

Name: \_\_\_\_\_

**Neuroscience 201A Exam, October 9, 2015**

**Question #1 – 25 minutes**

Neurons in the mammalian brain typically have resting potentials (in the absence of synaptic inputs) in the range of  $-60$  mV to  $-70$  mV. Skeletal muscle fibers in mammals, by contrast, have resting potentials that are about  $-90$  mV. Provide a plausible hypothesis for this difference (which you can even observe in cases where the two cell types are in the same recording chamber and exposed to the same extracellular solution) and design an experiment, or set of experiments, to test your hypothesis. If you propose multiple possible hypotheses for this difference, your experimental approach must allow one to distinguish among them.

**Question #2 – 35 minutes**

Excitatory ionotropic receptors like nicotinic receptors and AMPA (glutamate) receptors have channels that are less selective than voltage dependent channels of the sort that underlie the rising and falling phase of action potentials. Rather than passing sodium or potassium selectively, these channels pass most available cations about equally well. Nature has yet to produce an excitatory ionotropic receptor channel that is sodium selective: they are all cation selective, and as a result they have open channel conductances that are considerably larger than sodium selective channels. To gain some appreciation for why Nature has not built a sodium selective channel for excitatory synapses, work out the following set of calculations.

Part 1: Assume for a cell that  $E_K = -90$  mV,  $E_{Na} = +50$  mV,  $E_{Cl} = -70$  mV, and  $E_{leak} = -70$  mV. For a cell at rest, calculate the net inward current that will flow under each of the two following conditions:

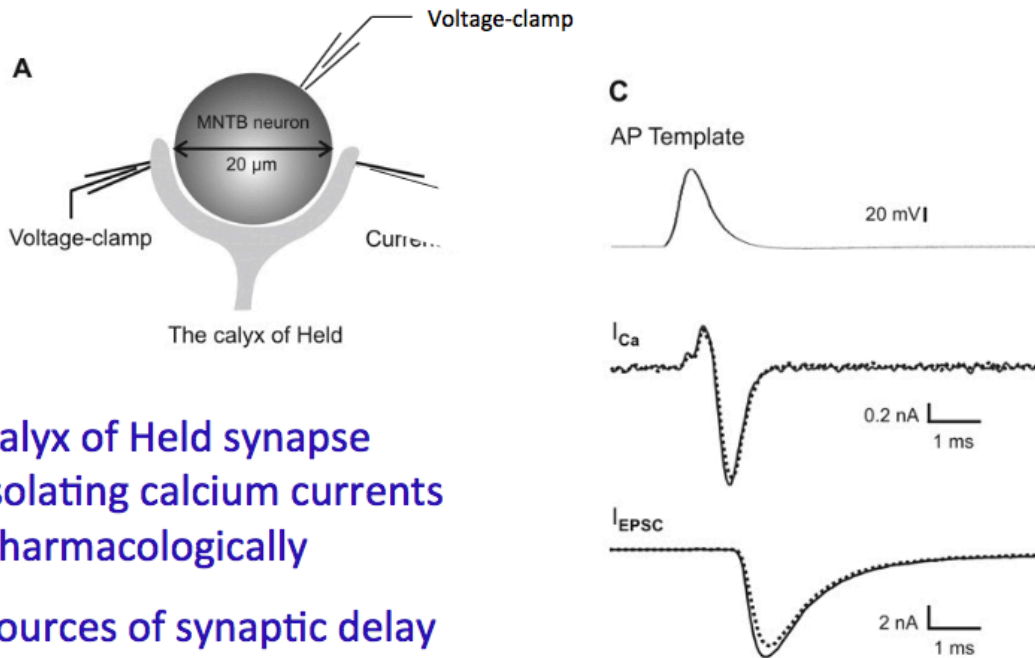
- a) The excitatory transmitter activates an ionotropic receptor having a completely sodium selective channel. 100 channels are opened simultaneously for 1 ms. The open channel conductance of each channel is 8 pS.
- b) The excitatory transmitter activates an ionotropic receptor having a cation selective channel with a  $g_{Na} / g_K$  ratio of 1. 100 channels are opened simultaneously for 1 ms. The open channel conductance of each channel is 50 pS.

For the sake of simplicity, assume that the cell is voltage-clamped at rest (i.e., the driving force does not change during the course of the ms when the channels are open).

Part 2: Calculate how much the cell will be depolarized by the inward current in the two cases presented in Part 1. Assume that all of the charge entering the cell stays in the cell during the ms during which the channels are open (it doesn't start leaking out until after the channels have closed). Assume that the cell is a sphere 25  $\mu\text{m}$  in diameter with no dendrites and that it has a specific membrane resistance at rest of 1000  $\text{ohm cm}^2$  and a specific membrane capacitance of  $10^{-2}$  farads  $\text{m}^{-2}$ .

## Question #3 – 20 minutes

## Calcium channels open in response to depolarization

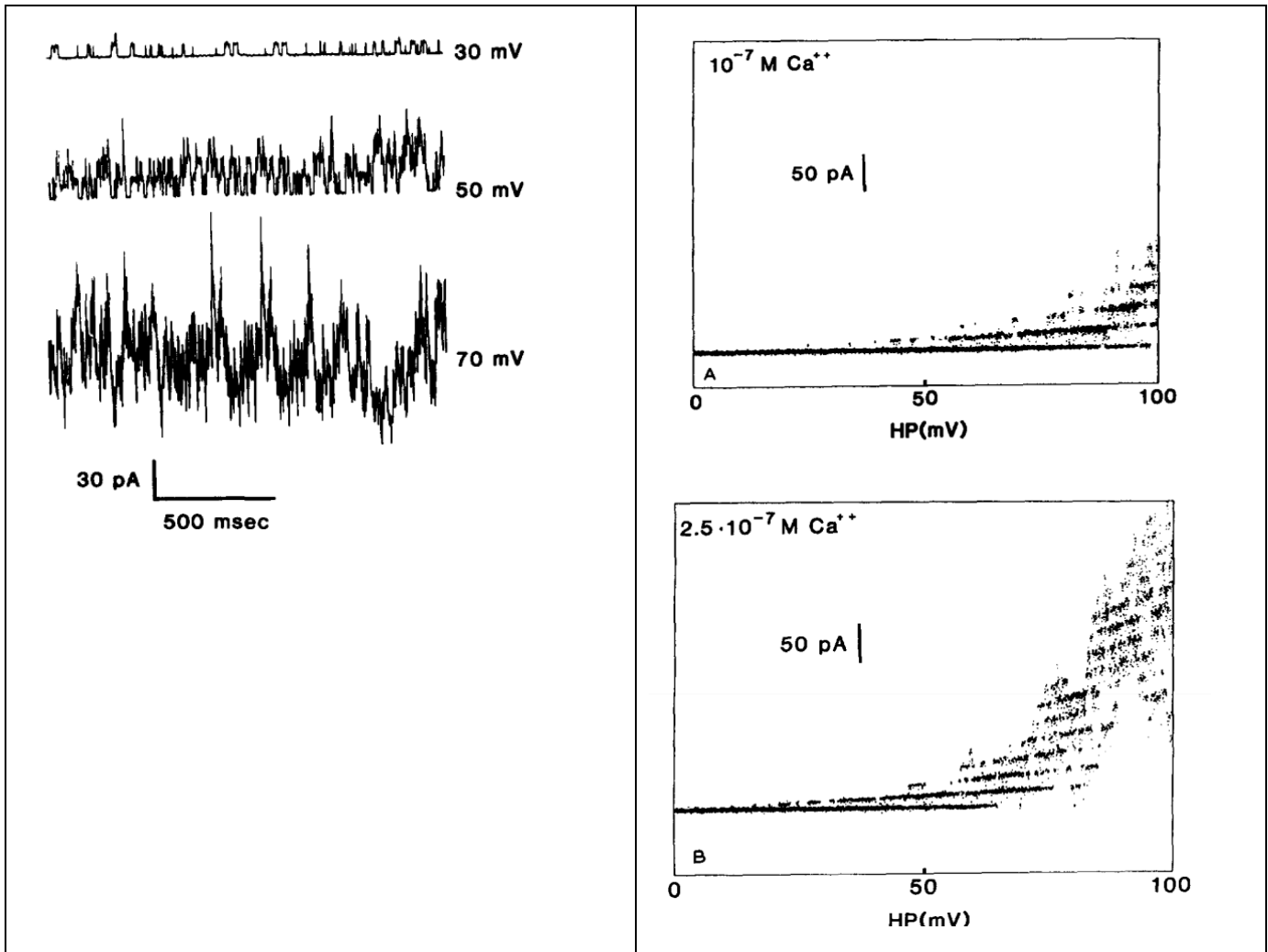


- Calyx of Held synapse  
Isolating calcium currents pharmacologically
- Sources of synaptic delay

The figure above was shown in lecture. In this figure the authors recorded the waveform of the action potential in current clamp configuration and later, in separate experiments, “played” this waveform through the voltage clamp circuit to mimic an action potential. The trace labeled  $I_{Ca}$  was the resulting current trace after blocking other obvious currents (sodium, potassium). We briefly discussed in class what might be the source of the brief outward current transient in the  $I_{Ca}$  trace, and it was suggested that this might be leak current.

- Does this current have the correct sign (positive) to be leak current?
- What would you expect the waveform of leak current to be during the action potential? Draw  $i_{leak}$  vs. time for this experiment.
- Assuming that this outward transient IS leak current, and armed with an educated guess about the time course of leak current during the AP, provide a method for correcting for leak current in this experiment to produce a better  $I_{Ca}$  trace.

## Question #4 – 30 minutes

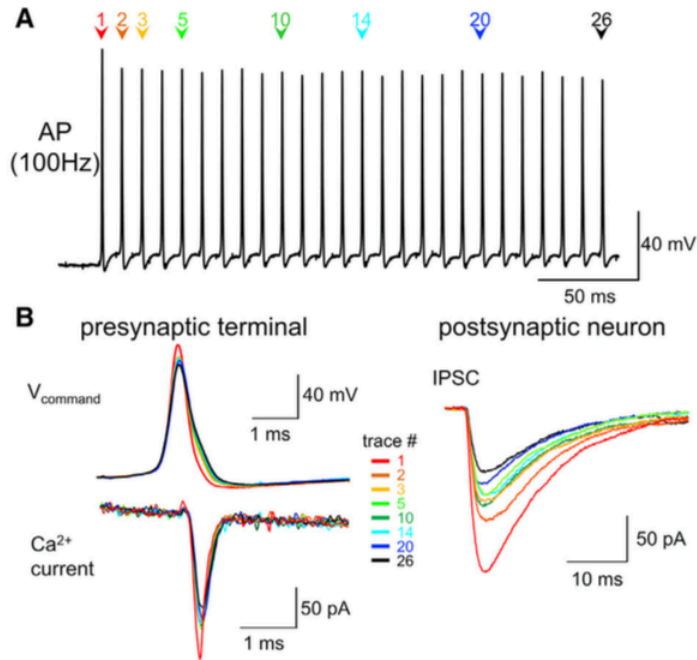


Part 1: The records above (left) were obtained during an experiment in which a patch of membrane was held at three different holding potentials. At “30 mV” and “50 mV” the zero current value is evident at the lower margin of the trace. To measure the probability that a channel is open,  $p_{\text{open}}$ , would it be appropriate to analyze the trace marked by “30 mV?” Why, or why not?

Part 2: The two records on the right were taken from patches such as that shown for the left figure and show current records at two different  $[\text{Ca}^{2+}]_o$ s (top, bottom) during a gradually changing ramp of voltage (see x-axis; HP is holding potential); thus, at the left margin of the graph, the holding potential is 0, and at the right margin, holding potential is 100 mV. What is the minimum number of channels in this patch (refer to the lower of the two graphs)?

Part 3: Make a very rough calculation (from the right figures) of the single channel conductance and  $E_{\text{rev}}$  of these channels?

## Question #5 20 minutes



The figure above is taken from Figure 5 of the Kawaguchi and Sakaba paper (2015). It shows a series of recorded APs from a nerve terminal in A and in B a set of  $I_{\text{Ca}}$  current curves in response to AP waveforms play back to mimic individual APs in the train (left) and the postsynaptic responses to the waveforms (right). The  $I_{\text{Ca}}$  current is noticeably larger for the first AP (red) as compared to the others, all of which have a smaller peak and a slower falling phase. Why do you think that the  $I_{\text{Ca}}$  current is so much larger for the first spike: in particular, do you think that it's because the AP is a bit bigger or do you think that it's because it's faster? Justify your reasoning.

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**Question #6 - 25 minutes**

Two important observations about voltage-gated  $\text{Ca}^{2+}$  channels have been made:

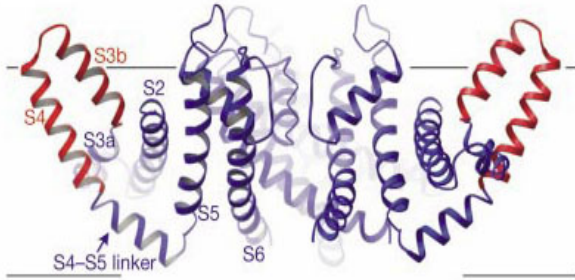
- 1) In the absence of  $\text{Ca}^{2+}$ , voltage-gated  $\text{Ca}^{2+}$  channels conduct  $\text{Na}^+$ ;
- 2) the amplitude of the  $\text{Na}^+$  current is usually larger than that of  $\text{Ca}^{2+}$  current.

How would you explain these two phenomena?

**Question #7 - 25 minutes**

Problem 2: Roderick MacKinnon published two structures of a voltage-gated K<sup>+</sup> channel (shown below). The voltage sensor domain in one of these structures is misfolded. Please say which structure is misfolded and why?

Structure 1



Structure 2

