(Due Wednesday, Sept 21, 2005)   HST 131/ Neuro 200

Problem Set 3 - Synaptic Transmission

1. Imagine you are recording from a slice of mammalian brain, where you can stimulate a presynaptic axon and record the voltage from the post-synaptic cell. For a typical excitatory synapse in the central nervous system, sketch the following as a function of time with emphasis on the *relative* timing of each event. (Assume that you have been able to block the postsynaptic neuron's voltage-gated ion channels so there is no action potential in the cell.)

   (1) the presynaptic action potential
   (2) the concentration of Ca^{2+} in the presynaptic terminal
   (3) the glutamate concentration in the synaptic cleft
   (4) the excitatory postsynaptic current (epsc) assuming that there are only AMPA-type glutamate receptors in the postsynaptic cell.
   (5) the excitatory postsynaptic potential (epsp).
   (6) Now show the postsynaptic current and potential with a relatively high concentration of TBOA (an inhibitor of the glutamate transporters that take up extracellular glutamate) in the solution bathing the slice.
   (7) Show the postsynaptic current and potential assuming there are only NMDA-type glutamate receptors (no TBOA)
   (8) Show the postsynaptic current and potential assuming there are both AMPA and NMDA receptors.

2. You are a neurophysiologist interested in $GABA_A$ currents in rat hypothalamic neurons. Using voltage-clamp recording you look at the responses of these neurons to pulses of muscimol, a $GABA_A$ agonist. Using a litter of newborn rat pups, you find that the reversal potential for the current evoked by muscimol is 0 mV. You also find that the $GABA_A$ conductance for the cell is 120 nS and the currents decay with a time constant of 25 ms at all potentials.

To follow this up, you spend a month writing programs to analyze and model the data. Ready with your powerful new analysis software, you return to experiments and use the remaining pups from the litter, now four weeks old. You are stunned to find that the reversal potential is now -70 mV, the conductance is 70 nS, and the time constant is just 5 ms.

Unsure whether the difference is due to the software, the animals, the experimental solutions, the laboratory temperature, or the phase of the moon, you prepare some figures to show your advisor (who is equally baffled).

a) Draw the I(V) curves of the GABA$_A$ currents at both ages (P0 and P28). Use the approximation $I=g(V_m-V_{rev})$.

b) Draw as a function of time the GABA$_A$-mediated currents at +20 mV, 0 mV, -20 mV, -60 mV and -80 mV, at both P0 and P28.

c) If the resting membrane potential is -50 mV for both P0 and P28 neurons and you pulse on a saturating amount of muscimol, how much GABA$_A$-mediated current is elicited at each age? Are these currents excitatory or inhibitory?

d) Suppose that you always used a bath solution with [Cl] of 120mM. What must be the internal concentrations of Cl⁻ at P0 and at P28 at 22°C? What physiological mechanisms might account for this change?

e) What physiological mechanisms might explain the conductance change over four weeks? The change in the time constant?

3. Use the program PSPSIM to answer the following questions. (You have already downloaded this program when you installed the NeuroSim programs for the second problem set, but may still download the NeuroSim programs from the course website or you can find PSPSIM on any student PC in the MEC building.

a) Select "active membrane" and examine postsynaptic response by selecting "EPSP". For these simulations, the stimulus is an action potential in the presynaptic terminal (you have no control over its timing or amplitude). The windows show the membrane potential and (optionally) conductances and currents of the postsynaptic cell. How does the cell respond to a single pulse, 2 pulses and 5 pulses? Explain.

b) To better understand the postsynaptic response switch from an "active" to a "passive" membrane. Think of this simulation as a block of the voltage-dependent conductances. What parameters govern the time course and amplitude of the EPSP evoked by a single pulse? In terms of these parameters how do you explain the EPSP evoked by 5 pulses?

c) Examine the membrane currents evoked by 5 pulses. Does the current mimic conductance exactly? Why or why not. By changing the leak conductance in the program, can you gain evidence to support your hypothesis? What is the evidence?