Simulation Exercises – Synaptic Transmission Part 2

These simulations should help you prepare to answer questions such as these that are highly likely to appear on a future exam:

1. How can a postsynaptic potential (PSP) that depolarizes the membrane be inhibitory? How did you demonstrate this?
2. Using the concept of the reversal potential for a PSP: What makes a PSP excitatory? What makes a PSP inhibitory? How did you demonstrate this in your simulations?

Inhibitory Postsynaptic Potentials

By blocking excitatory postsynaptic receptors pharmacologically and directly stimulating inhibitory interneurons, you can examine the inhibitory postsynaptic potentials in isolation from excitatory postsynaptic potentials. In SimCC, load and run IPSPS.CC5. Note that again we have a biphasic, or two-part, inhibitory potential. Through pharmacological investigation, you determine that the first part is mediated through the activation of $GABA_A$ receptors, while the second part is mediated through $GABA_B$ receptors (Figure 1). Then you investigate the ionic mechanisms of the generation of these different IPSPs by changing the membrane potential and the extracellular concentration of ions in the bathing medium. Change *Base current (nA)* from 0 to -0.38 nA and change the *Starting Vm* to -85 mV and choose Overlay. Notice now that the first IPSP is reversed (depolarizing) while the later IPSP is not (it is still hyperpolarizing) (Figure 1). This indicates that they are mediated by different ions. Let's examine the dependence of the different IPSPs on extracellular ion concentrations. First load and run IPSPS.CC5. You hypothesize that the early, GABA-A IPSP is mediatedby Cl - ions, since your investigations of voltage dependence show that it reverses at the equilibrium potential for Cl- (E_{Cl} = -75 mV). Therefore, you decrease $[Cl-]_o$ from 120 to 7 mM (do this now) and choose Overlay. Note that the $GABA_A$ IPSP is now depolarizing, indicating that changing the equilibrium potential for Cl^- so that it is positive to the membrane potential of the cell changed the direction of Cl^- flow. Whereas Cl^- originally flowed from outside the cell to in, it now moves from inside the cell to out (Figure 1; $[Cl^-]_i=[Cl^-]_o$). Similarly, you change the extracellular concentration of K^+ (first reload and rerun IPSPS.CC5) from 3.1 to 25 mM and *Base current (nA)* to -0.5 and find that now the late, $GABA_B$ IPSP is depolarizing, indicating that it is mediated by an increase in K^+ conductance (Figure 1; $[K^+]_o$ = 25).

An often confused aspect of synaptic transmission is the equating of depolarizing potentials with excitatory synaptic transmission and hyperpolarizing synaptic potentials with inhibitory synaptic transmission. However, we found in the previous simulation exercises that by hyperpolarizing the cell below E_{Cl}, a hyperpolarizing IPSP can become depolarizing. Does this make the previously inhibitory synaptic potential excitatory? No. The reason is that even though the IPSP is depolarizing, its equilibrium potential is still -75 mV and therefore 20 mV below the threshold for generation of an action potential (typically, -55 mV). To illustrate this, open IP_EPSP.CC5 and choose Begin. This is an isolated EPSP activated at -85 mV that makes the cell fire an action potential (Figure 2; EPSP alone). Now change *gEPSP* from 0.15 to 0, thus turning off the EPSP and change *gIPSP* to 0.1, thus turning on the IPSP ($GABA_A$ only in this case). Now choose Begin again and notice that the IPSP is depolarizing (Figure 2; reversed IPSP). Now change *gEPSP* back to 0.15 nS, choose Overlay, and notice that now the EPSP does not generate an action potential (Figure 2; EPSP + IPSP), since the IPSP "pulls" the peak of the EPSP towards E_{Cl} (-75 mV), and therefore away from action-potential threshold. Therefore, postsynaptic potentials that result from an increase in

membrane conductance and that have a reversal potential below action-potential threshold (e.g., -55 mV) are inhibitory, even if they are depolarizing.

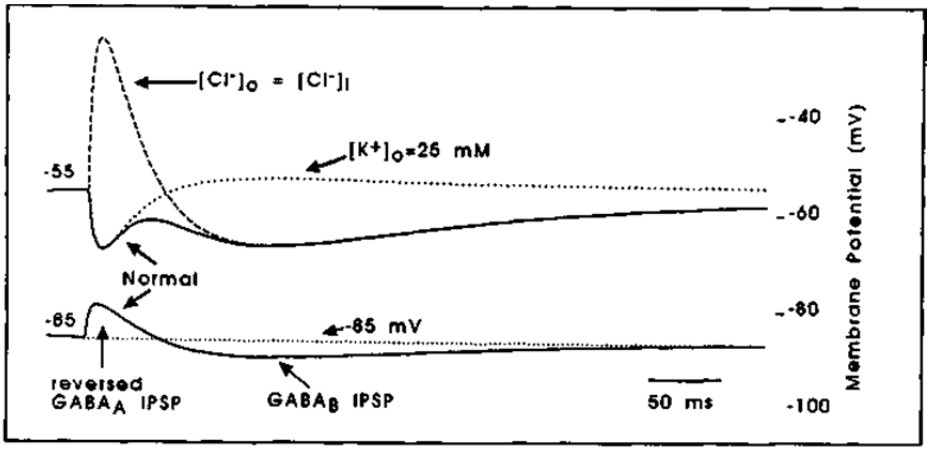

Figure 1. Ionic dependence of the two phases of IPSPs ($GABA_A$ and $GABA_B$). Changing chloride concentration affects the first, $GABA_A$-mediated IPSP; while changing potassium concentrations affects the later, $GABA_B$-mediated IPSP. The reversal potential of the $GABA_A$-mediated IPSP in normal solution is -75 mV, while the reversal potential the $GABA_B$-mediated IPSP is -100 mV.

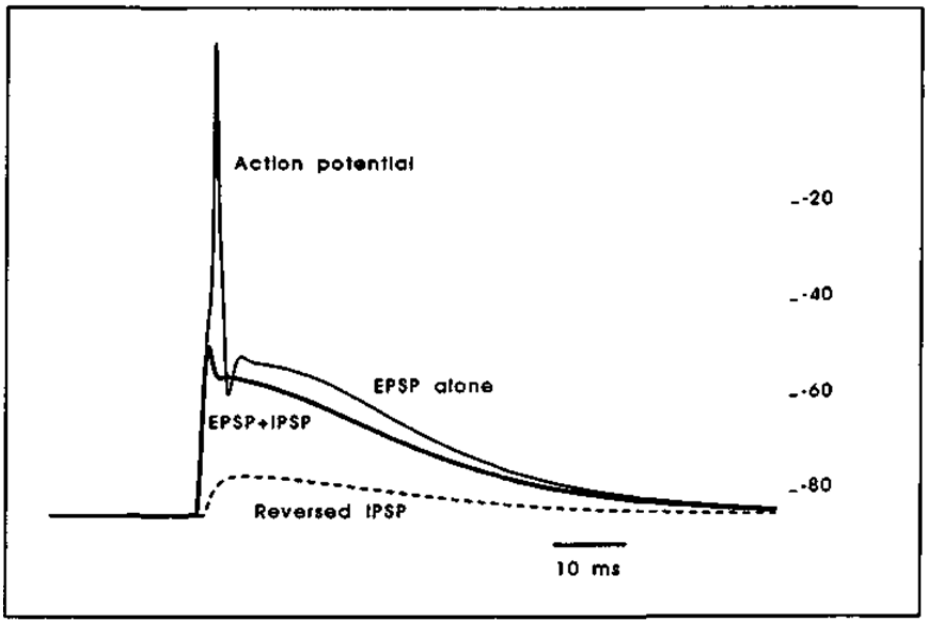

Figure 2. Reversed (depolarizing) IPSPs are inhibitory. Activation of the EPSP alone results in an action potential. Activation of the Cl^--mediated IPSP alone at a membrane potential of -85 mV results in a depolarizing IPSP *(dashed line).* Acti- vation of the EPSP and IPSP together results in inhibition of the EPSP so that it no longer activates an action potential.