Applied Neuroscience

Columbia Science Honors Program

Spring 2017

Sensory Systems and Neural Circuits II

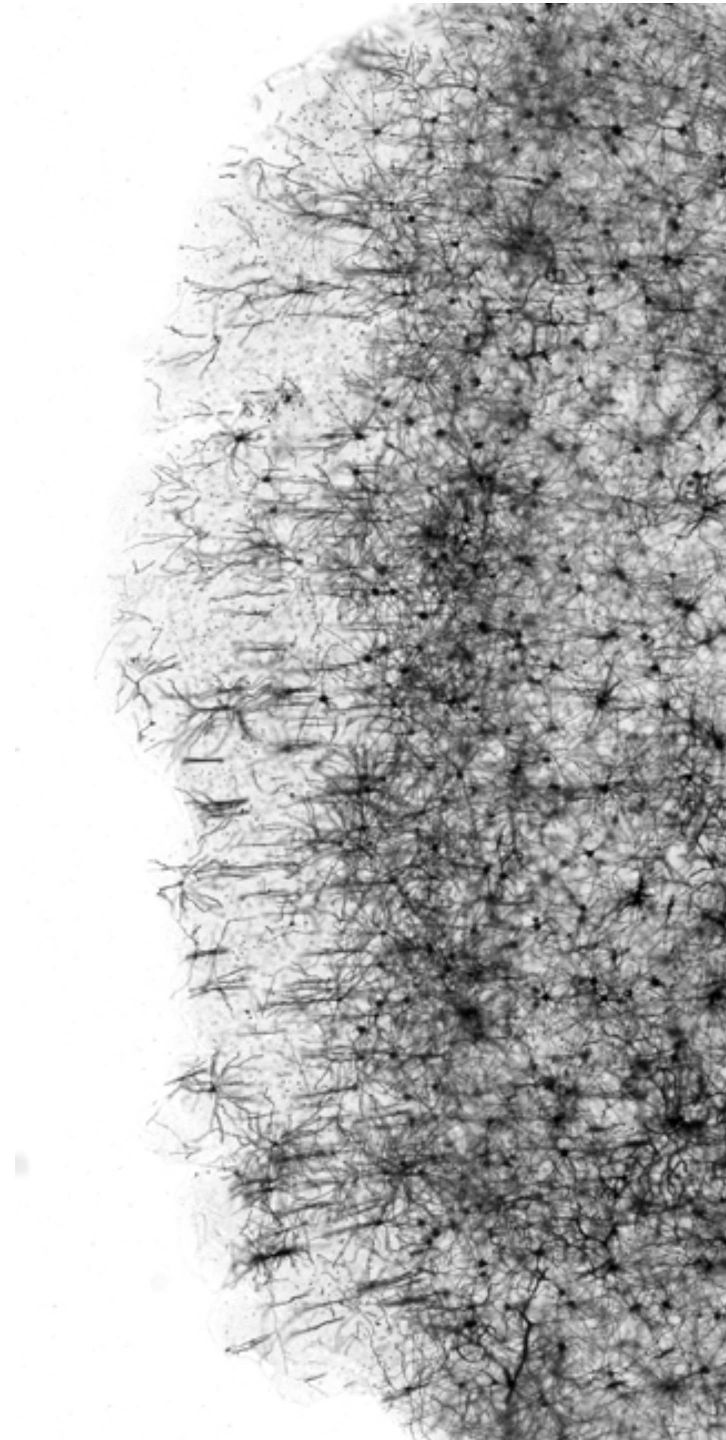


Sensory Systems and Neural Circuits

Objective: Gustatory and Olfactory Systems

Agenda:

1. Sensory Systems
   - Olfaction
   - Taste
2. Miracle Berry Demo
   - Flavor Tripping



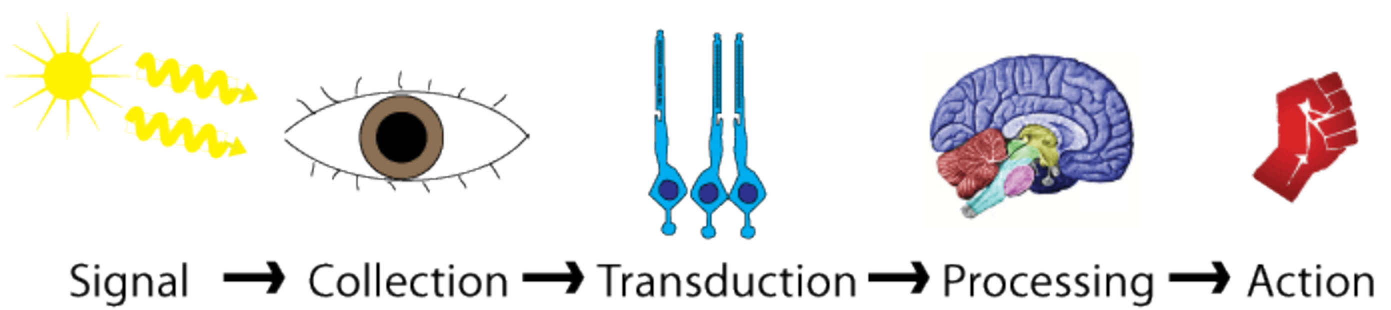
Sensory Systems

How do sensory systems work?

Neurons in sensory regions of the brain respond to stimuli by firing action potentials after receiving a stimulus.

Each sensory system follows a specific plan:

1. **Reception:** Stimulus molecules attach to receptors.
2. **Transduction:** Receptors convert the energy of a chemical reaction into action potentials.
3. **Coding:** The spatial and temporal pattern of nerve impulses represents the stimulus in a meaningful way.



Chemical Senses

Sensory systems associated with the nose and mouth (olfaction and taste) detect chemicals in the environment.

Gustatory System: detects ingested, primarily water-soluble, molecules called *tastants*
Olfactory System: detects airborne molecules called odors

These systems rely on receptors in the nasal cavity, mouth or face that interact with the relevant molecules and generate action potentials.

Olfactory System

Objective: Understand how the olfactory system works

Agenda:

1. Overview of Olfactory System
2. Neural Circuit for Smell

Functions of Olfaction

- Many animals are *macrosmatic*
  - ❖ A keen sense of smell is necessary for survival
- Humans are *microsmatic*
  - ❖ A less keen sense of smell that is not crucial to survive

- Rats are 8 to 50 times more sensitive to odors than humans
- Dogs are 300 to 10,000 times more sensitive than humans

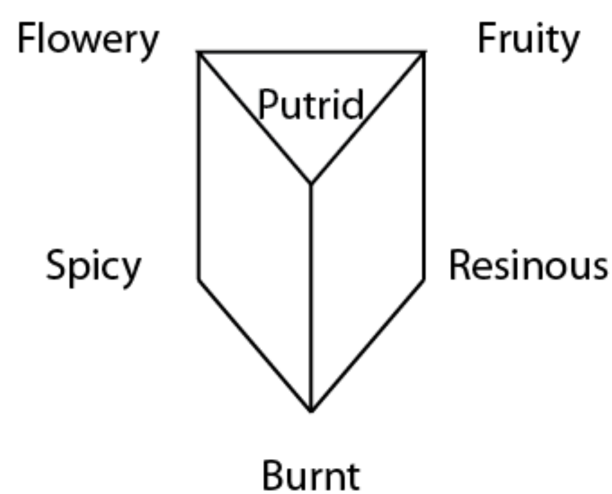
Why does this difference exist?
The difference lies in the number of receptors they each have. Humans have 10 million while dogs have 1 billion olfactory receptors.

Richard Axel on Olfaction

Olfactory System

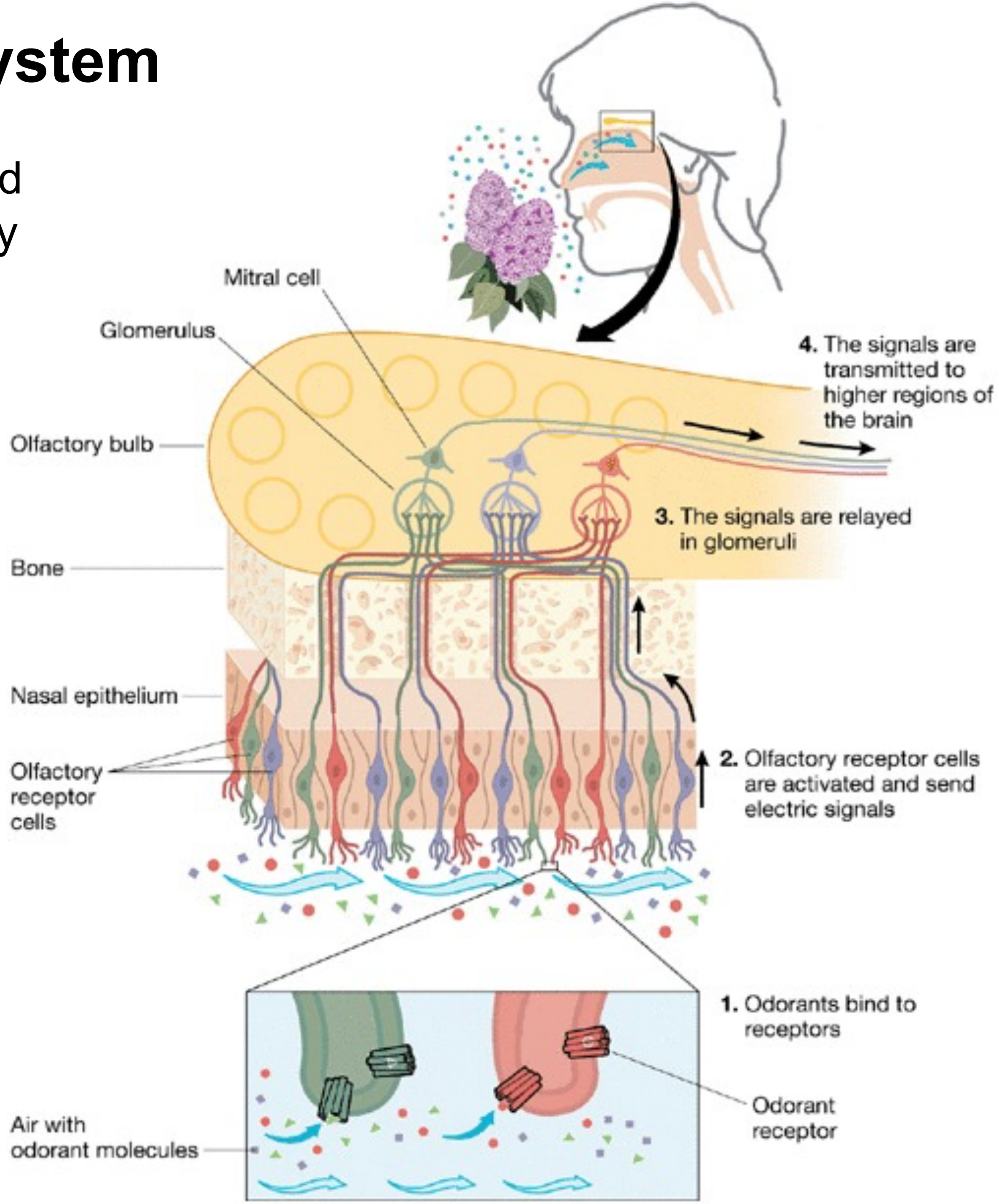
What is the olfactory system?

- Discriminative and sensitive chemosensory system
- Humans can detect between 1000-4000 odors
- All odors can be discriminated into six major groups: floral, fruit, spicy, resin, burnt and putrid
- Perception of odor begins with inhalation and transport of volatile odorants to the olfactory mucosa (located in the dorsal posterior region of the nasal cavity)

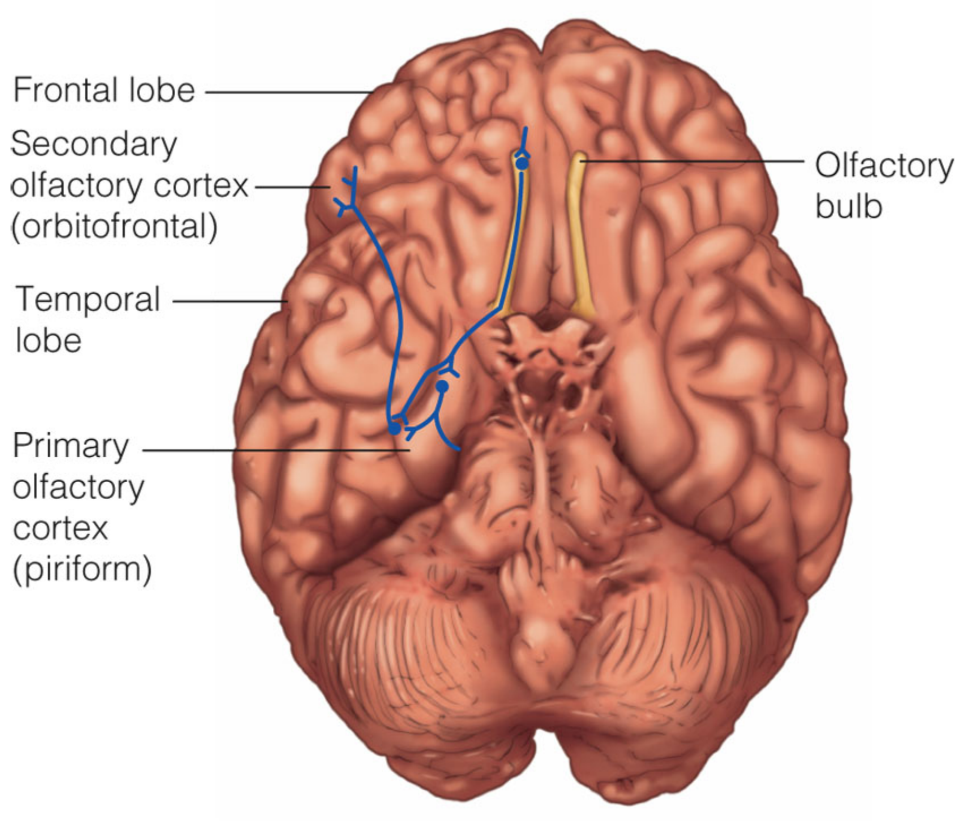


Human Olfactory System

- Olfactory **mucosa** is located at the top of the nasal cavity
- Odorants are carried along the **mucosa** coming in contact with the **sensory neurons**
- **Cilia** of these neurons contain the receptors
- Humans have about **350 types of receptors.**
- Signals are carried to the **glomeruli** in the **olfactory bulb**



Human Olfactory System



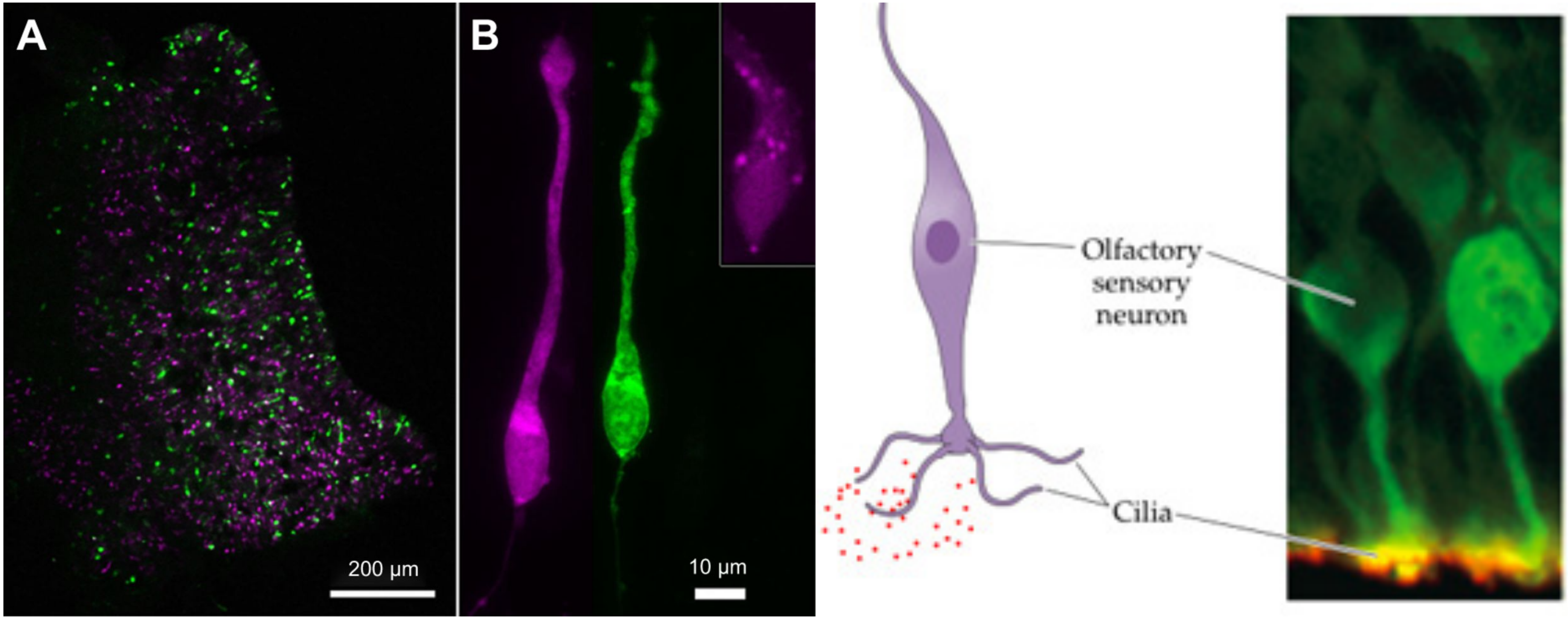
- Signals are sent to
  - **Primary olfactory (piriform) cortex** in the temporal lobe
  - **Secondary olfactory (orbitofrontal)** cortex in the frontal lobe
  - **Amygdala** deep in the cortex

Olfactory System

Morphology of olfactory mucosa and cells:

- The olfactory mucosa consists of a layer of columnar epithelium
- There are three major cells types:
  1. **Olfactory sensory neurons:**
     Each cell extends one dendrite to the epithelial surface, where odorants bind to specific odorant receptors on the cilia located in the mucus lining.
  2. **Supporting cells:**
     Provide metabolic and physical support for the olfactory cells and are analogous to neural glial cells.
  3. **Basal stem cells:**
     Located in basal lamina of olfactory epithelium and are capable of division and differentiation into either supporting or olfactory cells.

Olfactory System

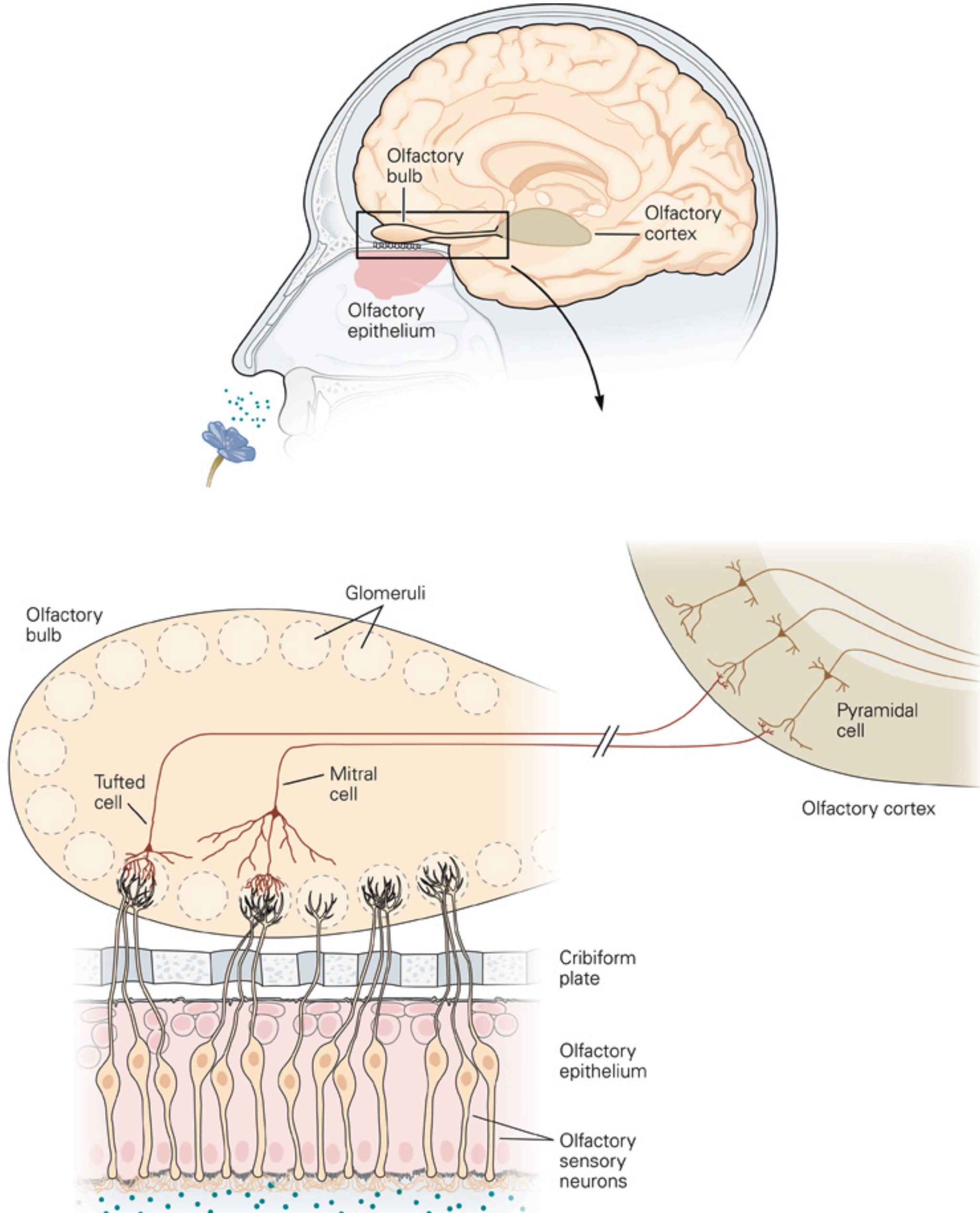


Olfactory sensory neurons have a single dendrite that projects down to the mucus:

- Terminal ending of dendrites have 5-25 cilia
- Each cilia has up to 40 GPCRs
- In lower animals, many more GPCRs are present (increased density of receptors)

Neural Pathway to Olfactory Cortex

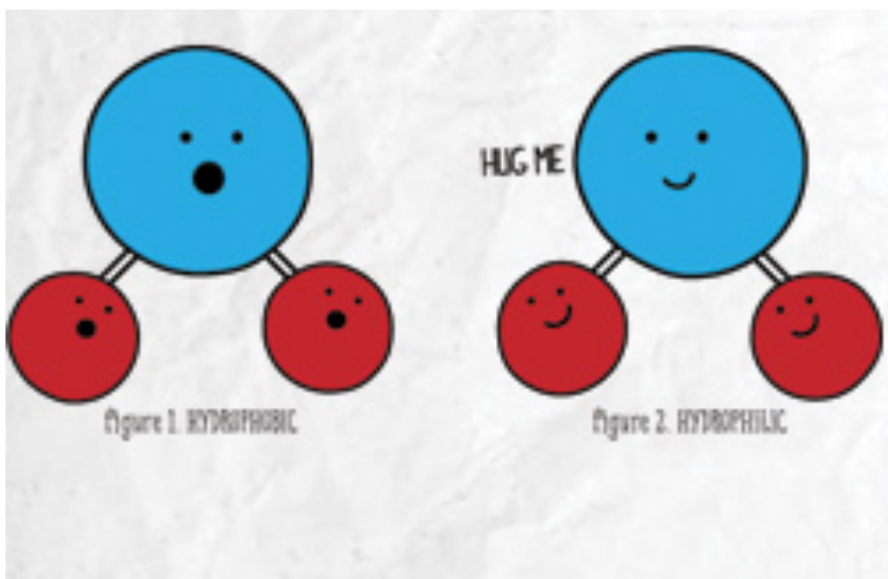
- Olfactory sensory neurons are located in the olfactory epithelium
- These neurons project axons into the olfactory bulb of the brain
- These projections innervate specialized regions of the olfactory bulb called glomeruli
- The terminations within the glomeruli are called mitral and tufted cells
- These relay neurons project to the olfactory cortex in the brain



Olfactory System

How do odorant molecules interact with sensory receptors?

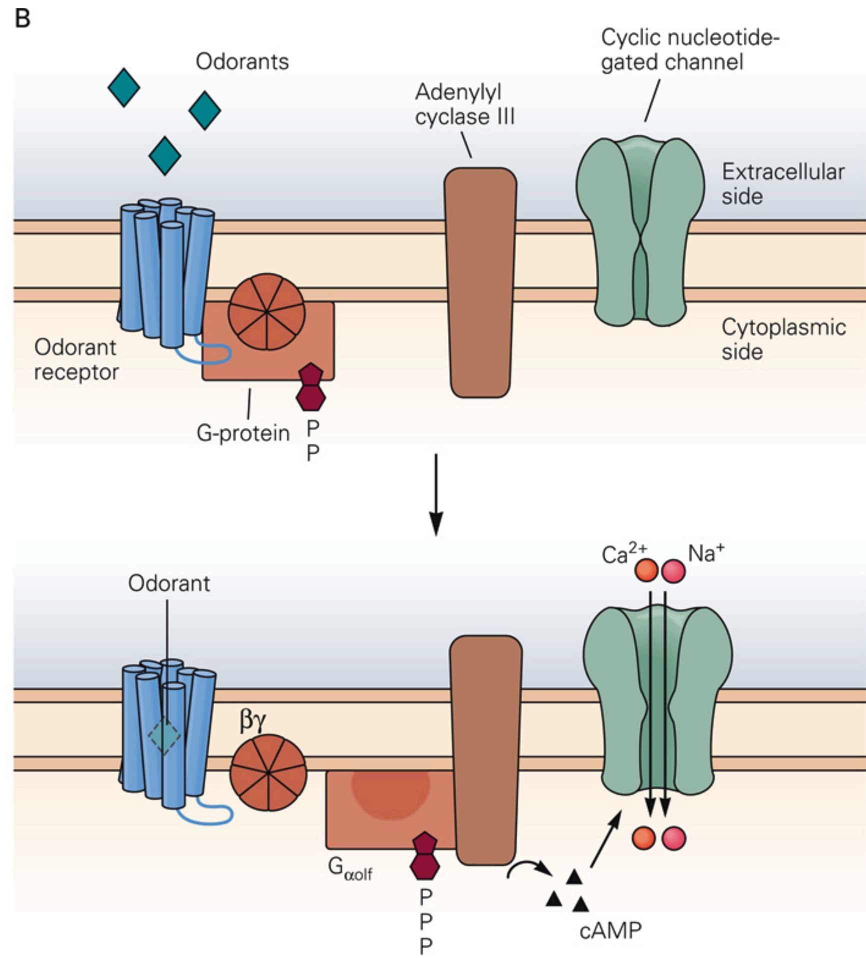
- Different for hydrophilic vs hydrophobic odors:
  - Hydrophilic (water loving): diffuse across mucus
  - Hydrophobic (water fearing): bound to specific odorant binding protein and transported to each cilium for interaction with specific receptors



Olfactory System

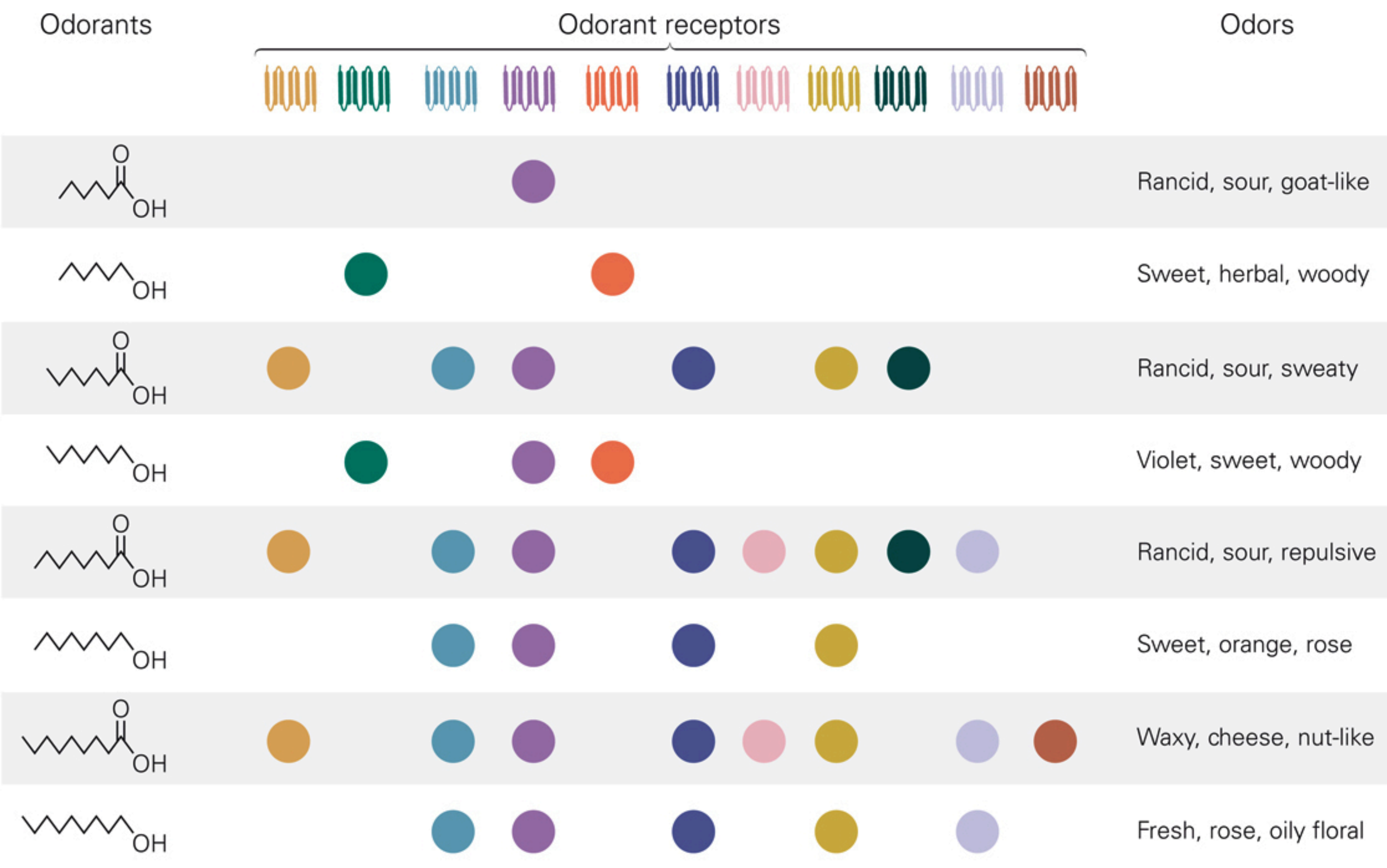
Transduction of olfactory stimuli

- Odorant molecules bind to the receptor which is coupled with G-proteins
- The activation of adenylyl cyclase leads to the formation of cAMP with the activation of Ca^{++}/Na^{+} cation channels
- The influx of these ions leads to depolarization
- The generated current is graded in response to the flow rate of the odorant molecules and their concentration



Olfactory System

Odorants are recognized by a unique combination of receptors



Neural Circuits

1. **Step 1:** Find one neuron involved in the circuit.
2. **Step 2:** Find additional functional neurons.
3. **Step 3:** Confirm role of all neurons in signal.
4. **Step 4:** Organize neurons by *epistasis analysis*.
5. **Step 5:** Draw Circuit.

A dimorphic pheromone circuit in *Drosophila* from sensory input to descending output

Vanessa Ruta, Sandeep Robert Datta, Maria Luisa Vasconcelos, Jessica Freeland, Loren L. Looger & Richard Axel

How to Read Scientific Papers

Drosophila show innate olfactory-driven behaviours that are observed in naive animals without previous learning or experience, suggesting that the neural circuits that mediate these behaviours are genetically programmed. Despite the numerical simplicity of the fly nervous system, features of the anatomical organization of the fly brain often confound the delineation of these circuits. Here we identify a neural circuit responsive to cVA, a pheromone that elicits sexually dimorphic behaviours[1–4]. We have combined neural tracing using an improved photoactivatable green fluorescent protein (PA-GFP) with electrophysiology, optical imaging and laser-mediated microlesioning to map this circuit from the activation of sensory neurons in the antennae to the excitation of descending neurons in the ventral nerve cord. This circuit is concise and minimally comprises four neurons, connected by three synapses. Three of these neurons are overtly dimorphic and identify a male-specific neuropil that integrates inputs from multiple sensory systems and sends outputs to the ventral nerve cord. This neural pathway suggests a means by which a single pheromone can elicit different behaviours in the two sexes.

Neural Circuit

DC1 Glomeruli Sensory Neuron

DA1 Projection Neuron

Olfactory Receptor Neuron (ORN)

DN1 Descending Motor Neuron

Ruta, V. et al. 2010 Nature

Gustatory System

Objective: Understand how the gustatory system works

Agenda:

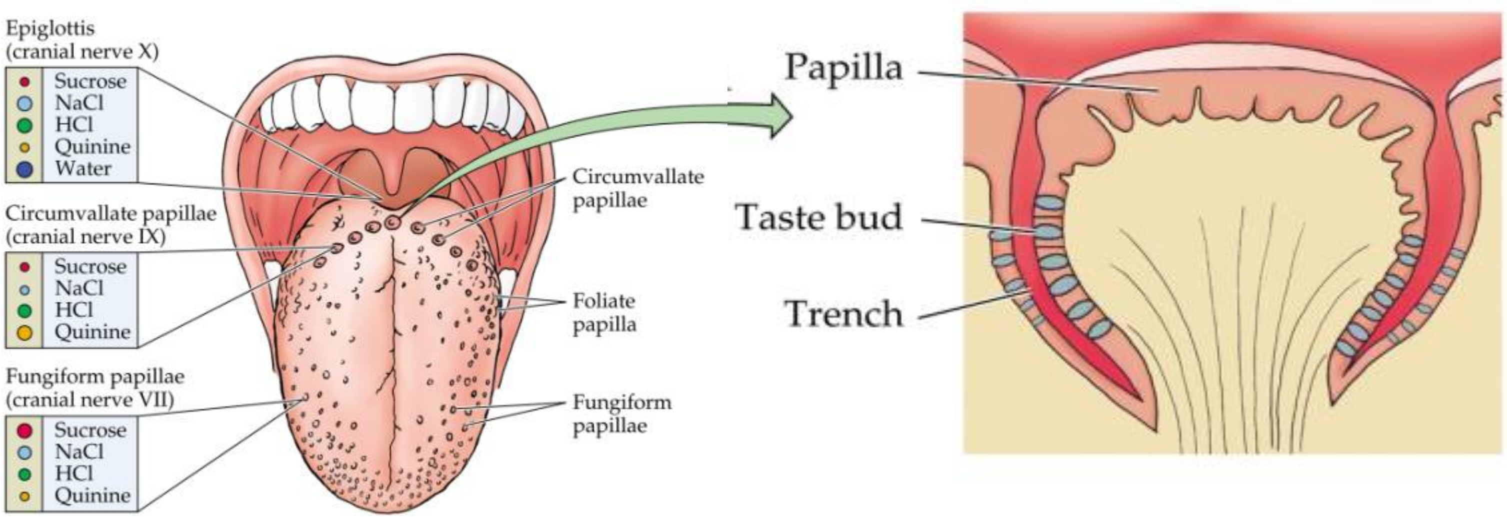
1. Morphology of Cells
2. Gustatory Pathway

    Miracle Berries Demo

Gustatory System

Morphology of taste buds and cell types:

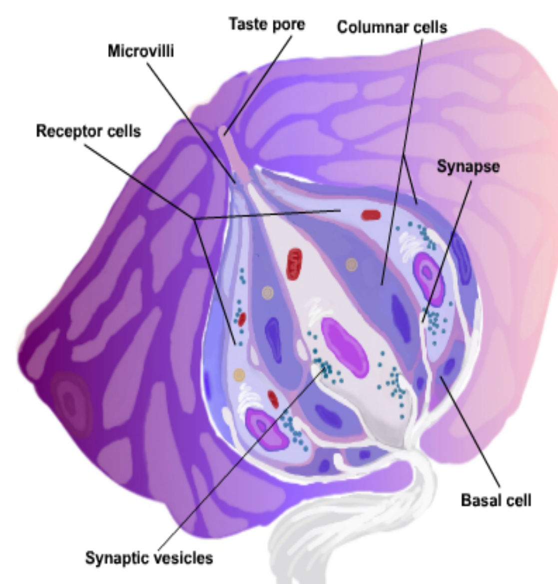
- Taste buds are located on papillae and are distributed across the tongue
- They are also found on the oral mucosa of the palate and epiglottis
- Taste buds contain 80 cells arranged around a central taste pore.



Gustatory System

Taste receptor cells:

- Spindle shaped cells that extend from the base to the apex of taste buds
- Taste solutes are transported to the taste pore and diffuse through the fluid layer to make contact with membrane receptor proteins on the microvilli and apical membrane
- Taste sensitivity is dependent on the concentration of taste molecules and their solubility in saliva



Gustatory System

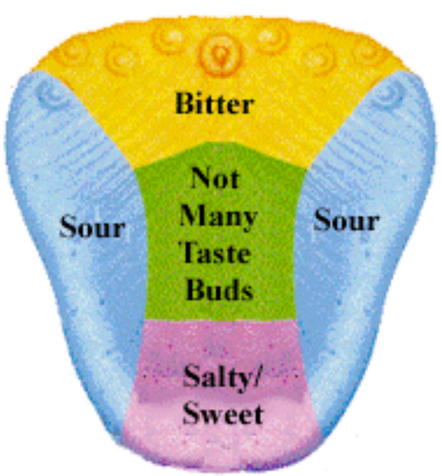
Sensory Transduction:

- Taste sensation can be caused by diverse *tastants*
- Action potentials in the taste receptor cells leads to an increase in Ca^{2+} influx through voltage-gated channels with a release of Ca^{2+} from intracellular stores
- In response to Ca^{2+}, neurotransmitter is released, which causes synaptic potentials in the dendrites of the sensory nerves and action potentials in the afferent nerve fibers

Gustatory System

Taste distribution:

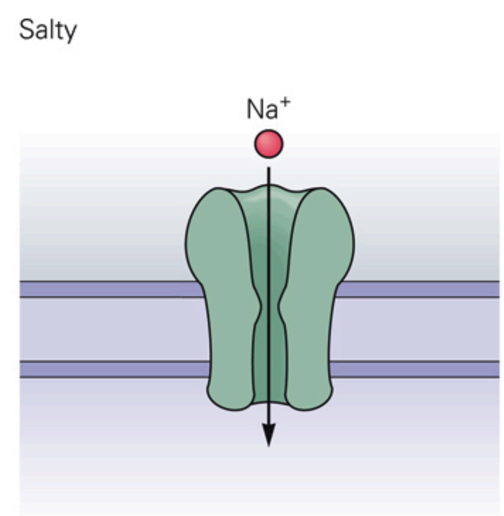
- Most of the tongue is receptive to all basic tastes
- There are certain regions that are most sensitive to a given taste
  - Bitter: across back of tongue
  - Sour: on side closest to the back
  - Salty: on side more rostral than sour
  - Sweet: across front of tongue



Gustatory System

How is salt processed?

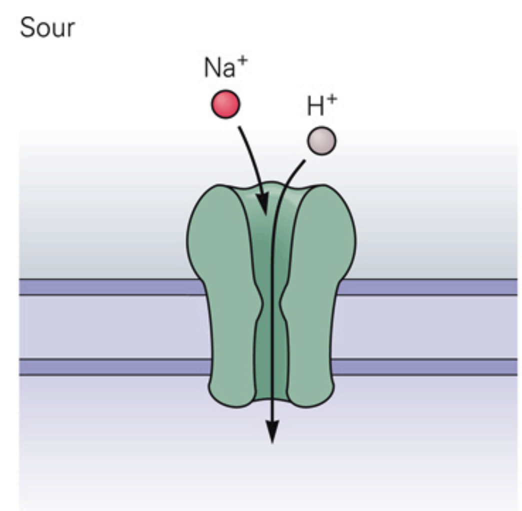
- Na^+ flows down a concentration gradient into the taste receptor cell
- Na^+ increases within the cell, which depolarizes the membrane and opens a voltage dependent Ca^{2+} channel
- Ca^{2+} increase causes the release of neurotransmitters



Gustatory System

How are acids (<u>sour</u> tastants) processed?

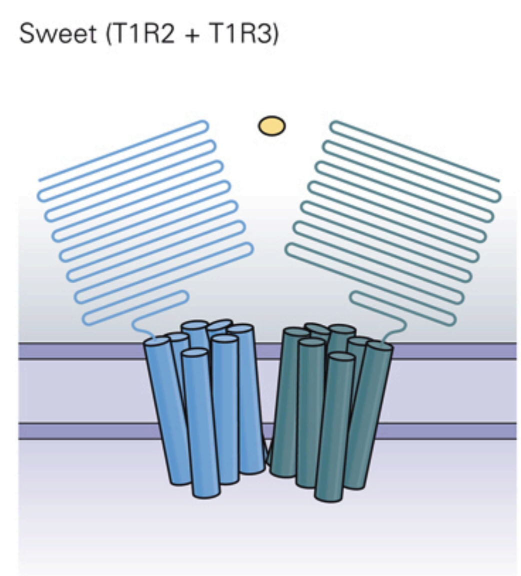
- Foods that are sour have high acidity (low pH)
  - When acids are dissolved in water, they generate H^+ ions
- H^+ ions pass through the same channel that Na^+ does
- H^+ blocks a K^+ channel as well
- The net movement of cations into the cell depolarizes the taste cell
  - This opens a Ca^{2+} channel
  - It causes neurotransmitter release



Gustatory System

How is sweet processed?

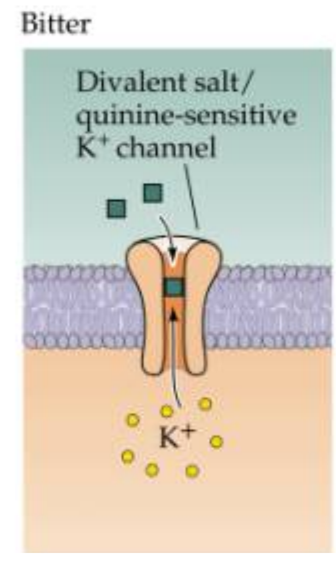
- Molecules that are sweet bind to specific receptor sites and activate a cascade of 2nd messengers in certain taste cells
- These molecules also bind to receptors
- G-protein activates an effector enzyme-adenylate cyclase and produces cAMP
- cAMP causes a K^+ channel to be blocked
- The cell depolarizes
- Ca^{2+} channel opens and Ca^{2+} enters the cell
- Neurotransmitter is released



Gustatory System

How is <u>bitter</u> processed?

- Noxious chemicals in the environment are often bitter
  - Senses have evolved to protect and preserve
  - The ability to detect bitter has two separate mechanisms

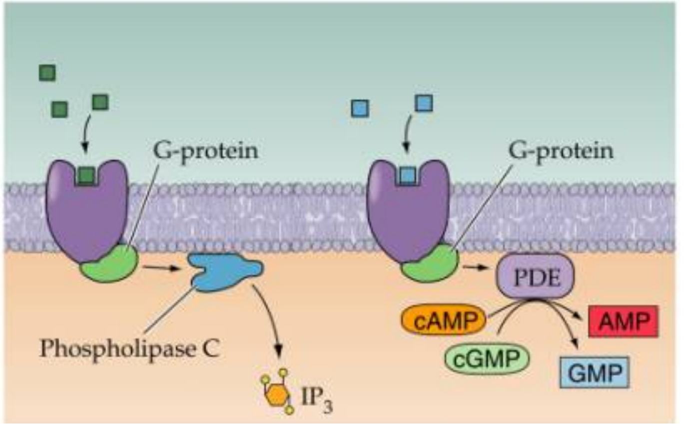


System 1:

- Bitter tastants can directly block a K+ channel
- Cell depolarizes
- Ca2+ channel opens and Ca2+ floods in
- Neurotransmitter is released

System 2:

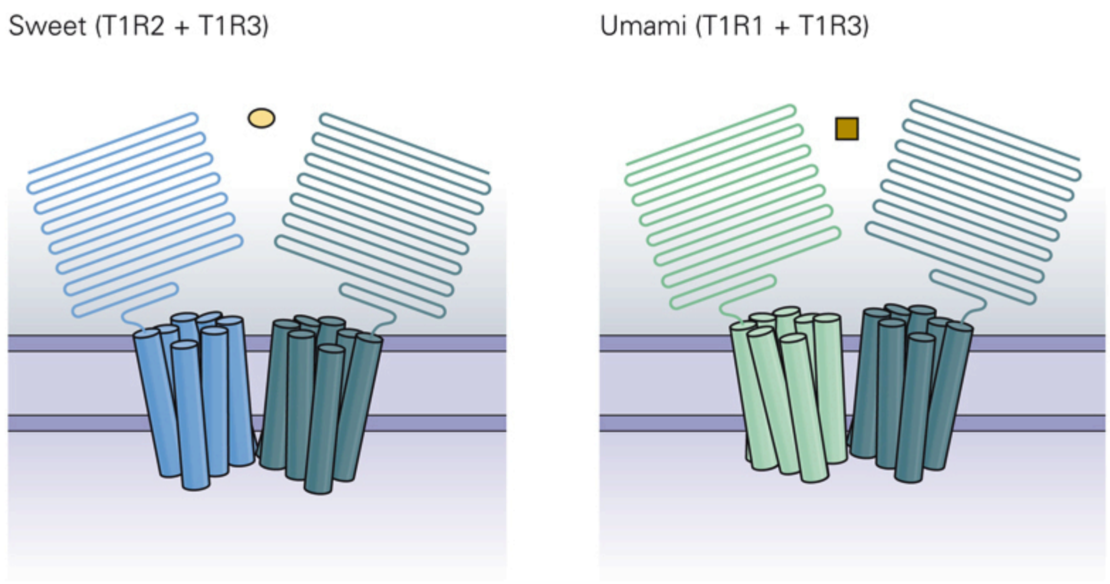
- Bitter tastants bind to bitter receptor
- G-protein activates an effector enzyme
- Ca2+ is released from extracellular storage
- Ca2+ increase causes neurotransmitter release



Gustatory System

How is umami processed?

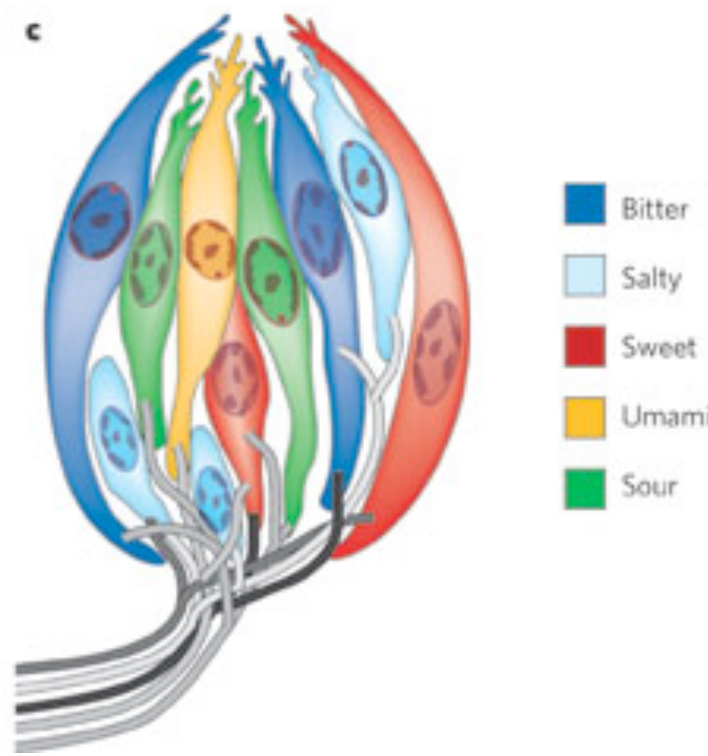
- Very similar to sweet, but slightly different downstream mechanism



Gustatory System

Taste Neural Circuitry

- There is no single fiber that conducts one taste quality (i.e. sweet, bitter), but some may respond best to one quality and less well to others
- Branches of nerve fibers innervate several cells within and in between different taste buds



Miracle Berry Demo

Miracle Berries

Synsepalum dulcificum is a plant known for its berry that, when eaten, causes sour foods subsequently consumed to taste sweet.

- Plant native to West Africa
- Contains a glycoprotein called **miraculin**, which binds to the tongue’s taste buds when the fruit is consumed
- Acts as a sweetness inducer when it comes into contact with acids
- Causes sour and bitter foods to taste sweet

Crystallographic structure of a dimeric miraculin-like protein.
Within each dimer, 2 miraculin glycoproteins are linked by a disulfide bridge.

Miracle Berry Demo







The following items will be used in our miracle berry demo.

Miracle Berry Demo

Instructions

1. Place one miracle berry tablet on your tongue and let it dissolve for **3 minutes**.
   The miracle berry needs to coat your mouth in order to have an effect, so don't just quickly swallow it down. You should hold it in your mouth and swoosh it around for a little bit on your tongue.
2. Taste the following items available after **5 to 10 minutes.**
3. Record how the different items taste.

The effect of a miracle berry can last somewhere between **15 minutes to 2 hours**.

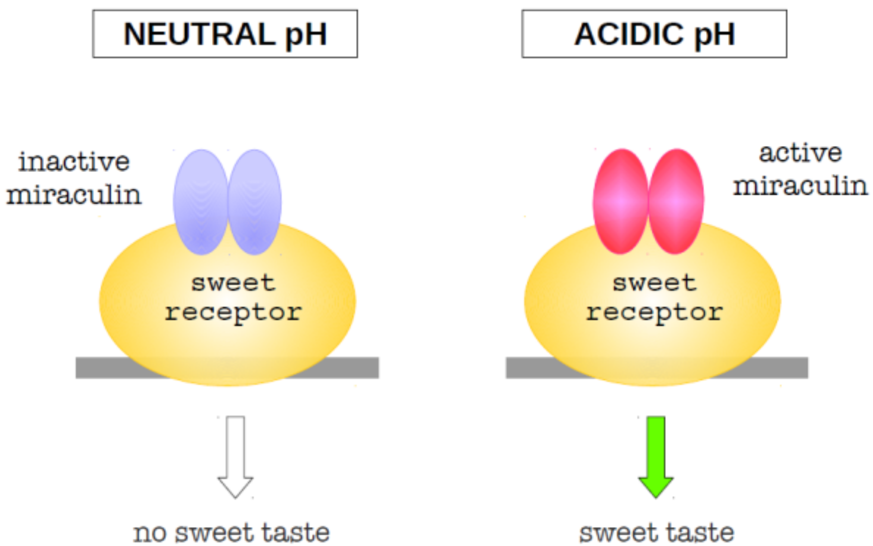
How do you think Miracle Berries work?

Miracle Berries

How do these berries work?

1. Mechanism understood by team of researchers at the University of Tokyo (led by Keiko Abe)
2. Used a system of cultured cells that let them test taste receptors at various levels of acidity and alkalinity
3. Found that miraculin bound strongly to sweet taste buds, but unlike sugar or aspartame, doesn’t activate them at a neutral pH
4. When acid is introduced, the protein changes shape and turns on the taste bud.

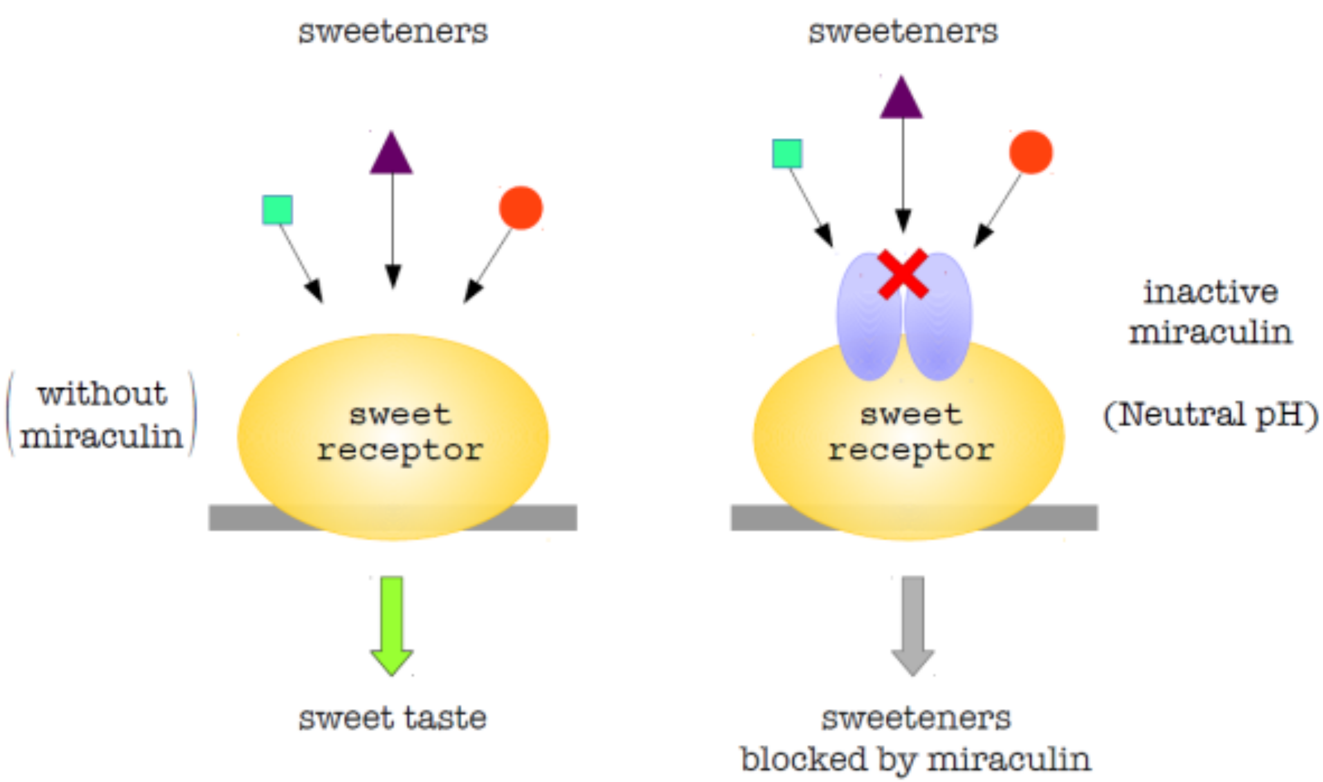
This causes the ultra-sweet sensation that drowns out the sour taste.



Miracle Berries

How do these berries work?

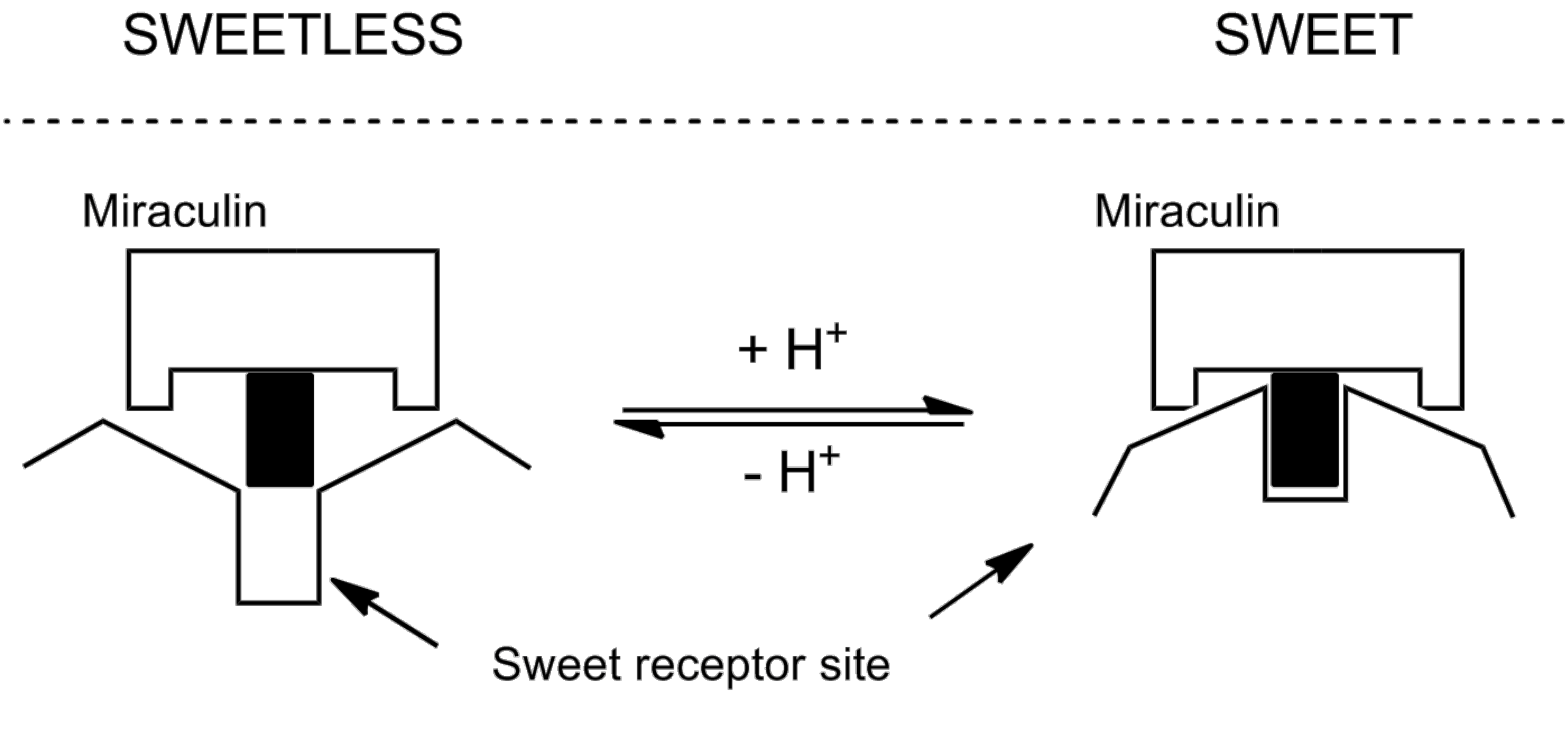
- When sour food is swallowed, miraculin returns to its old inactive shape and remains bound to the sweet receptor for an hour or so
- Miraculin also disrupts detection of sweet foods. If you have sugar after consuming a miracle berry, you cannot taste it. However, after introducing a little acid, the sugar tastes sweeter than ever.



Mechanism of Miraculin

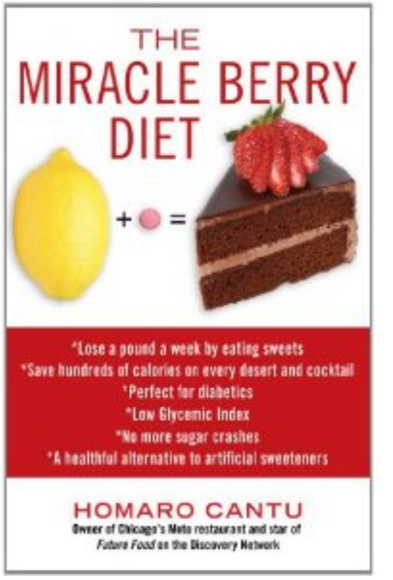
- **Miraculin is very unique glycoprotein**
  Most macromolecules do not directly affect and induce taste and smell sensations. Miraculin alters the overall flavor perception by dramatically reducing the sour acuity and augmenting the sweetness acuity.
  Note: *High temperatures and high pH substances (above 12) will render miraculin useless as will low pH substances (below 2).*
- **Acts as a lock-and-key model with sweet receptors**
  Scientists postulate that miraculin acts as a key and strongly binds to specific “sweet-taste” receptors on the tongue.
- **Adding acid causes initiation**
  When acid is present, miraculin changes its shape and and initiates sweet-taste bud receptors to fire.

Mechanism of Miraculin



Mechanism of taste-modifying activity of miraculin. Reproduced from Kurihara (1992)

The Future of Miracle Berries



1. Help Patients

<u>Diabetes and Cancer</u>

- Does not activate insulin
- No calories
- Taste enhancer
- Does not induce cravings as sugar does

Diabetics cannot produce adequate insulin and are on a constant watch to make sure their blood sugar remains in check. This results in sacrificing foods and drinks that contain copious amounts of sugar. Cancer patients often experience loss of taste sensation.

2. Dietary Aid

- Taste indistinguishable from sugar
- 400x sweeter than sucrose
- Used in combination with diet

Next Time:
Emotions and Language

Brain Bank Demo