Bi/CNS/NB 150

Problem Set 4

Due: Tuesday, Nov. 17, at 4:30 pm

Instructions:

1) Drop off in the Bi 150 box outside Baxter 331 or e-mail to the head TA (jcolas).

2) Submit with this cover page.

3) Use a separate sheet of paper for each problem.

4) Type all answers if possible.

5) Use complete, grammatically correct sentences.

6) Include your name and the page number on every page.

7) Note that late problem sets receive a 10% deduction for every day past the due date.

Name:

Time and date submitted:

Total pages (including cover page):

Comments:

Problem 1 grade:

Problem 1 comments:

Problem 2 grade:

Problem 2 comments:

Problem 3 grade:

Problem 3 comments:

Total grade:

Problem 1 (1.5 points): G-protein-coupled receptors

Problem 1.A (0.6 points): Mutants and toxins

1.A.a. G-protein-coupled receptors (GPCRs) activate G proteins by reducing the strength of GDP binding. This results in rapid dissociation of bound GDP that 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?

1.A.b. Compare the effects of this mutation with the effects of the cholera toxin.

1.A.c. Describe how the mechanism of the pertussis toxin differs from the mechanism of the cholera toxin on GPCRs. Describe how several subsequent actions cause prolonged neuronal activation.

Problem 1.B (0.4 points): Pathways

1.B.a. You have ascribed a G-protein pathway to two events. When you stimulate the presynaptic neuron while activating the GPCR on the presynaptic neuron's membrane, more neurotransmitter is released. You observe phosphorylation of a K^+ channel in the presynaptic neuron. Explain your hypothesis for linking these two results.

1.B.b. You have ascribed another G-protein pathway to two events. When you stimulate the pathway for several days, the target neuron expresses 36 genes more strongly than in the absence of stimulation. You find that the receptor activates G_q. Explain your hypothesis for linking these two results.

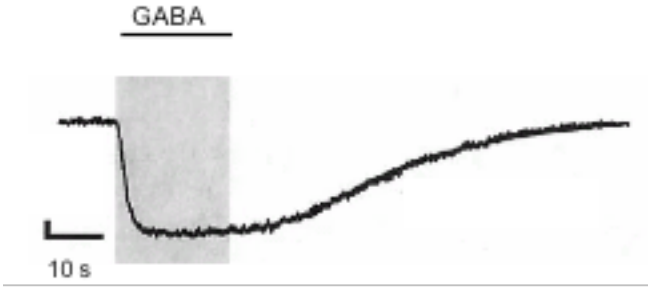
Problem 1.C (0.5 points): Inwardly rectifying potassium channels

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

1.C.a. Beginning with appearance of GABA near $GABA_B$ receptors, describe how GIRK current is activated in a neuron.

1.C.b. What role do GIRK channels play in neuronal function?

1.C.c. RGS4 encodes a GTPase-activating protein. The current trace below comes from a voltage-clamp experiment conducted at a holding potential of -80 mV with extracellular and intracellular K^+ concentrations of 30 mM and 140 mM, respectively. What effect do RGS proteins have on the activity of GIRK channels? Redraw the trace below and then superimpose the trace produced if the cell were to express RGS4.



1.C.d. Describe the effect on GIRK activity if a non-hydrolyzable GTP analog, GTPγS, were injected into the cell. What effect would this have on the activity of GIRK channels? Redraw the trace above and then superimpose the trace produced if GTPγS were present. Also consider changes that could occur before GABA is applied.

Problem 2 (1.5 points): Visual system

Problem 2.A (0.6 points): Impairments

Consider each of the following lesions and mutations:

1) Selective and complete loss of rod cells in both retinae
2) Bilateral and complete lesions of visual area V4
3) Lesion of the lower bank of the calcarine sulcus in the left hemisphere
4) Selective loss of function of parvocellular ganglion cells in both retinae
5) Selective and complete loss of cone cells in both retinae
6) Complete sagittal transection of the optic chiasm cutting only those fibers that would normally cross there
7) Bilateral lesions in posterior parietal cortex
8) Mutation of retinal cGMP-gated channels causing selective impermeability to Ca^{2+}
9) Selective loss of function of magnocellular ganglion cells in both retinae
10) Mutation of retinal cGMP-gated channels causing selective impermeability to Na^{+}
11) Lesion of the optic radiation fibers that curve into the temporal lobe in the left hemisphere

Match each of the following visual impairments with a single lesion or mutation in the visual system from the list above that could be responsible for the impairment. No lesion or mutation should be provided as an answer twice. Explain how the given lesion or mutation produces the specified visual impairment.

2.A.a. Complete loss of vision only in the temporal halves of both visual fields

2.A.b. Complete loss of vision only in the superior quadrant of the visual field on the right side and with the central visual field unaffected

2.A.c. Inability to perceive a pattern of bright and dark bars that have both low spatial frequency and high temporal frequency

2.A.d. Inability to see or dream in color

2.A.e. Difficulty to adapt to different light intensities quickly

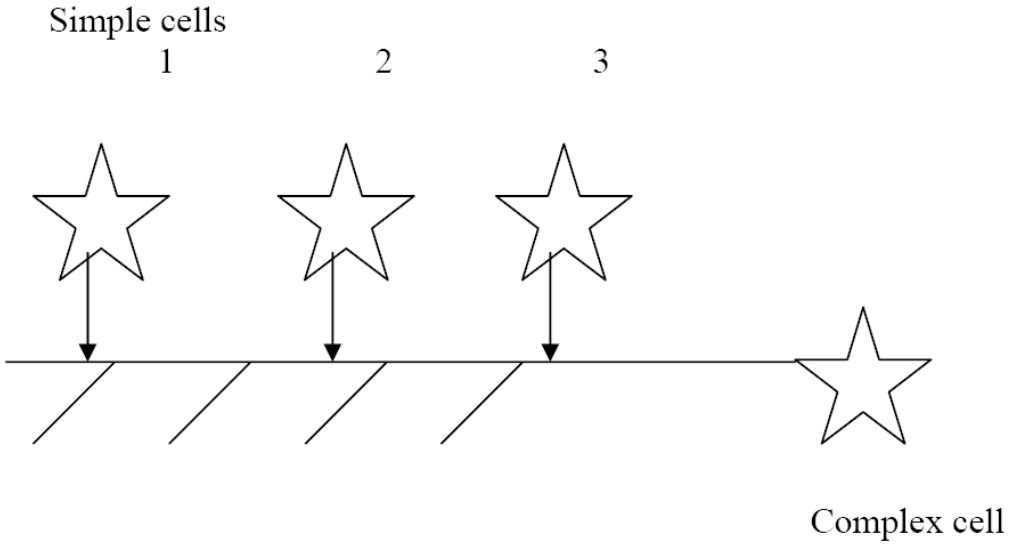
2.A.f. Inability to reach for visual objects normally

Problem 2.B (0.9 points): Simple and complex cells

2.B.a. A simple cell responds to bars of light with a specific orientation. Draw a network of on- or off-center ganglion-cell inputs to a simple cell that would enable it to respond to this stimulus. Draw the receptive fields of each ganglion cell needed and the spatial relationships of these receptive fields. Explain how your model works.

2.B.b. A complex cell also responds to bars of light with a specific orientation. However, unlike the simple cell, the receptive field of a complex cell is generally large enough that the position of bars of light in the receptive field is not critical to evoke the response in the neuron. These properties of complex cells are derived from their inputs from multiple simple cells. Draw a network of multiple simple cells with different receptive fields that all connect to a complex cell and enable it to have a larger receptive field with orientation tuning. Explain how your model works.

2.B.c. Furthermore, a complex cell can respond selectively to unidirectional movement across its receptive field in a specific orientation (e.g., a horizontal bar of light moving upwards). This could also be explained by the connectivity between multiple simple cells and one complex cell. In the network shown below, three simple cells with different receptive fields form synapses onto a complex cell at different locations along a single dendrite. This complex cell is most responsive to a bar of light moving from the receptive field of simple cell 1 through the receptive field of simple cell 2 to the receptive field of simple cell 3 but not as responsive to a bar of light moving in the opposite direction. Explain how this directional specificity might be achieved.



Problem 3 (1 point): Olfactory system

Problem 3.A (0.2 points): Anatomy

Beginning with the nose, describe the major excitatory synaptic connections in the main olfactory pathway of mammals.

Problem 3.B (0.8 points): Olfactory receptor neurons

3.B.a. Describe the intracellular signaling pathway in olfactory receptor neurons (ORNs) from odorant stimulation to action potentials. Explain the role of each molecule involved in this signaling cascade.

3.B.b. Individual odorant receptors show relatively low affinity for a range of ligands. What would be the selective advantage of this broad spectrum of ligand binding if two different concentrations of the same odorant were applied sequentially?

3.B.c. What would be the selective advantage of this broad spectrum of ligand binding if two similar odorants were applied sequentially?

3.B.d. The olfactory systems of most animals feature sensitivity on the order of only a few odorant molecules. Yet, we become less sensitive to an odor after being exposed to it for an extended duration. Using your knowledge of GPCR pathways, describe a possible mechanism in ORNs that might contribute to this phenomenon.