

Part 2. Answer only one of these two questions:

1. Dr. Maler (15 marks total):

Part A. Describe in detail the cellular basis of the action potential. **10 Marks**

Part B. You have discovered a neuron whose resting membrane potential is -70 mV and in which each action potential is followed by a strong hyperpolarization (AHP, down to -85 mV). The AHP lasts about 30 ms.

What is the biophysical basis of the AHP and how would you test your hypothesis. **5 Mark**

2. Dr. Beique (15 marks total):

Part A: **(5 marks)**

What is a 'silent' synapse? In your answer, provide the following: 1) a short (about 10 words), factual definition (**1 mark**). 2) Why is it called 'silent' (**1 mark**). 3) Briefly describe the electrophysiological experiment covered in class that documented the existence of such 'silent' synapses (**3 marks**).

Part B: **(5 marks)**

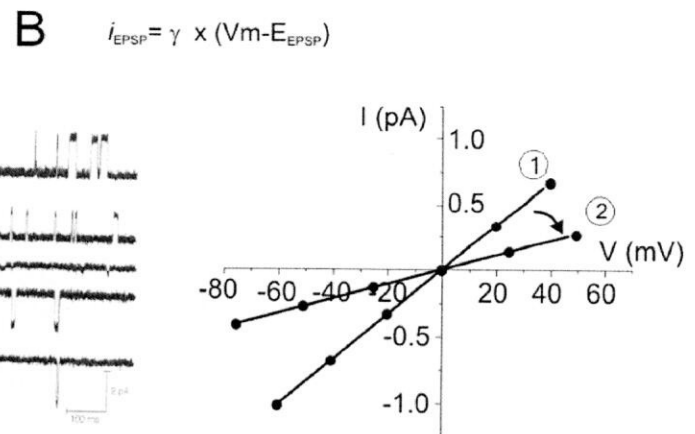
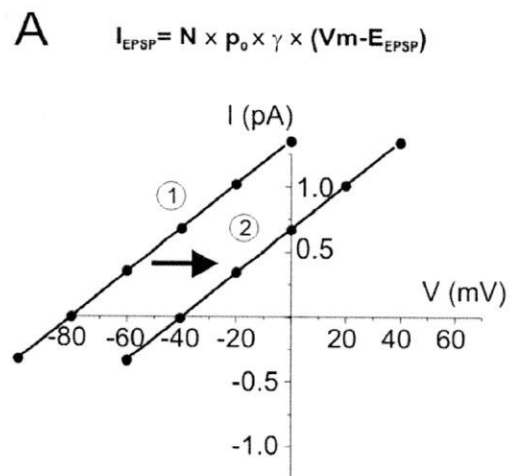
Given that the amplitude (A) of an evoked EPSC can be described as: $A = Npq$; define these 3 variables (N,p,q) (**1 mark**). In the search for the expression mechanism of LTP (*i.e.*, pre-vs postsynaptic mechanism), a number of clear experimental evidences seemed to contradict one another. Describe why an increase in the function of AMPA receptors, but not of NMDA receptors, following LTP favors a *postsynaptic* locus of expression (**2 marks**)? What was the main experimental evidence favoring a *presynaptic* mechanism (**1 mark**)? In this particular case, what was believed to increase following LTP (N, p or q) (**1 mark**)?

Part C: **(5 marks)**

Some men in black wearing sunglasses have given you brain tissues to analyze in your electrophysiology laboratory under their supervision. You suspect that the tissue is of alien origin. You carried out whole-cell electrophysiological recordings from cells in this tissue. In **A**, you obtained

some nice **synaptic currents** elicited by a stimulating electrode and obtained an I-V relationship (curve #1) of these synaptic currents. You suspect you are activating a Chloride conductance analogous to a GABA-A receptor. The men in black then changed something in your solutions and the next day you obtained an I-V curve that was shifted to the right (curve #2). Solely from the shape of the I-V curves, state: 1) the reversal potential for these 2 curves (**0.5 mark**); 2) based on your suspicion outlined above (*i.e.*, a GABA-A receptor-like conductance), state and very briefly describe what the men in black most likely did to your recording solutions to elicit a curve that was shifted to the right (**1 mark; be qualitative, no need to be quantitative**); and 3) Define the parameters (N, p_o, g and E_{EPSP}) in the equation above the graph (**1 mark**). Which one of the parameters (N, p_o, g or E_{EPSP}) in the equation above the graph most likely changed between those two curves (**1 mark**)?

In **B**, from cells in this alien tissue, you carried out **single-channel** recordings and obtained the current traces shown on the left (obtained at different holding potentials). You plotted the peak amplitude of these single-channel openings against holding potentials and obtained the curve #1. Your men in black friends then did something and the same experiment yielded the curve #2. Solely from the shape of the I-V curves, state: 1) the reversal potential for these 2 curves (**0.5 mark**); and 2) Which one of the parameters (g or E_{EPSP}) in the equation above the graph (for single-channel recording) most likely changed between those two curves (**1 mark**)?



Part 3. Answer **two** of these three questions (15 marks each, **total 30 marks**):

1. Dr. Ngsee (15 marks total):

Briefly describe the SNARE hypothesis, and explain how a constitutively “open” syntaxin mutant might affect calcium-triggered neurotransmitter release. Briefly describe the SNARE hypothesis, and explain how a constitutively “open” syntaxin mutant might affect calcium-triggered neurotransmitter release.

2. Dr. Tiberi (15 marks):

Describe at least 6 potential mechanisms involved in the control of neurotransmitter and neuropeptide-induced intracellular responses by G protein-coupled receptors (GPCRs). **Do not discuss** the role of the structural motifs found in GPCRs.

3. Dr. Albert (15 marks):

Draw a model of the dopamine system involved in movement control.

In the drawing (and in a written description) show the site of lesion in Parkinson's disease, and changes in activity, receptor levels, neurotransmitter and neuropeptide levels that occur in Parkinson's disease. Describe a gene knockout or drug-induced mouse model of Parkinson's disease.

Part 4. Answer only **one** of these two questions (**15 marks total**) :

1. Dr. Slack (15 marks total):

- a) Describe how the cerebral cortex develops. (6 marks)
- b) Describe the regions where adult neurogenesis occurs and explain what is meant by Type I-II-III cells and Type B-C-A cells. (3 marks)
- c) Explain what is meant by stem cell niche. (3 marks)
- d) Describe a transgenic mouse model that can be used to study adult neurogenesis. (3 marks)

2. Dr. Slack (15 marks total):

You have an animal with a developmental defect where the cortex develops inside out. (a) What could account for the underlying developmental defect? (**7 marks**) and (b) What tests can you do to determine exactly where the defect is? (**8 marks**)

Part 5. Answer any **two** of these three questions

1. Dr. Colavita (15 marks total):

- A.** What is the motile structure at the tip of the axon responsible for axon pathfinding? (1 mark) What molecules within this structure are the ultimate targets of axon guidance pathways and are ultimately responsible for axon motility? (1 mark)
- B.** In the developing spinal cord, commissural axons make a series of guidance decisions in order to reach their final targets: first, they grow ventrally toward the floor plate; second, they cross the midline to the contralateral side; and third they turn and extend anteriorly. We have discussed several axon guidance pathways involved in commissural axon pathfinding. Describe at least one receptor/ligand pathway involved in axon guidance towards the floor plate (1 mark). Also, describe any two receptor/ligand pathways that ensures that commissural axons cross the midline and/or do not recross (2 marks). In each case, mention if chemoattraction or chemorepulsion is involved and where the receptors and ligands are expressed. Next, provide one example of how commissural axons at the midline (floor plate) switch responses from one guidance cue to another (remember to mention which guidance cues are involved) (2 marks). After commissural axons cross the midline, they turn to grow anteriorly. What guidance cue is involved in guiding these commissural axons anteriorly (1 mark)?
- C.** You study commissural axon guidance in the mouse and you have just cloned a gene expressed at the floor plate of the developing spinal cord that is highly homologous to a secreted axon guidance molecule in *C. elegans*. The commissural neurons are located in the dorsal part of the spinal cord and extend axons ventrally toward the floor plate. Before embarking on an expensive and time-consuming mouse knock-out, what in vitro experiment could you perform to show that your mouse gene encodes a diffusible chemoattractant secreted from the floor plate? (2 marks) What would you expect to see if it was a chemorepellent? (1 mark) Using this same assay or another, how would you show that your molecule is capable of acting instructively to guide axon growth? (2 marks) Finally, previous work has identified a candidate receptor for this putative guidance molecule. Using your in vitro assay, describe an experiment that could be used to test if this receptor mediates the response to your guidance cue. Don't forget to mention control experiments. (2 marks)

2. Dr. Chen (15 marks total):

- A.** Name 3 major neurotrophins and their high affinity receptors, respectively. **(2 marks)**
- B.** Describe with a diagram a general scheme of the signaling cascade whereby neurotrophins promote cell survival **(3 marks)**.
- C.** In contrast to their original well-known anti-apoptotic roles, many studies in the past 8 years have reported that neurotrophin receptors could also activate apoptotic processes. Is this a general phenomenon for all neurotrophin receptors? What's the role of the kinase function in this process? Please give one example and describe how neurotrophin receptors activate cell death and how this process is implicated in diseases that may revolutionize therapeutic treatment for the diseases. (You are welcome to use but are not restricted to the examples discussed in the lecture.). **(10 marks)**.

3. Dr. Albert (15 marks):

Draw a model of calcium-dependent signaling pathways that lead to early vs. late phases of LTP (longterm potentiation) in the hippocampus. Describe the different processes that lead to early vs. late LTP.

Part 6. Bonus Question – from papers in class (**2 marks**). Answer any **2** of these questions. **DO NOT** choose the paper that you presented in class.

1. Wrann paper: How does exercise improve cognitive function?
2. Karalay paper: How is Prox1 regulated and what is its role?
3. Giros paper: Describe the behavioral phenotype and response to stimulants in the dopamine transporter knockout mouse.
4. Alarcon paper: How did these investigators increase CREB-CBP function in CBP \pm mice, and what was the behavioral effect they measured?