

The key: 7.013 Recitation 19 – Spring 2018

1. When the growth cone of an axon encounters an attractive signal, the growth cone extends, but when the growth cone of an axon encounters a repulsive signal, the growth cone collapses. What protein plays a key role in this behavior, and what is particular about these proteins that allows this behavior?

Polymerization and depolymerization of the cytoskeletal proteins is critical for the contraction or extension of the growth cone.

2. What is the difference between long-range guidance signals and short-range guidance signals? Give an example of each.

Long-range guidance signals (example netrins) are diffusible signals in comparison to short-range (example ECM proteins) that are non-diffusible and need direct contact to mediate their action.

3. Netrins can act as an attractive signal or a repulsive signal. Explain how netrins can act as either. *They are attractive for the commissural neurons where they cause the homodimerization of the DCC receptors. They are repulsive for the tectal neuron where they cause the heterodimerization between DCC and UNC5 receptors. Therefore the ultimate response depends on the type of receptor on growth cone to which netrins bind.*

4. If a neuron is repeatedly stimulated by a neurotransmitter over a long period of time it may show an upregulation of receptors specific for that neurotransmitter. Of what is this an example?

Long term potentiation.

5. Neuronal path-finding is crucial for structured cellular organization and development of neural circuits. The elongation or retraction of the growth cone is dependent on the guidance cues. You are looking at the response of the growth cone to the following guidance cues.

- **Guidance cue 1: Fibronectin** protein that is a part of ECM.
- **Guidance cue 2: Ephrins**, which diffuse along their concentration gradient.

i. Classify the two guidance cues as **short-** or **long-** range signals.

Cue one, is short range since it is non-diffusible and needs a direct contact with its receptor to mediate its effect unlike cue 2, which is diffusible, long- range and influence the growth of an axon in a concentration dependent manner.

ii. A Stripe assay is very often used to test the response of a growth cone to a guidance signal. Briefly explain how this assay works.

You add a guidance cue on one side of a strip and see the response of growth cone to this cue. If the cue is an attractant the growth cone will grow towards higher concentration gradient but if it is a repellent the growth cone will retract and the axon will not grow on the stripe.

6. Nicotine is a chemical that can cross the blood-brain barrier. In the brain, it can bind to nicotinic acetylcholine receptors (nAChRs). As a consequence, the nAChRs, selectively open and allow diffusion of Ca^{2+} ions.

a) Choose **all** that apply: The nAChRs are:

- **Ionotropic**
- **Metabotropic**
- **Depolarizes the neuron**
- **Repolarizes the neuron**

b) As a result of an action potential, dopamine is released by neurons associated with addiction. The increase in dopamine secretion makes the patient “feel good”. Addicts get accustomed to these high levels of dopamine. What changes could be happening at the synaptic cleft of patients that makes this higher levels of dopamine be registered by the postsynaptic neuron as normal or lower levels?

Increase in the receptor numbers, increase in affinity of receptors or increase in dopamine uptake.

c) A patient decides to quit smoking. But the sudden drop in dopamine levels makes the patient crave for more nicotine, making it difficult to quit. The patient's doctor prescribes varenicline, a partial agonist of $\alpha 4\beta 2$ nAChRs (a subtype of nAChRs). The partial agonist binds and activates a fraction of the $\alpha 4\beta 2$ nAChRs. **Explain** how taking a partial agonist of $\alpha 4\beta 2$ nAChRs might lessen the patient's cravings for nicotine compared to suddenly stopping taking nicotine without pharmacological help.

Since a fraction of $\alpha 4\beta 2$ nAChRs are being activated, this might be enough to release dopamine, but not as much dopamine as smoking a cigarette would. This way, the patient can get used to a lower dose of dopamine levels before going back to the even lower, normal dopamine levels.

d) Varenicline is a popular drug for helping patients quit smoking. Nevertheless, it has many side effects, including hostility, agitation, depression and unusual dreams. Upon further scientific research, it is discovered that varenicline is a full agonist of other subtypes of nAChRs that are expressed in other parts of the brain, not associated with addiction. Yet, there are some patients that do not experience any side-effects. How can you **explain** the big range of behavioral side-effects?

Different patients have a different genetic background and the hyperactivation of some receptors may have a bigger effect on a patient with a particular mutation in one of the receptors. Depending on the expression pattern of the receptor that is being hyperactivated, the behavioral effect may be different. Also, the dosage of the drug may need to be changed for some patients in order to minimize the side-effects.

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