

Bi150 Problem Set 3

Due: Tuesday, October 25th, 2011, at 4:30 P.M.

At the “Bi 150 Box”

3rd floor of Kerckhoff in front of Room 326

(The building may be locked after 5 P.M.)

INSTRUCTIONS

Please:

- 1) Turn in your work with this cover page.**
- 2) Use separate sheets of paper for the answer to each question, so that graders can work in parallel.**
- 3) Write or type your answers neatly.**
- 4) Put your name on each page of your answers.**

Name: _____

Section #: _____

Mail Code: _____

TA Name: _____

Date and Time turned in: _____

Number of pages including this one: _____

There are 3 questions.

Grade and Comments:

1 _____

2 _____

3 _____

Total: _____

Problem 1. Synaptic integration (1.5 points)

A. (0.9 point) Inhibition

Many inhibitory synapses in the CNS utilize GABA_A and glycine receptors. Both GABA_A and glycine receptor channels are permeable to Cl⁻ ions. Calculate the Nernst potential for Cl⁻ ions, E_{Cl}, at 25°C. Consult the ionic concentrations on slide 5 of lecture 1.

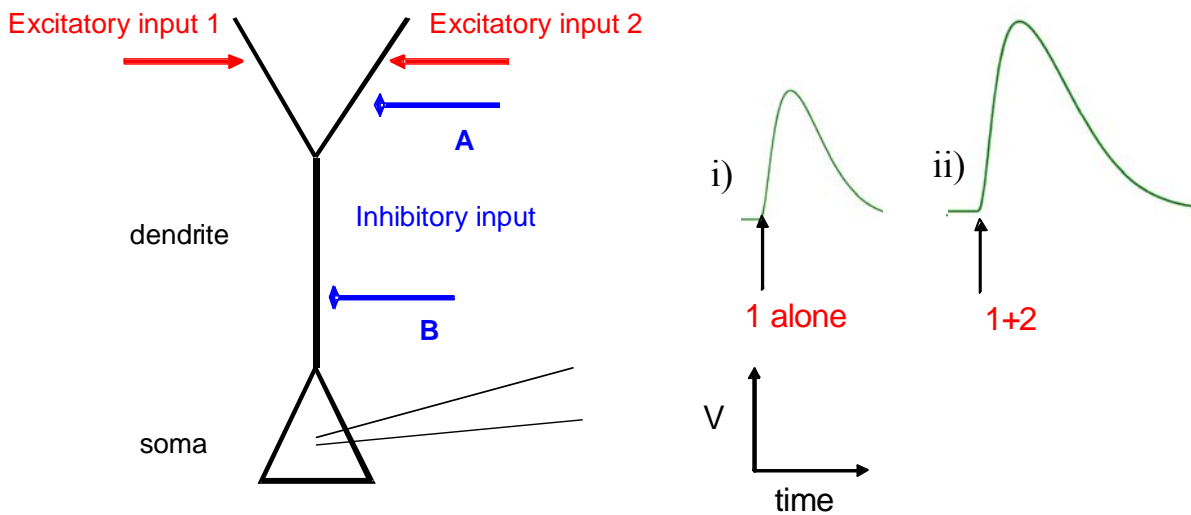
Resting membrane potentials of neurons are sometimes close to E_{Cl}. When this is the case:

- a. How does the membrane voltage change if only GABA_A receptors are activated?

Consider a neuron receiving two excitatory inputs as shown below. The traces at the right show the membrane potential in the soma without inhibition.

- i) excitatory input 1 is stimulated alone
- ii) excitatory input 1 & 2 are stimulated

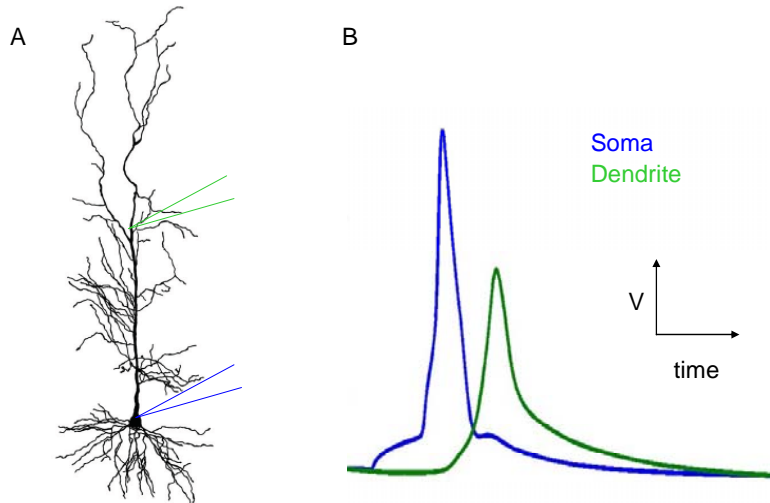
- b. For each trace, redraw the trace, then superimpose the trace if a GABAergic input is active at location A during the excitatory stimuli.
- c. For each trace, redraw the trace, then superimpose the trace if a GABAergic input is active at location B during the excitatory stimuli.



B. (0.6 point) Active dendrites

The figure below shows simultaneous recordings of membrane potential from the soma and dendrite when the action potential is induced by current injection into the soma (panel A shows recording sites, and panel B shows membrane voltage).

- a. Redraw the dendritic traces; then superimpose the dendritic voltage trace during action potentials in a mutant animal that lacks “dendritic” voltage-gated Na^+ channels. Explain.



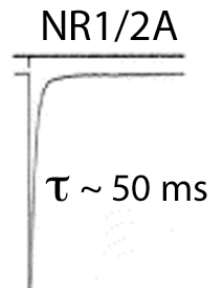
- b. What is spike timing dependent plasticity, STDP?
- c. How might back-propagating spikes, due to dendritic Na^+ channels, influence synaptic plasticity?

Problem 2. NMDA receptors and plasticity (1.5 points)

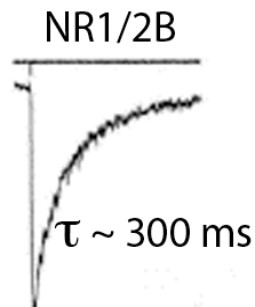
Recall from lecture the “Ca²⁺ hypothesis for control of synaptic plasticity” which holds that the direction of activity-dependent long term changes in synaptic strength (i.e. LTP vs. LTD) is determined by the level and the timing of Ca²⁺ influx into postsynaptic spines when the NMDA receptor is activated.

Note the following experimental observations about NMDA receptors:

Receptors containing 2 NR1 subunits and 2 NR2A subunits (NR1/2A) show the following activation and deactivation kinetics:



In contrast, receptors containing 2 NR1 subunits and 2 NR2B subunits (NR1/2B) show the following activation and deactivation kinetics:



EC₅₀ is the effective concentration for activating 50% of the receptors.

NR1/2A receptors have an EC₅₀ value for glutamate of 4.8 μM.

NR1/2B receptors have an EC₅₀ value for glutamate of 1.8 μM.

Consider the following hypothetical situation:

Equal numbers of NR1/2A receptors and NR1/2B receptors are randomly distributed in the postsynaptic membrane of synapses in a brain area. Recordings from the synapses in this brain area display frequency-dependent synaptic plasticity as described by Graph 1.

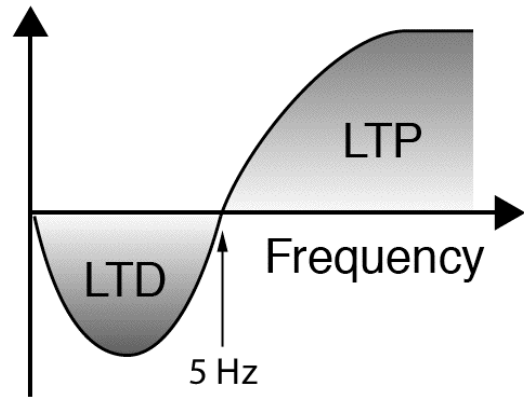
A stimulus at a frequency < 5 Hz produces LTD.

A stimulus at a frequency > 5 Hz produces LTP.

A 5 Hz tetanic stimulus produces no change in synaptic strength.

Therefore, 5 Hz is referred to as the “cross-over frequency” for this synapse.

Graph 1. The ordinate represents synaptic strength, and the abscissa represents frequency of a brief tetanic stimulation.



A. (0.8 pt) If all of the NR1/2A receptors were changed to NR1/2B receptors, what change would you expect in the crossover frequency for the synapse? Explain.

B. (0.7 pt) If, instead, all of the NR1/2B receptors were changed to NR1/2A receptors, now what change would you expect in the crossover frequency for the synapse? Explain.

Problem 3. GPCRs (1.5 points)

A. (0.6 point)

- a. G protein-coupled receptors activate G proteins by reducing the strength of GDP binding. This results in rapid dissociation of bound GDP, which is then replaced by GTP, which is present in the cytosol in much higher concentrations than GDP. What consequences would result from a mutation in the α_s subunit of a G protein that caused its affinity for GDP to be reduced without significantly changing its affinity for GTP?
- b. Compare the effects of this mutation with the effects of cholera toxin.
- c. Describe how the mechanism of pertussis toxin differs from the mechanism of cholera toxin on GPCRs. Describe how several subsequent actions cause prolonged neuronal activation.

B. (0.4 point)

a. You have ascribed a G protein pathway to two events:
When you stimulate the presynaptic neuron while activating the GPCR, more transmitter is released.

You observe phosphorylation of a K^+ channel in the presynaptic neuron.

Explain your hypothesis for linking these two results.

b. You have ascribed another G protein pathway to two events:
When you stimulate the pathway for several days, the target neuron expresses 3 dozen genes more strongly than in the absence of stimulation.

You find that the receptor activates Gq.

Explain your hypothesis for linking these two results.

C. (0.5 point)

The phenotype of Down syndrome (DS) may be a consequence of overexpressed genes in an extra chromosome 21. One such gene is *Kcnj6/Girk2*, which encodes the G protein-coupled inward rectifying K^+ channel subunit 2 (GIRK2). The DS mouse model, Ts65Dn, overexpresses GIRK2 throughout the brain, particularly in the hippocampus. Increased expression of GIRK2 containing channels has functional consequences that likely affect the balance between excitatory and inhibitory neuronal transmission.

- a. Beginning with appearance of GABA near GABA_B receptors, describe how GIRK current is activated in a neuron.
- b. What role do GIRK channels play in neuronal function?

- c. RGS4 is a GTPase activating protein. The current trace below comes from a voltage-clamp experiment with 30 mM external K^+ and 140 mM intracellular K^+ , conducted at a holding potential of -80 mV. What effect do RGS proteins have on GIRK channel activity? Redraw the trace below, and superimpose the trace if the cell expresses RGS4.
- d. Describe the effect on GIRK activity if a non-hydrolyzable GTP analogue, $GTP\gamma S$, were injected into the cell. Redraw the trace below, and superimpose the trace if $GTP\gamma S$ is present. Don't forget possible changes that could occur before GABA is applied.

