NEUR0010 Exam 1 Review
Prepared by Ronnie Li

You have a lot of multiple choice questions to practice from, but do you truly understand the concepts behind what you're studying? Test yourself here, for starters.

Some of these questions are more food-for-thought **(FFT)** questions than test questions, but they do have reasonable and unreasonable answers.

Neurons and Glia

1. The guy who proposed the Reticular Theory was not completely wrong. Some neurons are actually physically connected. What are these connections called? **FFT:** It turns out that these connections are very prevalent in astrocytes, a glial cell type in the brain. Although they don't fire action potentials, overactivation of astrocytes can be dangerous and contribute to seizures. How might these connections play a role?

Physical connections from one neuron to another are called gap junctions, and they are an example of electrical transmission, whereas typical synapses rely on electrical and chemical transmission. In cells like astrocytes, if they are connected by these gap junctions, then ions can flow through, resulting in a much faster response. Overactivation of astrocytes can be dangerous because electrical transmission is much faster than electrochemical transmission. This would mean that cells like astrocytes practically activate at the same time, and generally speaking, this kind of simultaneous, coordinated activity can contribute to seizures.

2. Abnormalities in axoplasmic transport can have serious consequences. Besides neurotransmitter, name one other major class of macromolecules that needs to travel along the axon. What is one function performed by this class of macromolecules?

Proteins. As for the function, pretty much anything! Enzymes, phosphorylation, phagocytosis, forming ion channels, etc. Proteins are usually not made in axon terminals because there are no ribosomes there.

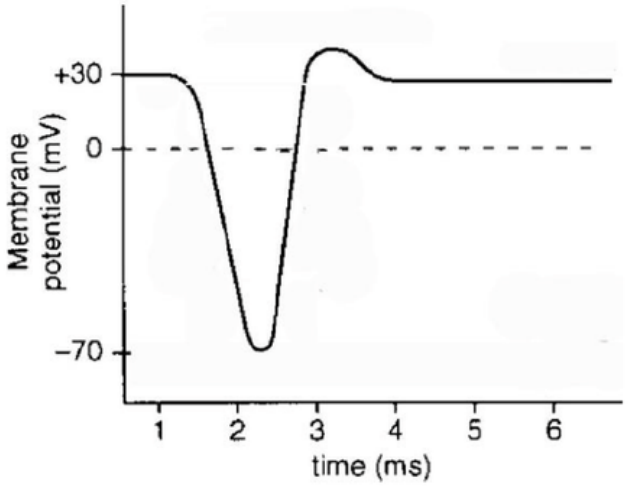
3. **FFT:** Recall how things go wrong in Alzheimer's disease (AD). You're a genius synthetic organic chemist and pharmacologist, and you are able to synthesize a drug to perform any function you want. How might you go about treating AD in terms of the cellular processes you might target?

This fact might not have been covered in class; it tends to change every year, depending on whether the professors remember. If you're not aware of this, then don't worry about this question. The fact is that there is a protein called *tau* that normally supports the cytoskeleton, but in diseases like Alzheimer's, it gets stuck to each other to form these neurofibrillary tangles, which kill the cell and spread to nearby cells, killing them too. The *tau* protein is hyperphosphorylated, which just means there are way too many phosphate groups on it. This is thought to cause tau to detach from the cytoskeleton and bundle together, creating structures called neurofibrillary tangles. So one approach to treat AD would be to inhibit phosphorylation of tau, such as by using a drug to block the kinases that contribute to the hyperphosphorylation. Obviously, things are more complicated in real life, but these are the basics.

Resting Membrane Potential and Action Potential

1. All credit goes to Dr. Ken Miller, Dr. John Stein, and Jody Hall, who teach BIOL0200, for this diagram and question. You are instructed to design an upside-down action potential

that resembles the diagram below. Assume you have the ability to manipulate any feature in the cell you want, such as the relative concentrations of ions inside and outside, the gating and opening of ion channels, and so on.



a. Keep the relative concentrations of Na+ and K+ the same inside and outside of the cell. With that in mind, design an action potential that would look like this. Make sure you address: (i) relative permeability to ions at rest, (ii) what ion channels open and when they open, and (iii) the state of ion channels at each phase of this action potential.

I need to keep this answer brief, but you're always welcome to contact me if you want more detail. If the relative concentrations of Na+ and K+ are the same, then we need to change the types of ion channels and the permeability. If the resting membrane potential is +30 mV, that means that at rest, the membrane is more permeable to sodium because it's closer to the equilibrium potential of Na+. If you mentioned that there is a Na+/K+ exchange pump, be careful because this pump must *not change* and continues to pump K+ into the cell and Na+ out of the cell. It needs to do this to make sure that the resting membrane potential can be positive. When you reach threshold, you need to open voltage-gated K+ channels first in order to get the cell to hyperpolarize first. When the membrane potential dips down to -70 mV, activate delayed voltage-gated Na+ channels to let the membrane potential go back up. Then the Na+/K+ pump, working normally, re-establishes the resting membrane potential.

b. **Reverse** the relative concentrations of Na+ and K+ inside and outside of the cell. Keep in mind that these are relative concentrations; you do not need specific numbers in order to do this problem. Now, design an action potential that would look like this. Make sure you address: (i) relative permeability to ions at rest, (ii) what ion channels open and when they open, and (iii) the state of ion channels at each phase of this action potential.

I need to keep this answer brief, but you're always welcome to contact me if you want more detail. If you reverse relative concentrations of Na+ and K+, this is a bit trickier compared to the answer in (a). First, you start out having the Na+/K+ pumps working *in reverse* so they pump Na+ into the cell and K+ out of the cell (remember: we reversed it!). This would cause the equilibrium potential for K+ to be positive, and the equilibrium potential for Na+ would be negative. So at rest, the cell still has higher permeability to K+ because the resting membrane potential is given to be +30 mV, and therefore it is closer to the new equilibrium potential for K+. Upon reaching threshold, the voltage-gated Na+ and K+ channels essentially will operate

normally. This is a tricky concept, but it would help to think about what equilibrium potential means and to make up some numbers for E_{Na} and E_K when the relative concentrations are reversed. Take your time going through this. Back to the explanation: when voltage-gated Na+ channels open, the Na+ will cause the membrane potential to be more negative. At the lowest point of this new action potential, delayed-rectifier K+ channels will open, causing the membrane potential to become more positive again. Finally, Na+/K+ pumps work in reverse to re-establish the electrochemical gradient.

2. Credit also goes to the instructors of BIOL0200 for this question. As you might recall from high school biology, a proton (H+) gradient along the mitochondrial inner membrane is necessary for ATP synthesis. At normal body temperature, suppose there are 1,000 times more protons (H+) on the outside of the membrane (intermembrane space) than on the inside (mitochondrial matrix). What is the equilibrium potential for H+? Please give a numerical answer.

Use the simplified version of the Nernst equation because we are at body temperature. The equation is $E = \left(\frac{61}{+1}\right) \log\left(\frac{[H+]out}{[H+]in}\right)$, with +1 indicating the electrical charge for the H+ ion. Because there is 1,000 times more protons (H+) on the outside than on the inside, the ratio inside the logarithm simplifies to 1,000. The log of 1,000 = 3. Finally, we multiply +3 and 61 to get E_{H+} = +183 mV.

3. What phase of the action potential most closely correlates with the absolute refractory period? Why? What phase of the action potential most closely correlates with the relative refractory period? Why?

The falling phase correlates most closely to the absolute refractory period. Recall that the absolute refractory period means that you can't get the neuron to fire no matter how much you stimulate it. On a molecular level, voltage-gated sodium channels are mostly inactivated, and if you recall the ball-and-chain activation model, inactivation is when the peptide "ball" blocks the channel opening, so you can't get another action potential no matter how much you stimulate.

The undershoot correlates most closely to the relative refractory period. Around this stage, the delayed-rectifier K+ channels are beginning to close, and the voltage-gated Na+ channels are in a resting state – technically, they are *deinactivated*. In this state, there pore is not blocked by the peptide "ball," but the Na+ channels have gone a conformational change, so they are essentially closed (deinactivated). However, with enough stimulation, you *can* get enough voltage-gated Na+ channels to open and fire another action potential because the electrical current can depolarize the membrane and cause the Na+ channels to open.

4. **FFT:** You can get an action potential to travel "backwards" from the axon to the soma if you electrically stimulate the end of the axon — this is called backpropagation. Suppose you stimulate the end of the axon at the same time as the neuron fires its own naturally occurring action potential. When these two action potentials collide, what will happen and why?

For many students, they have an intuition on what should happen: They should cancel out, right? That's correct, but not many people can explain why! Essentially, when the two action potentials meet, they run into each other's absolute refractory periods. And because there is nothing you can do to overcome this refractory period, the two action potentials are not able to travel further and therefore "cancel each other out."

Synaptic Transmission

1. Parkinson's disease (PD) is largely caused by degeneration of dopamine neurons in the substantia nigra of the brain. In his seminal book *Awakenings*, neurologist Oliver Sacks documents that delivering a drug could bring people out of a Parkinsonian state. Sacks could not give these patients dopamine or tyrosine because neither molecule can cross the blood brain barrier. What molecule did Sacks give these patients?

Dr. Sacks gave them L-dopa; recall the synthesis pathway for the catecholamines. Since dopamine could not be administered, Dr. Sacks must have given patients L-dopa, which is the immediate precursor to dopamine.

Side note: I highly recommend watching the movie *Awakenings*, which is based on this story. Robin Williams (RIP) was brilliant in it, which is completely unsurprising. Dr. Sacks wrote a book by the same name, although I didn't enjoy it at all because the writing was so technical.

2. Botulinum toxin (Botox) is a drug that prevents the release of acetylcholine at the neuromuscular junction. It is commonly used for cosmetic purposes, but it also has medicinal uses. Botulinum toxin inhibits neurotransmitter release by directly inhibiting presynaptic vesicle fusion. Based on this information alone, what is the likely target of Botox?

Admittedly this question is a little vague, but I was hoping for the answer "SNAREs." Remember that vesicle fusion is mediated by the fusion of V-SNAREs on the vesicle and T-SNAREs in the membrane. Theoretically, if you answered that Botox blocks the actions of synaptotagmin, that would be acceptable as well, although I specified that Botox "directly inhibits presynaptic vesicle fusion," which definitely requires SNAREs.

3. You are informed that one of your patients has a disease in which his PIP_2 pathway is overactive. Using your remarkable knowledge of synthetic chemistry and pharmacology, you try to make a drug that will most effectively inhibit this pathway. You have four choices: you can (a) inhibit phospholipase C, (b) block IP_3 receptors in the smooth endoplasmic reticulum, (c) inhibit protein kinase C, or (d) inhibit calcium/calmodulin-dependent protein kinase. Which choice most would effectively shut down the overactive pathway and why?

There is a concept called "amplification" when we talk about cell signaling. Let's use this PIP_2 pathway as an example. Remember that the enzyme phospholipase C (PLC) cleaves PIP_2 to form DAG and IP_3. This process is an example of amplification because one molecule of PLC can cleave multiple PIP_2 molecules. It's not like the PLC gets tired after one reaction and leaves! So if you started with one molecule of PLC, you can easily end up with thousands of DAG and IP_3 because of this idea of amplification. At other steps in the process, you might not get amplification. For example, recall that IP_3 binds to receptors on the smooth endoplasmic reticulum to enable the release of calcium. There is no amplification for this step because *one* molecule of IP_3 binds to *one* receptor. The immediate next step, though, is an example of amplification because one IP_3 receptor lets many, many calcium ions out.

Anyway, I mention amplification because the question asks for which process or protein you would block. In signaling pathways that involve amplification, it is better to try to block the pathway as early on as possible. This makes sense because it would be much more difficult to stop a flood of calcium ions than to stop a few PLC enzymes. Therefore, the correct answer is simply the earliest step among the choices, which is (a) inhibit phospholipase C.

Neurodevelopment and Neuroanatomy

1. **FFT:** You inject a drug intraperitoneally (into the abdominal cavity) into a mouse, thinking it will have some effect on the mouse's behavior. However, you don't observe any changes, and you think that the drug might not have gotten to the brain. What experimental approach can you take, without having to kill the mouse, to see whether or not the drug has gotten into the brain?

The key here is to realize that we cannot kill the mouse, so we can't really extract tissue from the mouse brain. Even if we can, it's probably too much work. To see whether the drug got into the brain, you can test for its presence anywhere there is cerebrospinal fluid (CSF)! Therefore, you can perform a spinal tap on the mouse and get a sample of CSF from the spinal cord, which is much easier than performing brain surgery and biopsy.

2. **FFT:** Many of the structures, like the caudate nucleus and lateral ventricles, have a C-shape to them. Why do you think this makes sense from an evolutionary perspective?

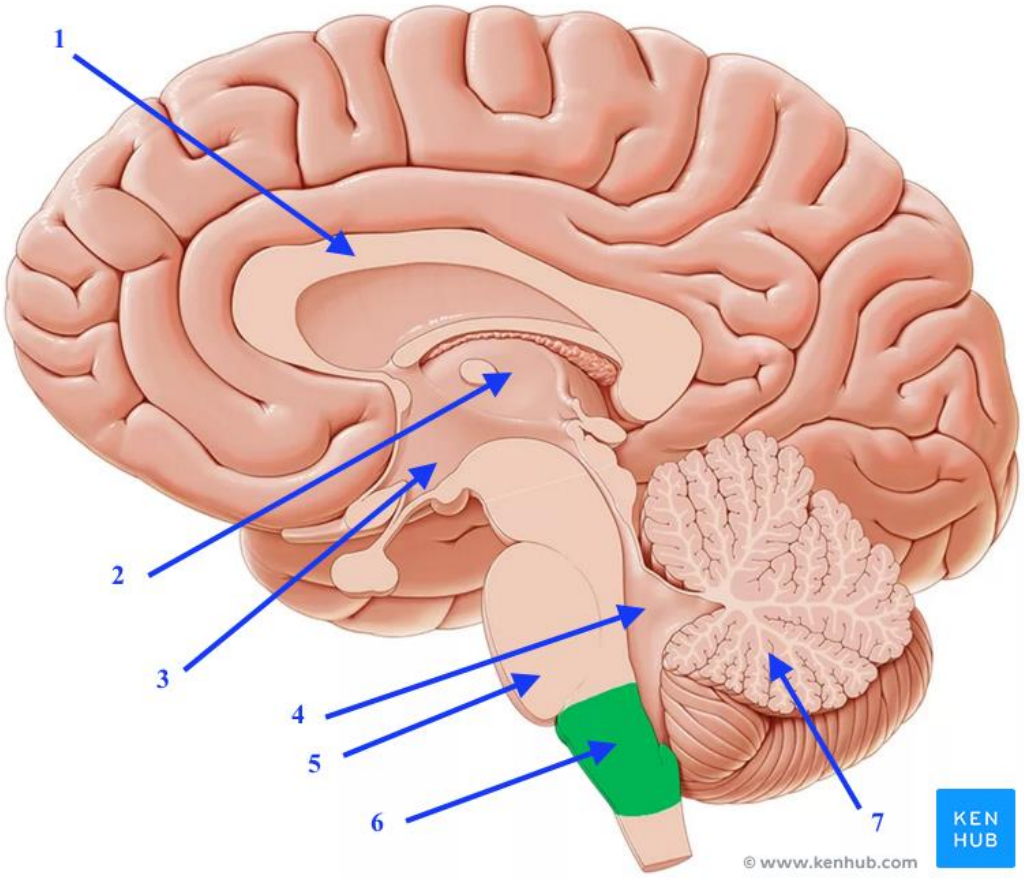
Some researchers think the C-shapes might be due to the brain growing in size over evolutionary history, so these structures had to "fold over" to make room for a larger brain.

3. For each adult structure, name the embryonic division from which it is derived. The choices are telencephalon (T), diencephalon (D), mesencephalon (M), metencephalon (Me), or myelencephalon (My). Only one choice is valid for each structure.
    a. Anterior nuclei of the thalamus
    b. Internal capsule
    c. Corpus callosum
    d. Hypothalamus
    e. Cerebral aqueduct
    f. Substantia nigra
    g. Medullary pyramids
    h. Pons
    i. Lateral ventricles

ANSWERS

Part	a	b	c	d	e	f	g	h	i
Answer	D	T	T	D	M	M	My	Me	T

4. Name structures 1-7 on the following diagram. What plane of section is this?

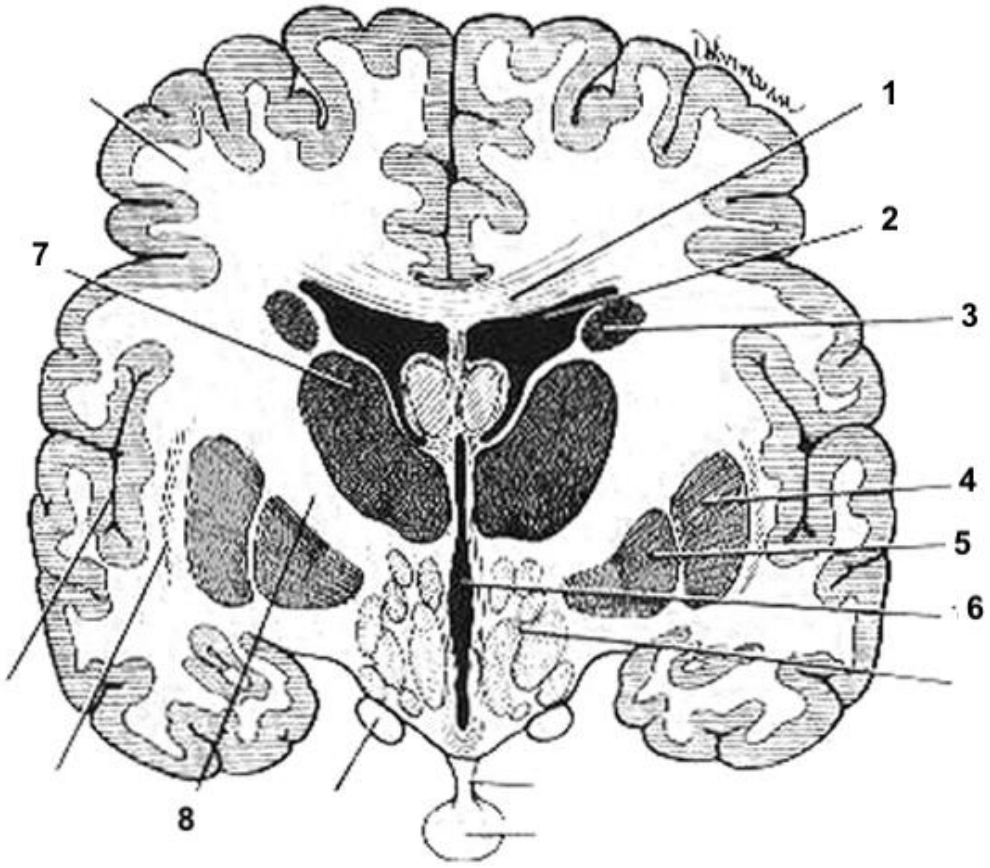


ANSWERS

1. corpus callosum
2. thalamus
3. hypothalamus
4. fourth ventricle
5. pons
6. medulla
7. cerebellum

This is a sagittal section.

5. Name structures 1-8 on the following diagram. What plane of section is this?



ANSWERS

1. corpus callosum
2. lateral ventricle
3. caudate nucleus
4. putamen
5. globus pallidus externus
6. third ventricle
7. thalamus
8. internal capsule

This is a coronal section.

6. Name the structures as specifically as possible:
    a. I am the structure following the lateral wall of the lateral ventricles
    b. I am the largest white matter tract connecting the two hemispheres of the brain
    c. I am the large structure surrounding the third ventricle
    d. I am the structure on the dorsal side of the cerebral aqueduct
    e. I am the fluid-filled structure anterior to the cerebellum
    f. I am the space that contains the majority of the cerebrospinal fluid in the central nervous system

ANSWERS
a) caudate nucleus
b) corpus callosum
c) thalamus
d) tectum
e) fourth ventricle
f) lateral ventricles

Good luck on the exam! Feel free to reach out to me with questions.

Email: ronnieli0114@gmail.com
Phone: (516) 987-2885
Website: www.ronnieli.com/neur0010