receptor allowing the passage of Na⁺ and Ca²⁺ ions into the postsynaptic neuron depolarizing the cell. NOTE: A small amount of K⁺ ions may also pass out of the postsynaptic neuron through the NMDA receptor.)

10b. In what two ways can ketamine affect neural transmission of an NMDA receptor? (Ketamine may block the open NMDA channel and reduce the mean open time or ketamine may decrease the frequency of the channel opening.)