

## 7.013 Recitation 19 – Spring 2018

(**Note:** The recitation summary should NOT be regarded as the substitute for lectures)

### Summary of Lectures 33 (5/9) and 34 (5/11)

**Pathfinding:** Neurons connect to form circuits a typical example of which is a sensory neuron connecting with a motor neuron with an intermediary interneuron in between. In some cases, these neurons grow and innervate areas based on guidance cues. In other cases, neurons project axons in a more random fashion, and those whose axons make useful connections survive whereas those failing to make useful connections die. The migration of the neurons can be detected by the stripe assay. The axon tip has a specialized actin-based structure called a growth cone that is mobile and dynamic. The membrane of a growth cone has receptors that sense signals and direct the axon movement.

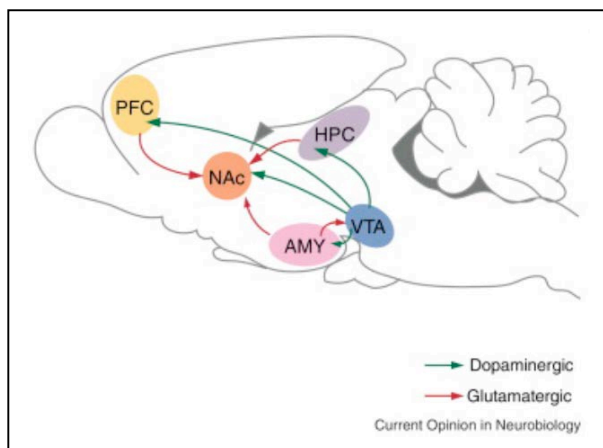
**Neuronal connections:** There are approximately  $10^{10}$  neurons in the human brain each of which makes approximately  $10^5$  synapses. Furthermore, there are approximately 500 different kinds of neurons based on different locations, the neurotransmitters they secrete and neurotransmitter receptors they have. Taken together these can form a very complex circuitry, mapping of which is an extremely challenging task! Numerous techniques can now be employed to map the neuronal circuits.

**Optogenetics:** In this technique, the idea is, you can control neuronal activity by light. This technique makes use of the light gated channels that are found in many microorganisms. You express the gene encoding these channels as a transgene in a specific neuron. These channels are ionotropic that are activated by light of a specific wavelength and allows the diffusion of ions and may be used to understand neuronal circuitry. This can be used to understand the function of a particular class of neuron in a specific location at a given time. The following link and the lecture slide further describe this technique and its importance.

[Optogenetics: Controlling the brain with light](#)

**Circuits & Motifs:** Motifs are defined as patterns of connections that are made in a circuit. Simple motifs may be joined to make the final circuit. Circuits can be simple (few neurons) or complex. They may have a fixed output, or may have variable outputs. Some circuits can be latent, they exist already but are inactive.

**Reward and Addiction:** Humans, as well as other organisms engage in behaviors (natural or artificial) that are rewarding; the pleasurable feelings provide positive reinforcement so that the behavior is repeated. The reward behavior is often associated with the release of the dopaminergic and glutamatergic neurotransmitters in the neuronal circuitry.



**Dopaminergic pathway:** The ventricular tegmental area (VTA) is connected to and sends dopaminergic signals to nucleus accumbens (NAc) and the prefrontal cortex (PFC) and hippocampus (HPC).

**Glutamatergic pathway:** The NAc receives glutamatergic signals from PFC, HPC and amygdala (AMG). The AMG also sends glutaminergic signals to VTC.

Addiction is a state in which an organism engages in a compulsive rewarding behavior, even when faced with negative consequences. A major feature of addiction is the loss of control in limiting intake of the addictive

substance. Heroin (morphine) and cocaine are examples of addictive drug that produce euphoria or pleasurable feelings and interact with the reward pathway in the brain. When drugs such as heroin are used repeatedly over time, tolerance may develop and the person no longer responds to the drug in the way that person initially responded.

Tolerance to drugs can be produced by several different mechanisms, but in the case of morphine or heroin, tolerance develops at the level of the cellular targets. For example, when morphine binds to opiate receptors, it triggers the inhibition of an enzyme (adenylate cyclase) that orchestrates several chemicals in the cell to maintain the firing of impulses. After repeated activation of the opiate receptor by morphine, the enzyme adapts so that the morphine can no longer cause changes in cell firing.

Dependence is an adaptation to drug that is irreversible.

Cocaine inhibits re-uptake of the neurotransmitters dopamine, serotonin and norepinephrine. A leading hypothesis guiding current molecular and cellular research into drug addiction as pathologically modifying neuroplasticity mechanisms that normally mediate normal learning and memory processes, but are hard to change after addiction ([Dong & Nestler et al](#))

Overexpression of  $\Delta$ FosB is associated with an increase in drug sensitization and incentive. It arises from the alternate splicing of FosB, which is a transcription factor and lacks proteasomal degradation ubiquitylation sequence, which makes it very stable. ([Nestler et al 2009](#)).

Addiction may be partly mediated by mechanisms normally involved in development. Juvenile substrates of molecular or neural plasticity reemerge after cocaine exposure. Rejuvenated neural circuits are highly plastic and mature during cocaine withdrawal. This creates strong and durable maladaptive changes underlying addiction ([Nestler et al 2015](#)).

For more information please follow the link below: <http://www.drugabuse.gov/publications/teaching-packets/neurobiology-drug-addiction>

### **Questions**

1. 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?
  
2. What is the difference between long-range guidance signals and short-range guidance signals? Give an example of each.
  
3. Netrins can act as an attractive signal or a repulsive signal. Explain how netrins can act as either.
  
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?

5. Neuronal pathfinding 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.
  - 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.

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  $\text{Ca}^{2+}$  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?

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.

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?

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