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Cori Bargmann's Lecture Part 2:
Cracking the Circuits for Olfaction: Odors, Neurons, Genes and Behavior

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1. Review Questions

1. Review the complexity of the human brain and the nervous system of *C. elegans*, and compare the similarities of genetic structure and functionality between the two organisms. Why do we use *C. elegans* as a model organism to study olfaction?
2. What are the functions of AWC and ASH in *C. elegans*?
3. Define probabilistic behavior and deterministic behavior.
4. What is the AWC response to the odor of isoamyl alcohol?
5. How does AWC interact with target interneurons? What effect does this have on turning frequency, and chemotaxis toward an odor?
6. How does AWC communicate with the interneuron AIB at a molecular level?

7. How does AWC use neuropeptides and receptors to communicate with AIA?

2. Answers to Review Questions

1. The genes conserved between species may indicate conserved functionalities throughout evolution. *C. elegans* has a much simpler nervous system structure than humans and it has been fully mapped through EM reconstruction. Understanding the *C. elegans* nervous system may shed light how the human nervous system works.
2. They are sensory neurons that detect external cues and then mediate attraction and repulsion, respectively.
3. A deterministic behavior is one where all of the animals give the same, reliable and predictable response to a stimulus. A probabilistic response is one in which most animals will eventually respond to a stimulus in the same way but they will arrive at that response or destination by different paths.
4. Removal of the isoamyl alcohol odor elicits AWC neuronal activation.
5. AWC communicates with interneurons through a complicated network of synapses. For example, when an animal leaves the odor source, AWC as well as its post-synaptic partners AIB will be activated. This results in a reorientation behavior in which the animal readjusts its position during chemotaxis.
6. AWC releases vesicles of glutamate during neuronal activation, and activates the interneuron AIB through glr-1, an excitatory glutamate receptor.
7. AWC produces the neuropeptide NLP-1 to communicate with AIA through the GPCR NPR-11. An insulin-like peptide INS-1 is synthesized in AIA and feeds back onto the sensory neuron AWC.

3. Discussion Questions

1. Review how can we visualize single neuron activity in live worms upon stimulus delivery.
2. How do we get quantitative insights into *C. elegans* behavior by using a microfluidic device?

3. What do the glutamate receptors glr-1 and glc-3 do to the targeted interneurons that express them? How do we know this from calcium imaging experiments?

4. Compare the *C elegans* odor circuit with the vertebrate retinal circuit – what are the differences and similarities?

5. What are the functions of the neuropeptide molecules NLP-1 and INS-1 in odor adaptation?

6. AWC-evoked chemotaxis is a probabilistic behavior and ASH-evoked escape is a deterministic behavior. Channelrhodopsin is a light-gated ion channel that can depolarize a neuron in which it is expressed upon light activation. If we express channelrhodopsin in ASH, what is the probability that you will expect a worm to perform reversal upon light activation? How about in AWC?

4. Answers to Discussion Questions

1. By delivering a single worm into the microfluidic chip, and genetically expressing the calcium indicator (which is a indirect readout of neuron activities), we can record the change of fluorescence in real time when delivering stimuli into the microfluidic chip in a controllable manner.

2. The microfluidic device will allow us to deliver odor stimuli onto the nose of the worm, at an exact concentration, and within a millisecond, without being concerned about diffusion effects.

3. glr-1 will depolarize the neuron and glc-3 will hyperpolarize the neuron, when glutamate is released. We know this because there will be an increase of calcium signal when a neuron is depolarized, and decrease of calcium when hyperpolarized.

4. *C. elegans* has a much simpler circuits with only 302 neurons, while a vertebrate has a much complex one – a human has ~100 billion neurons. However there are common rules in the wiring of the neural circuits in *C. elegans* and vertebrate. Examples are the AWC/AWB neurons that encode attraction and repulsion, which is similar to the T1 and T2 cells in mice that encode sweet and bitter taste (Bargmann Lecture 1).

5. They are neuropeptides that are evoked by the sensory neuron responses, and feedback to reshape the neuronal activities. NLP-1 is released from AWC to act on interneuron AIA to allow adaptation through its receptor NPR-11, and INS-1 is

released from AIA to impact the AWC activity. They provide an alternative form of communication, besides synaptic wiring, between AWC and AIA.

6. In ASH: you should see worms reverse (the escape behavior) almost 100% when the light is on to activate the neuron. In AWC: it is not deterministic that worms will react to the light on, but the probability of the reaction in a population of worms should remain constant from trial to trial.

5. Explain or Teach These Concepts to a Friend

1. Explain the advantages of using *C. elegans* as a model organism to understand olfaction behaviors, and why this information will help us to understand the functionality of human olfaction.
2. Explain how the sensory neuron AWC uses glutamate to communicate with interneurons, with both excitatory and inhibitory outputs, to enable chemotaxis behaviors.
3. Explain how the neuropeptides NLP-1 and INS-1 function in AWC and AIA to shape the chemotaxis circuitry and enable slow processes like adaptation.

6. Research the Literature on Your Own

1. What is the biased random walk theory of *C. elegans* chemotaxis? How do bacteria perform chemotaxis? Do they also apply random biased motion theory? See Howard Berg's iBioSeminar
2. Genetic evidence suggests that a TAX-2/TAX-4 channel is required for AWC chemotaxis. Learn about TAX-2/TAX-4, members of the cGMP-gated channel family, and how cGMP signaling is involved in AWC chemotaxis, as well as mammalian vision.
3. ASH is a polymodal nociceptor, as it is responsible for the response to many repellents, such as chemicals, high osmolarity, touch to the nose, etc. Genetic evidence suggests that the OSM-2/OCR-2 channel is required for ASH nociception.

Learn about OSM-2/OCR-2, as a class of the transient receptor potential (TRP) channel superfamily.

7. Papers for Journal Club

This paper explains biased random walk theory and how can worms use a behavior called pirouettes to perform chemotaxis toward odor. The fundamental role of pirouettes in C. elegans chemotaxis. J. Neurosci., 1999.

GCY-28 is a receptor-like guanylate cyclase that acts on one of the AWC neurons to enable attraction. Mutants of this single gene gcy-28 will avoid the odor. This paper will help us understand how downstream G protein signaling can couple one sensory neuron and one odor stimuli with different behavioral outputs. A behavioral switch: cGMP and PKC signaling in olfactory neurons reverses odor preference in C. elegans. Neuron, 2008