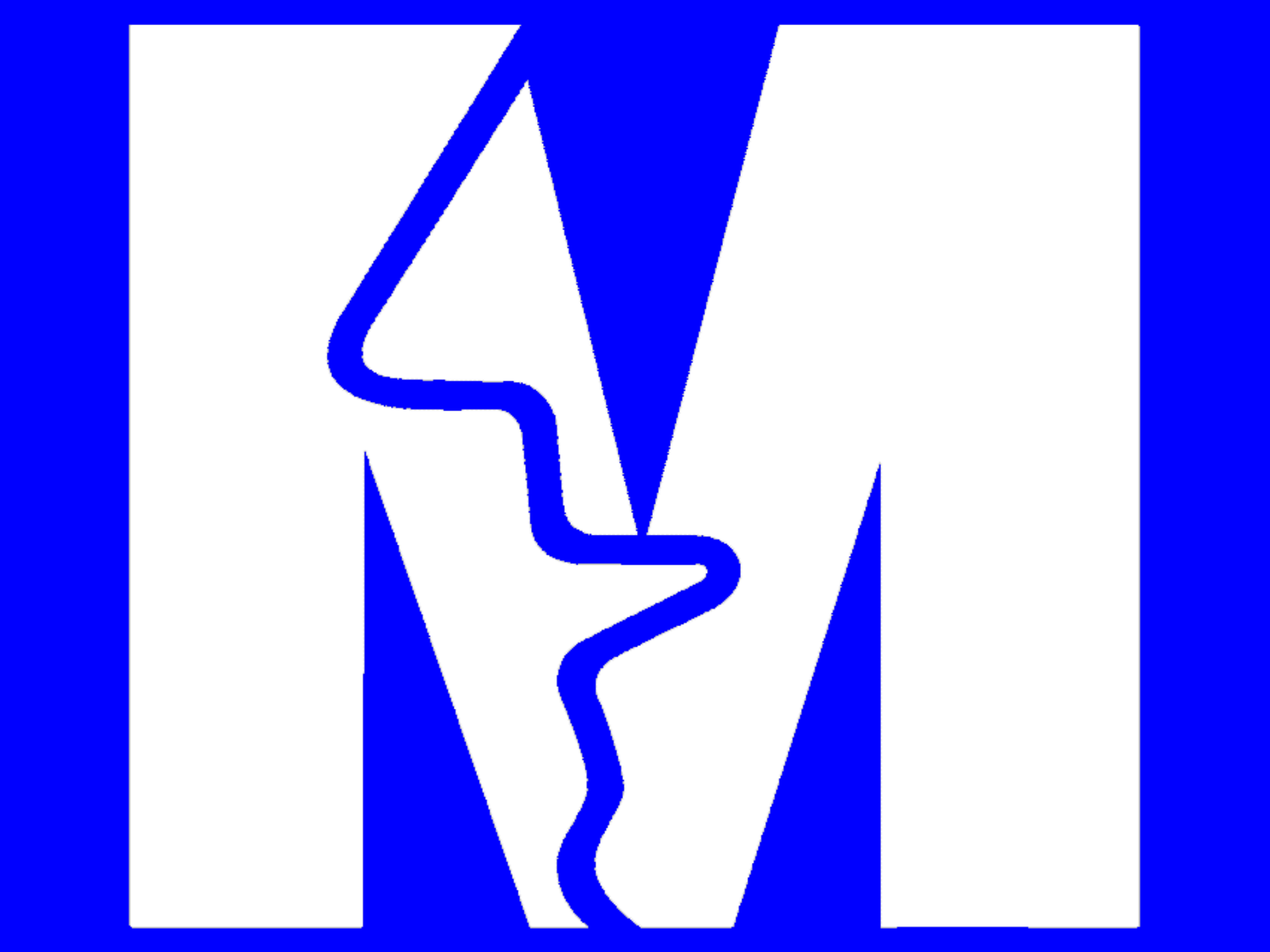

Presenter disclaimer

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Overview of Presentation:

Why care about flavor
What is flavor
Flavor dissected
    Smell - Androstenone
    Taste - Salt
    Chemesthesis - Oleocanthal
Flavor expanded
Future research directions

Flavor and the Chemical Senses

The Senses

Vision

Hearing

Touch

Smell

Taste

The Senses: Impact of Loss

Vision

Hearing

Touch

Smell

Taste

The Senses: Health Impact

Vision

Hearing

Touch

Smell

Taste

The Senses: Health Impact

Vision

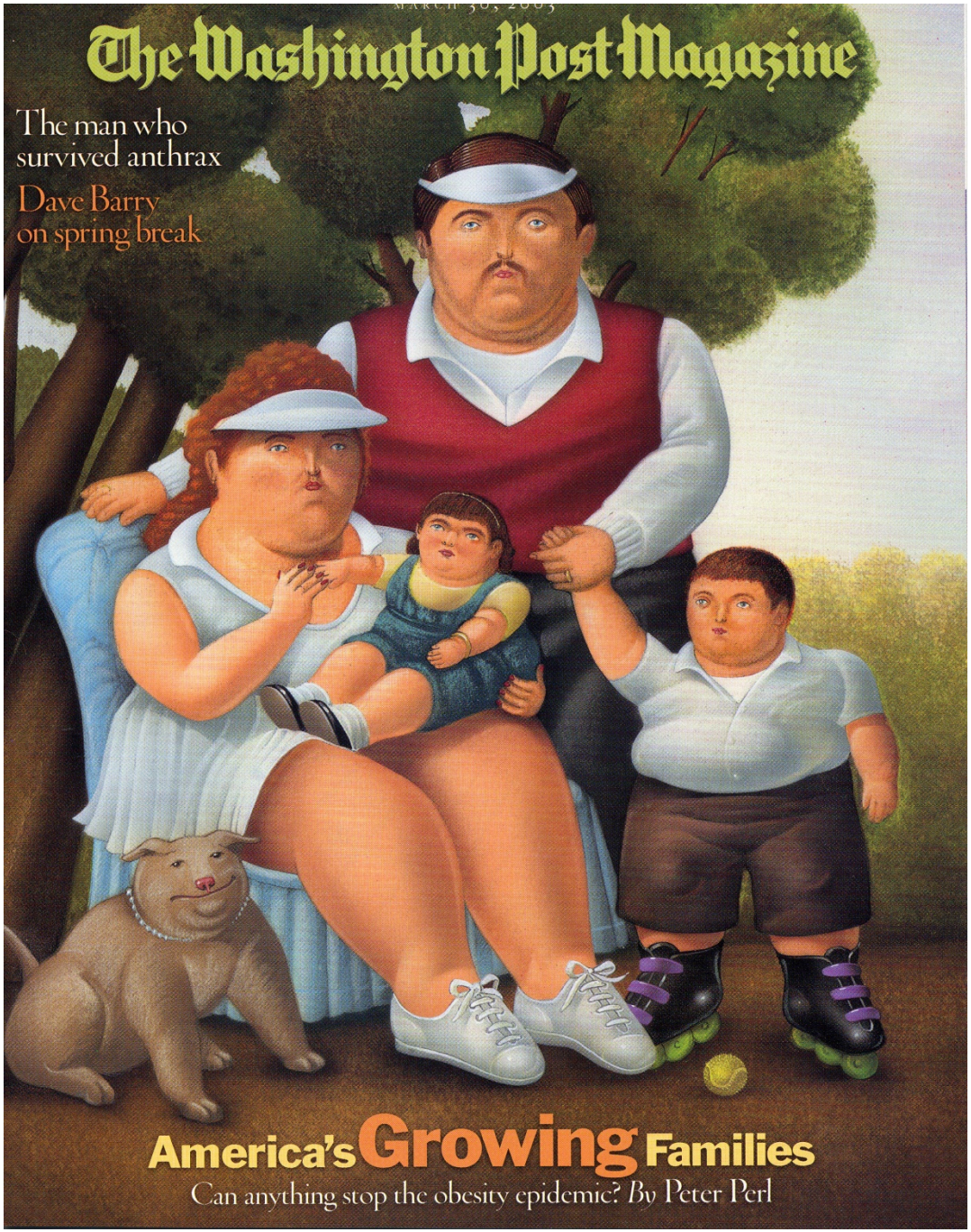
Hearing

Touch

Smell

Taste

Food


The Washington Post Magazine
The man who survived anthrax
Dave Barry on spring break
America's Growing Families
Can anything stop the obesity epidemic? By Peter Perl

Diseases related to excess food intake

- Obesity
- Diabetes
- Hypertension
- Some cancers
- Probably many others

What is flavor?

Smell

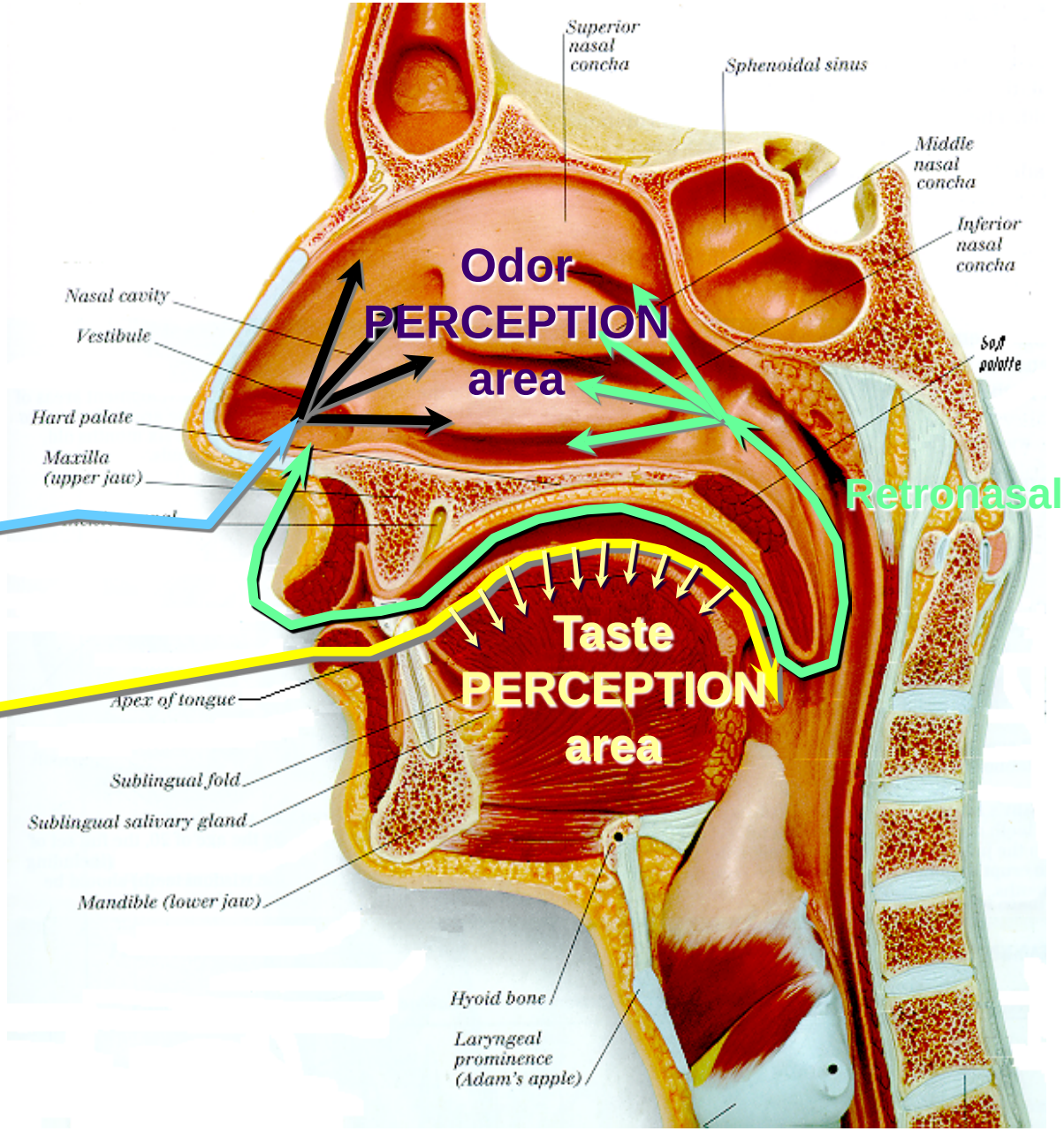
Taste

Chemesthesis – irritation (tingle, burn, cool)

Odorants

Tastes

Irritants- all skin surface



Flavor Drives Behavior

If it doesn’t “taste” good, people won’t eat it.

If it does “taste” good, you can’t stop people from eating it.

Smell

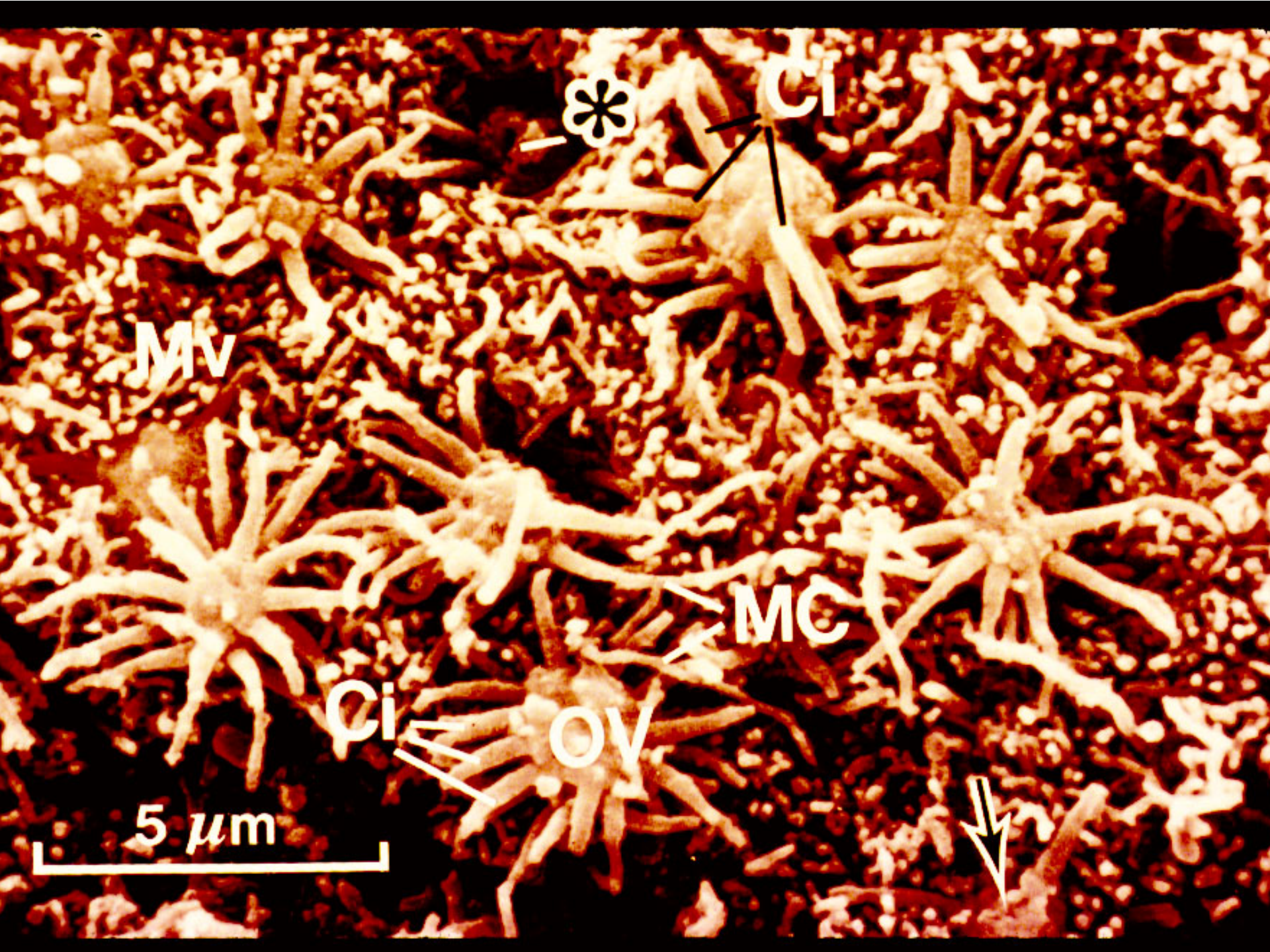
Functions: Sex, food, warning

Nobel Prize for ~1000 receptors. Combinatorial code: each receptor responds to multiple odorants and each odorant can activate multiple receptors

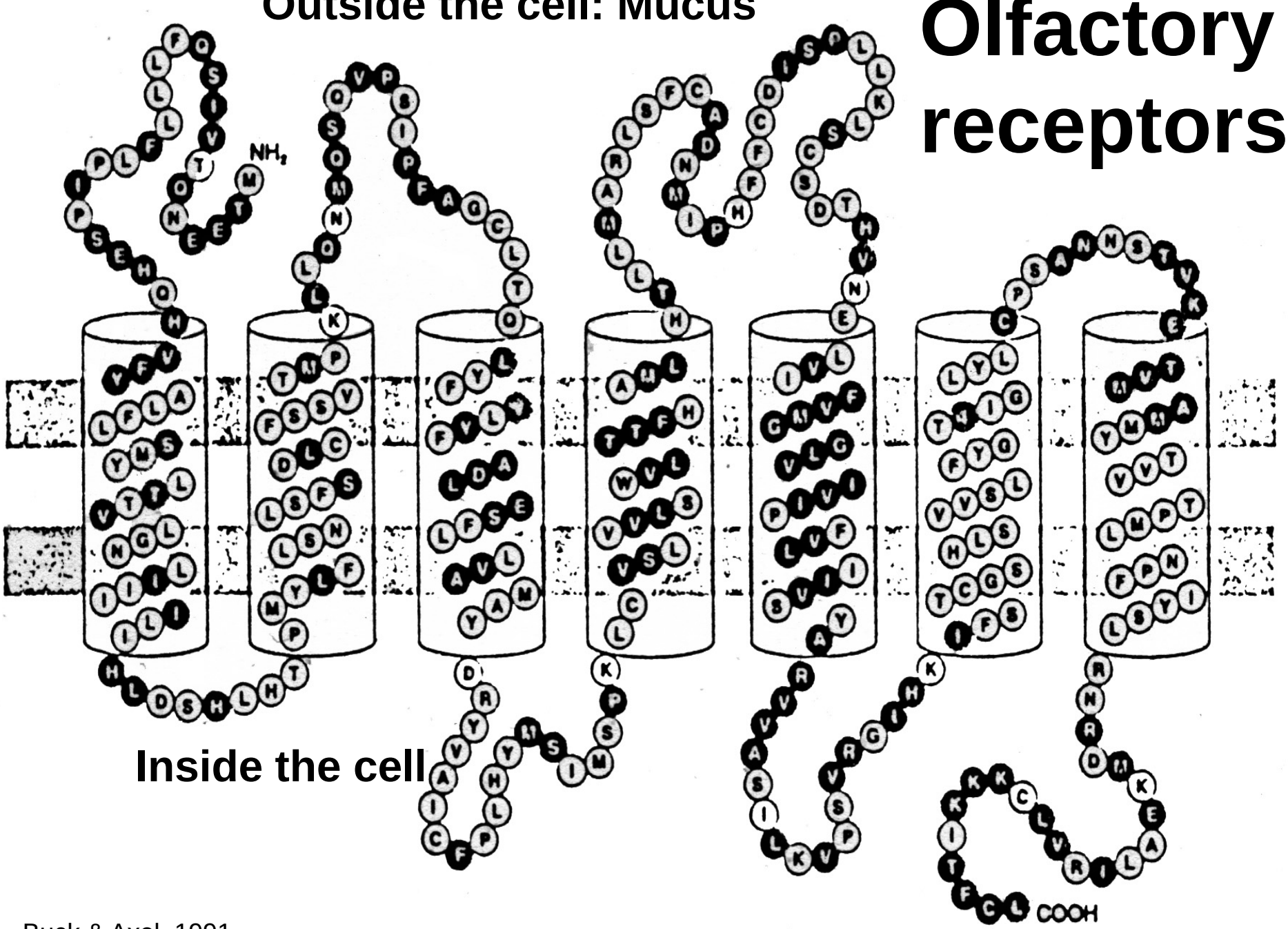
Many different qualities; claim – there are thousands of different smells

Difficult to name – it smells like…

Learning relatively more important for liking than taste

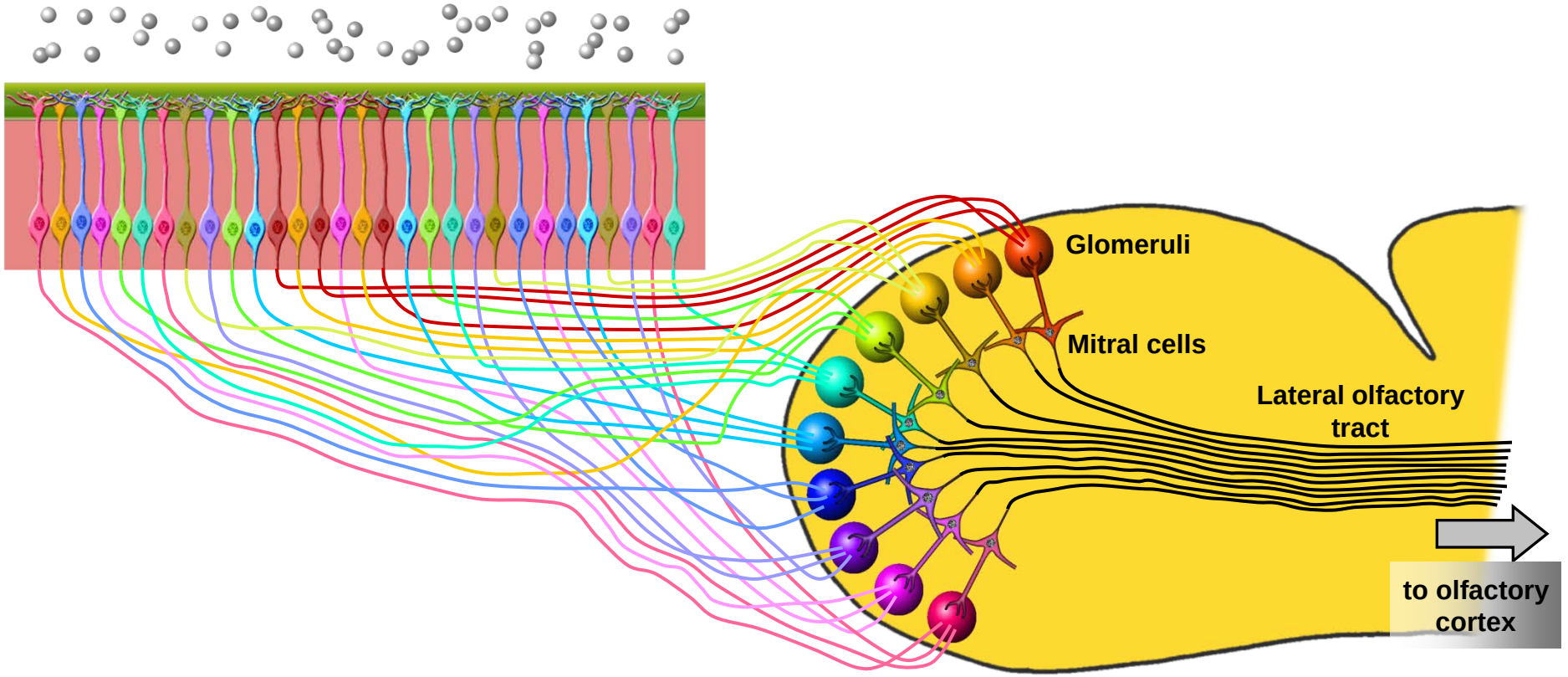

Ci
Mv
MC
Ci
OV
5 μm

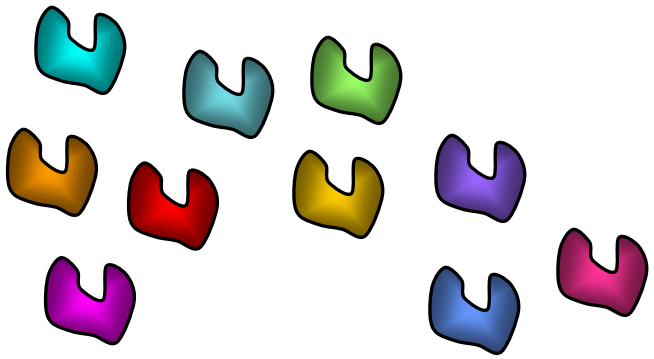
Olfactory receptors

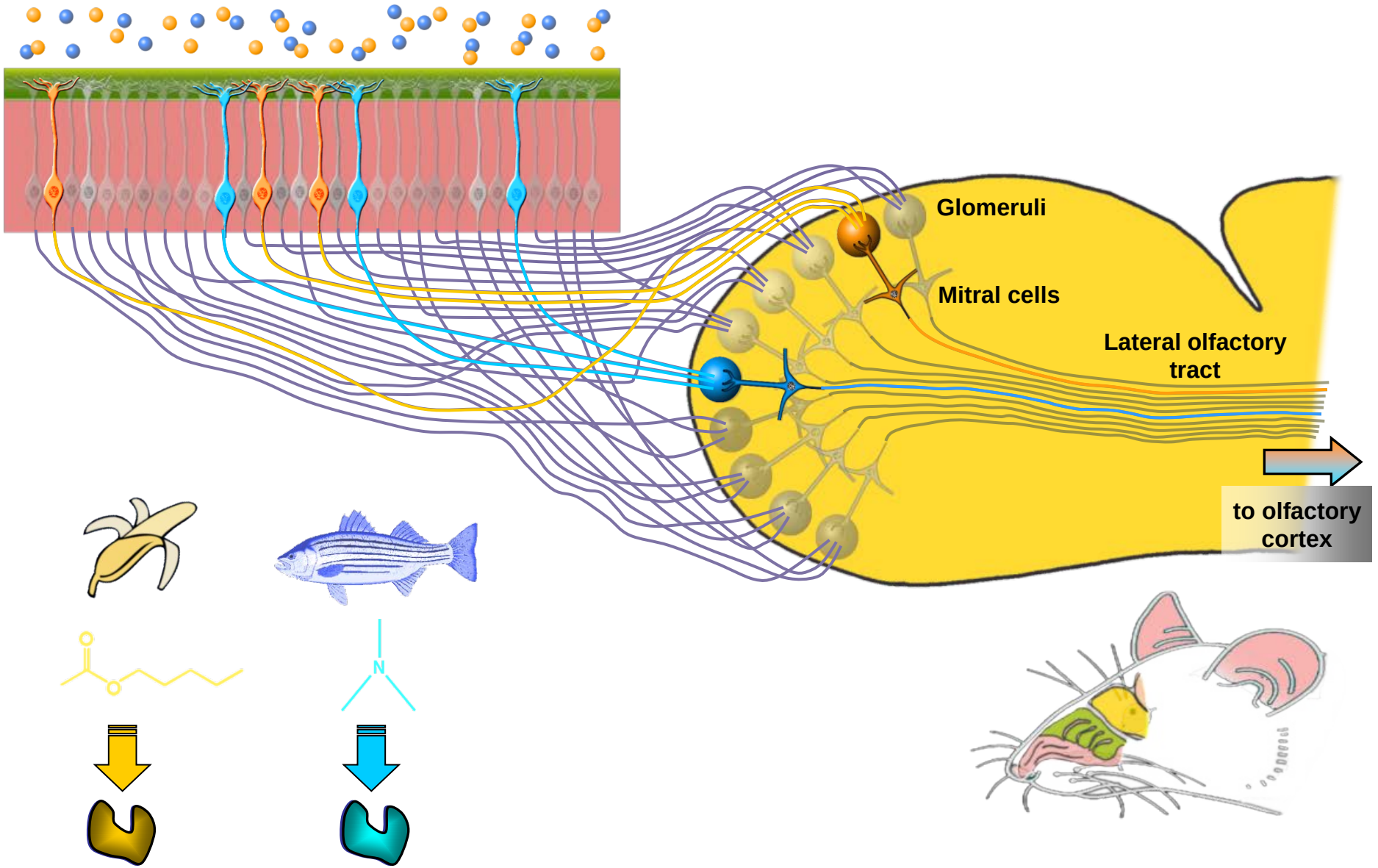


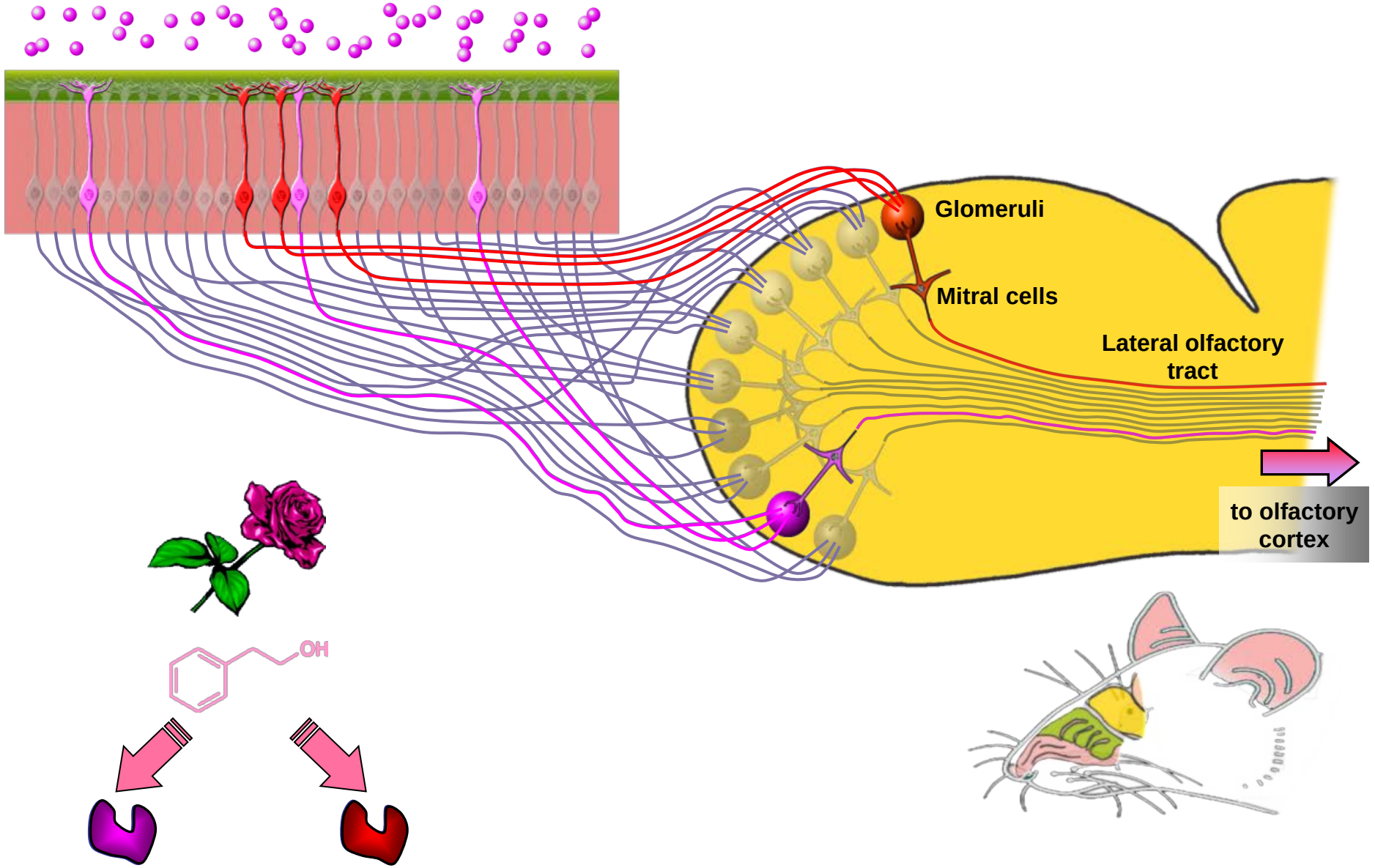
Buck & Axel, 1991

Odor receptors: In humans ~350 distinct variants

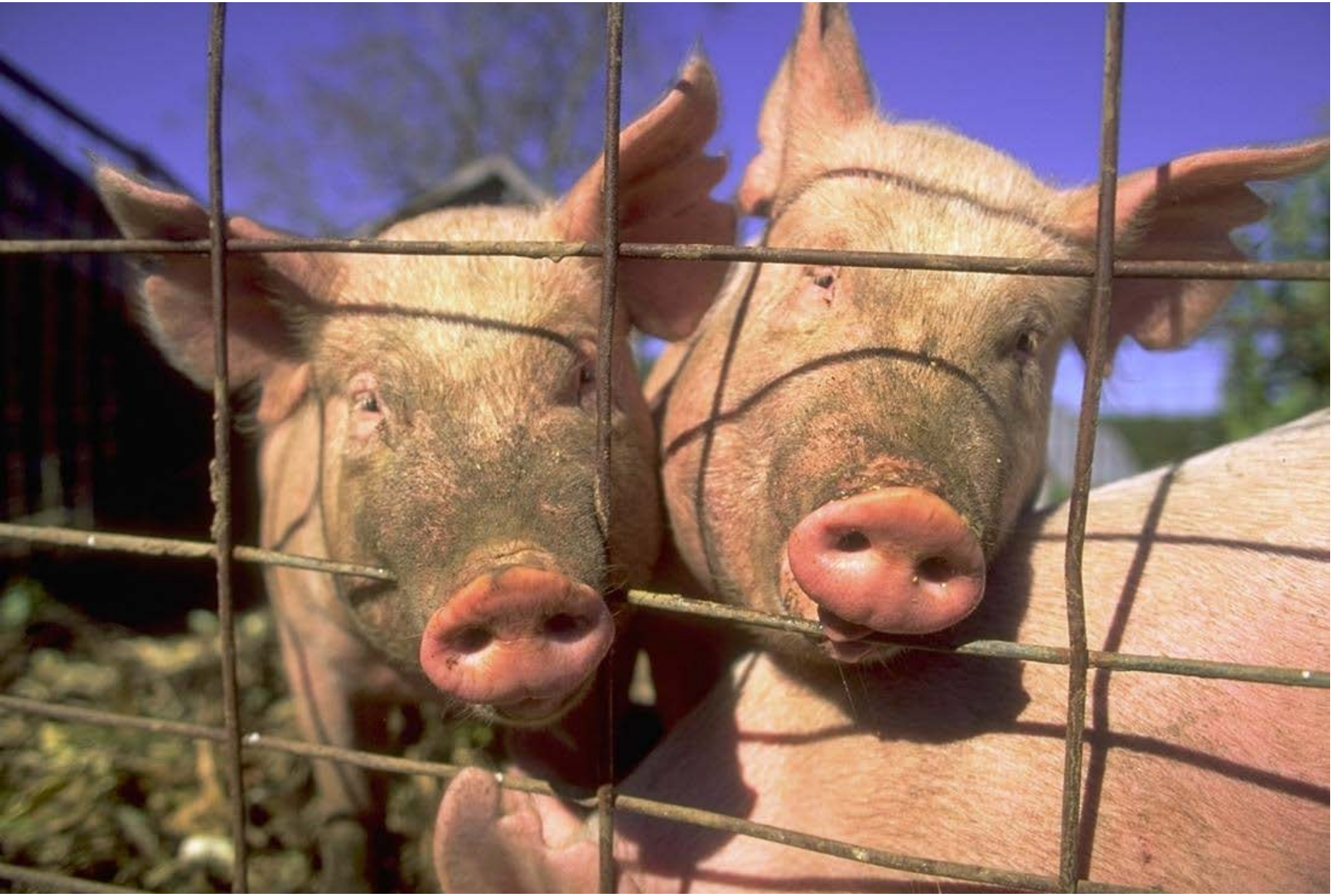




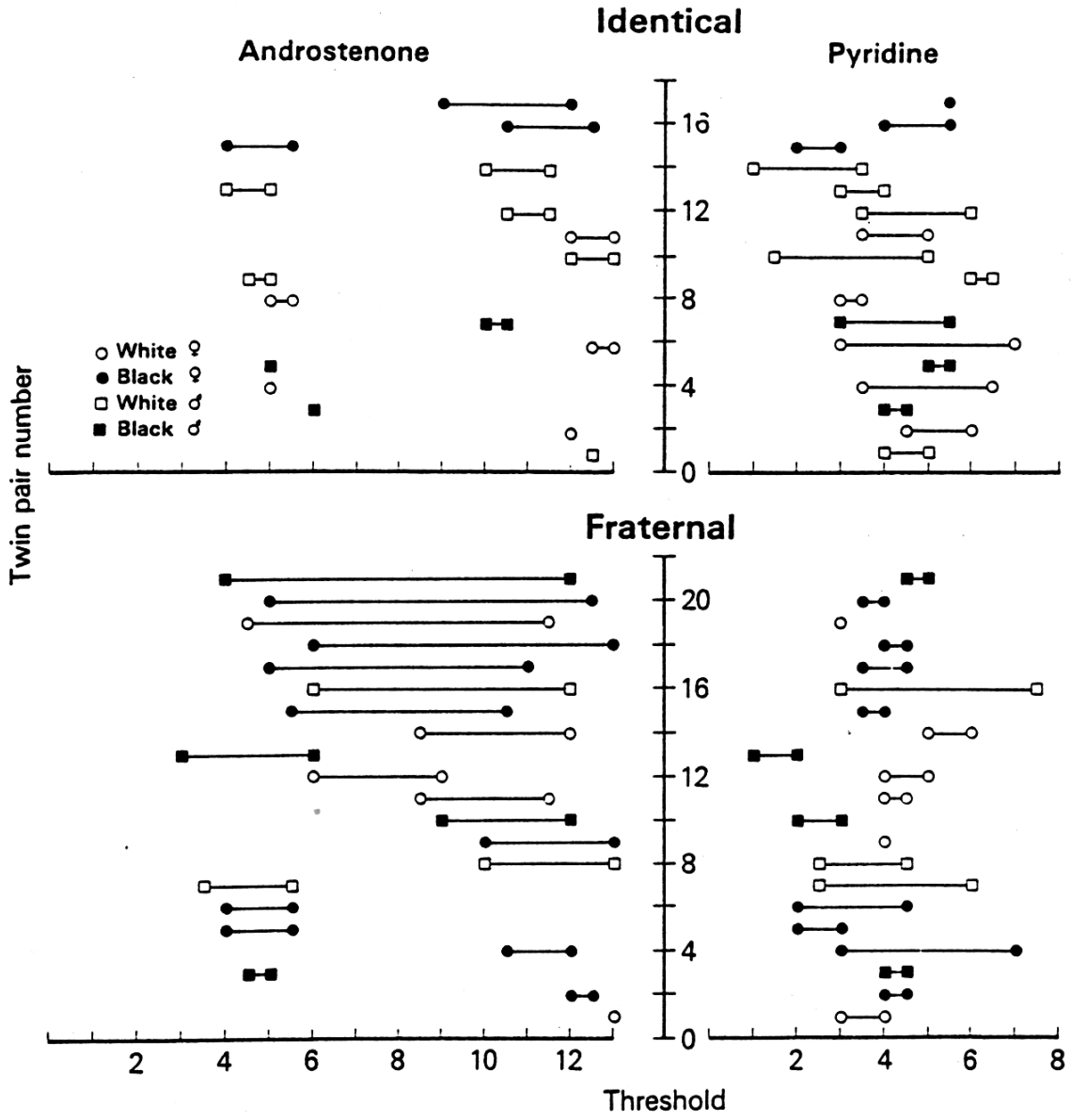

Glomeruli
Mitral cells
Lateral olfactory tract
to olfactory cortex
N


Glomeruli
Mitral cells
Lateral olfactory tract
to olfactory cortex
OH

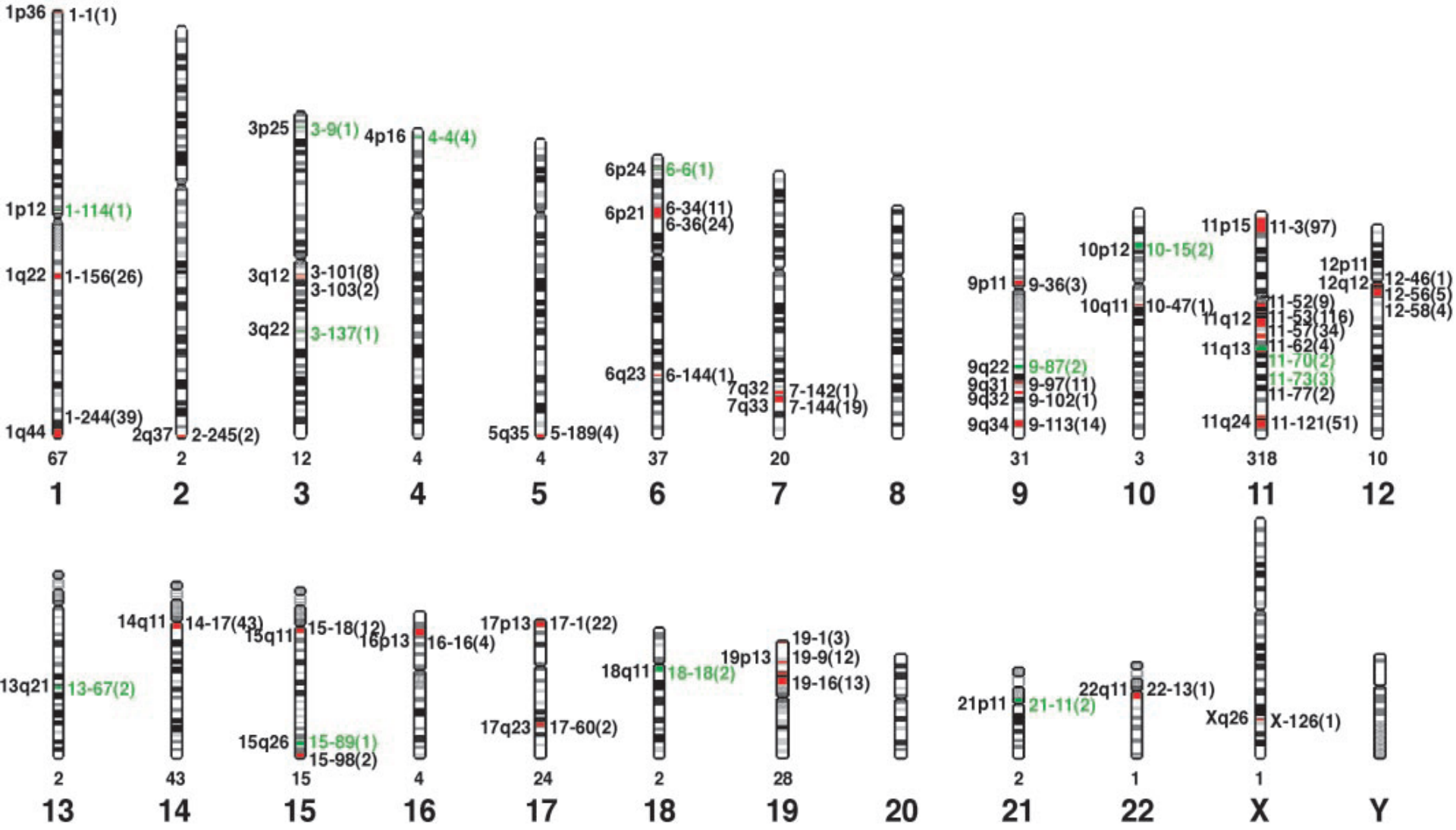
Androstenone




PRETZELS
2002
STANLEY CUP
Stanley Cup
CHAMPIONS
DETROIT RED WINGS

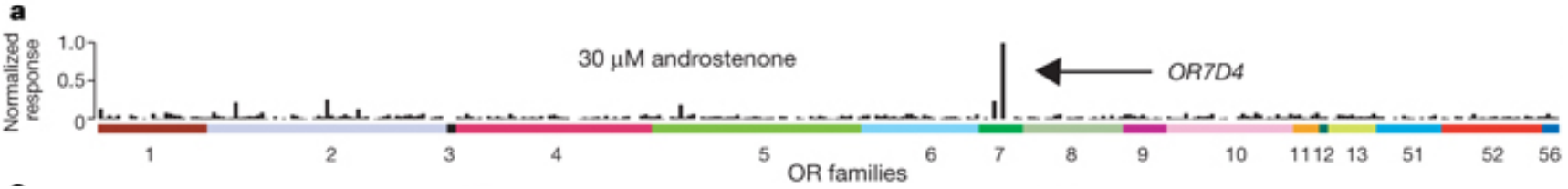


Wysocki & Beauchamp, PNAS, 1987



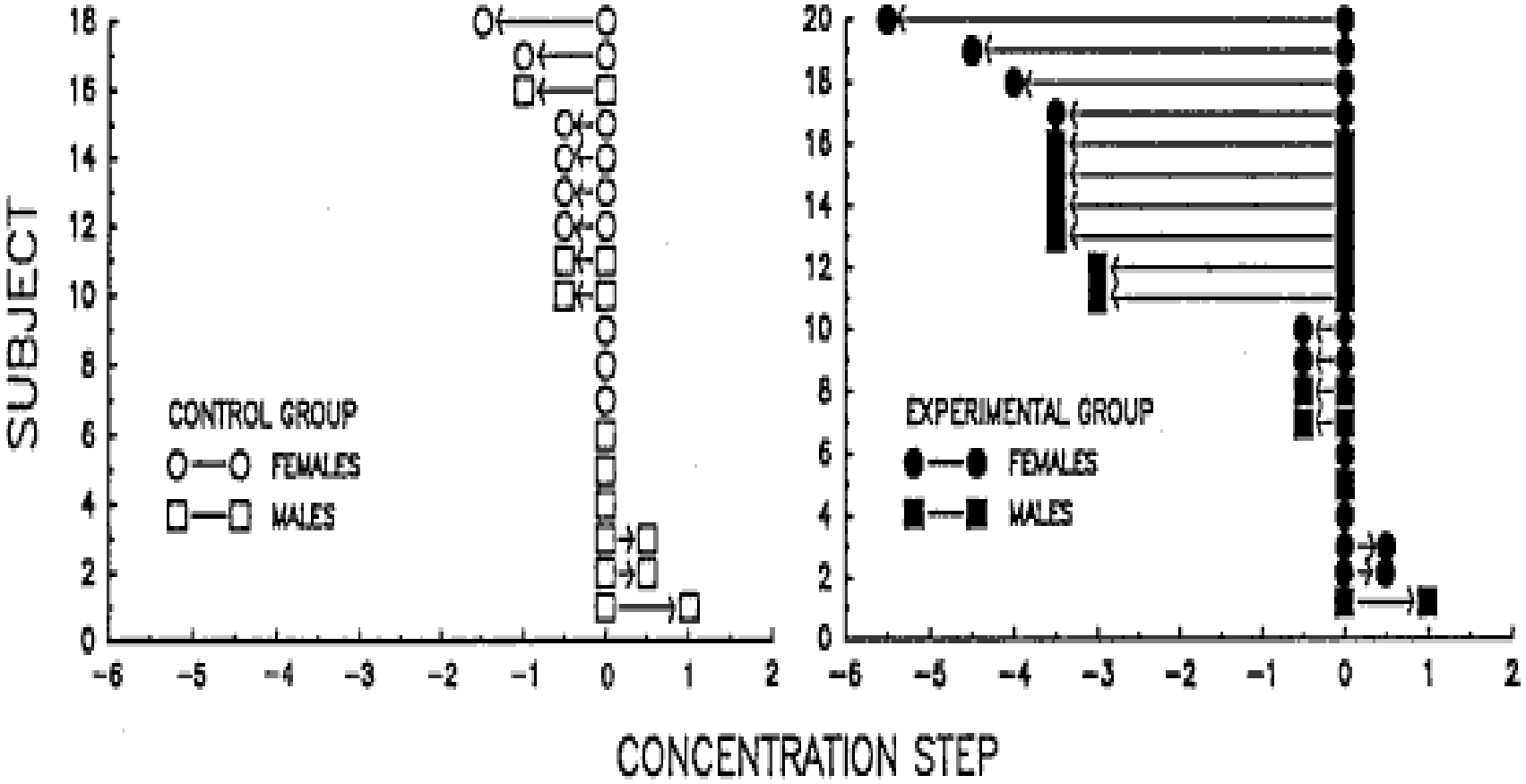
Malnick et al., 2004, red = intact ORF.

Putative androstenone receptor
OR7D4



Keller et al., Nature, 2007

A fly in the ointment: Effects of experience



Wysocki, Dorries & Beauchamp, PNAS

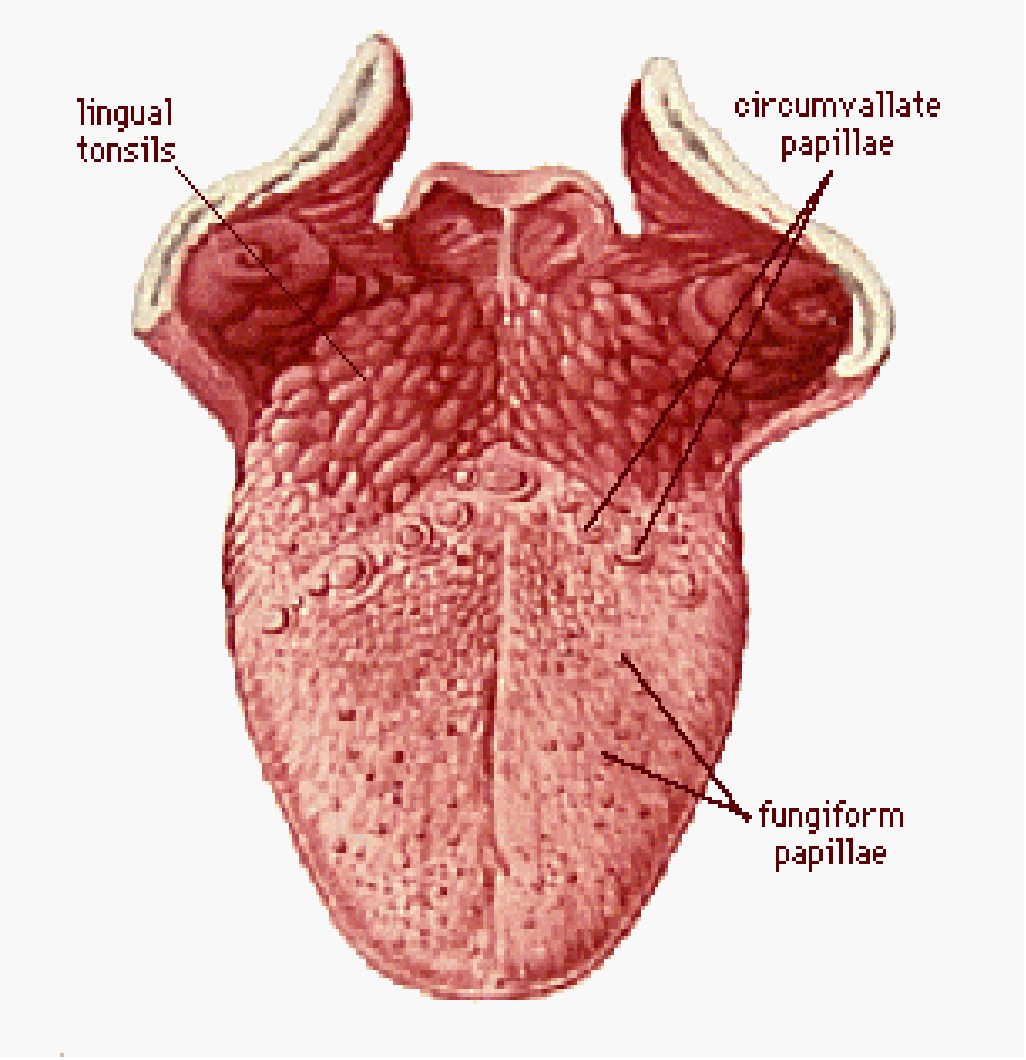
Taste

Dedicated to food choice: accept or reject

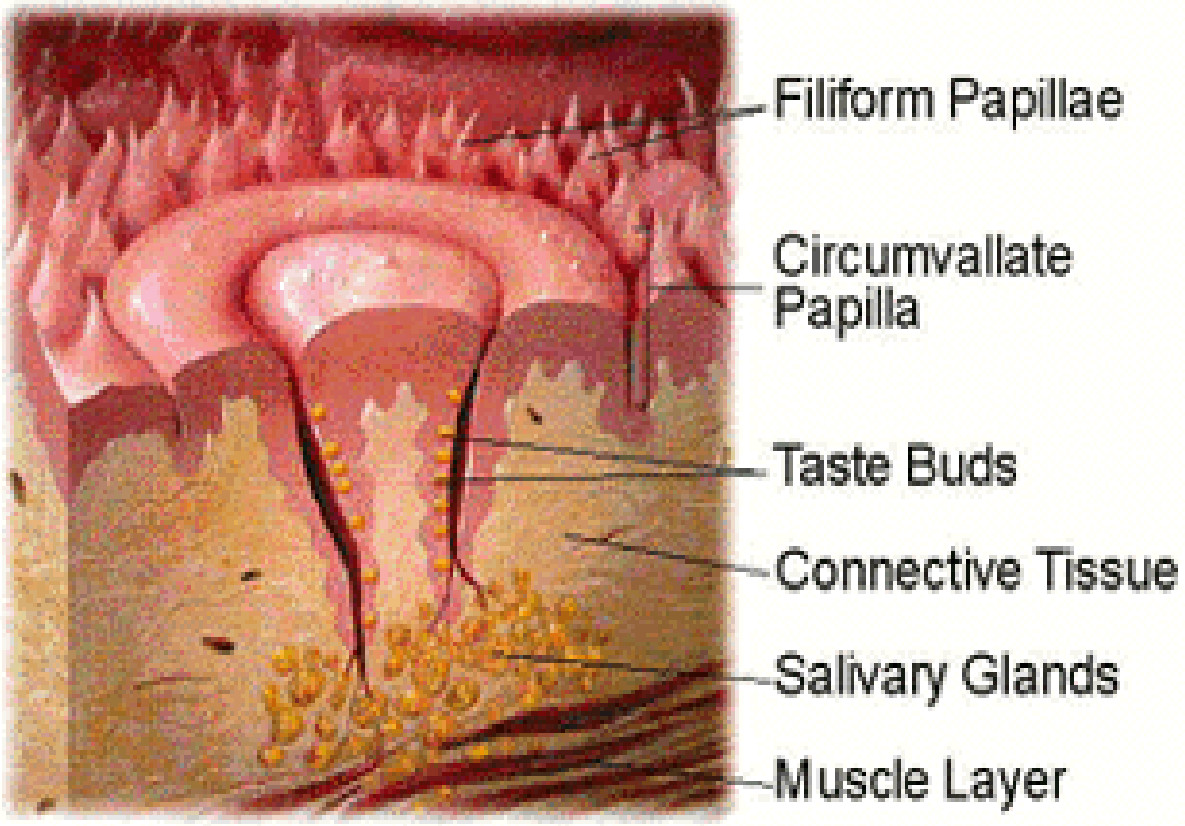
Five basic tastes:

- Sour - acids: Ripeness?
- Salty - NaCl, LiCl: Sodium, minerals?
- Bitter - Alkaloids, peptides, toxins: Poison avoidance?
- Umami - Glutamate, aspartate, nucleotides: Protein? Calories?
- Sweet - sugars, high intensity sweeteners: Calories for plant eating animals
- Others? – fat, calcium, starch

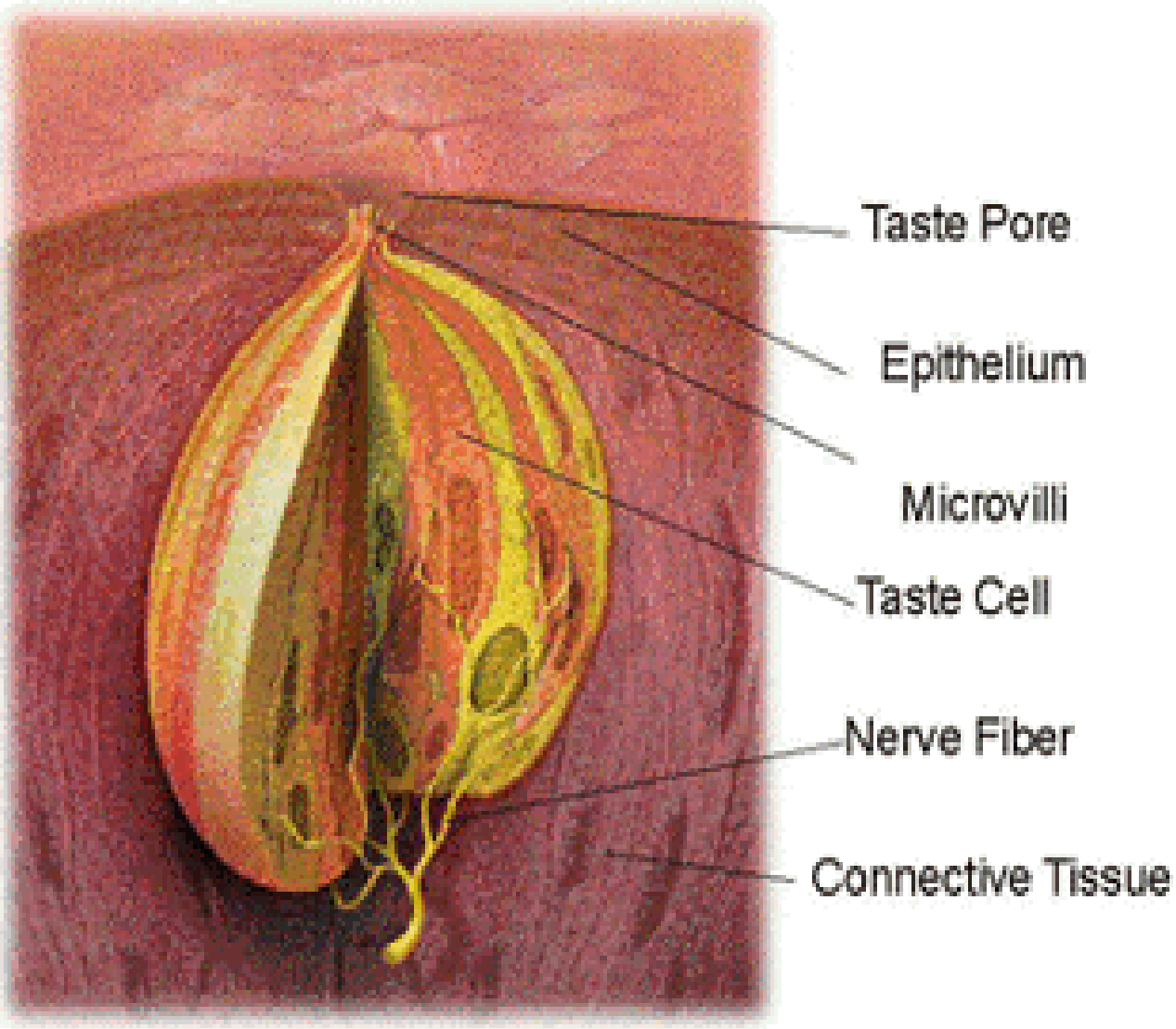
Innate responses to many taste stimuli but learning also occurs


lingual
tonsils
circumvallate
papillae
fungiform
papillae

Circumvallate Papilla



Taste Bud


Taste Pore
Epithelium
Microvilli
Taste Cell
Nerve Fiber
Connective Tissue

Taste

Beginning in 1999 with a paper from Zucker and Ryba group, a series of taste receptors have been identified:

Sweet: GPCRs – heterodimer T1R2+T1R3

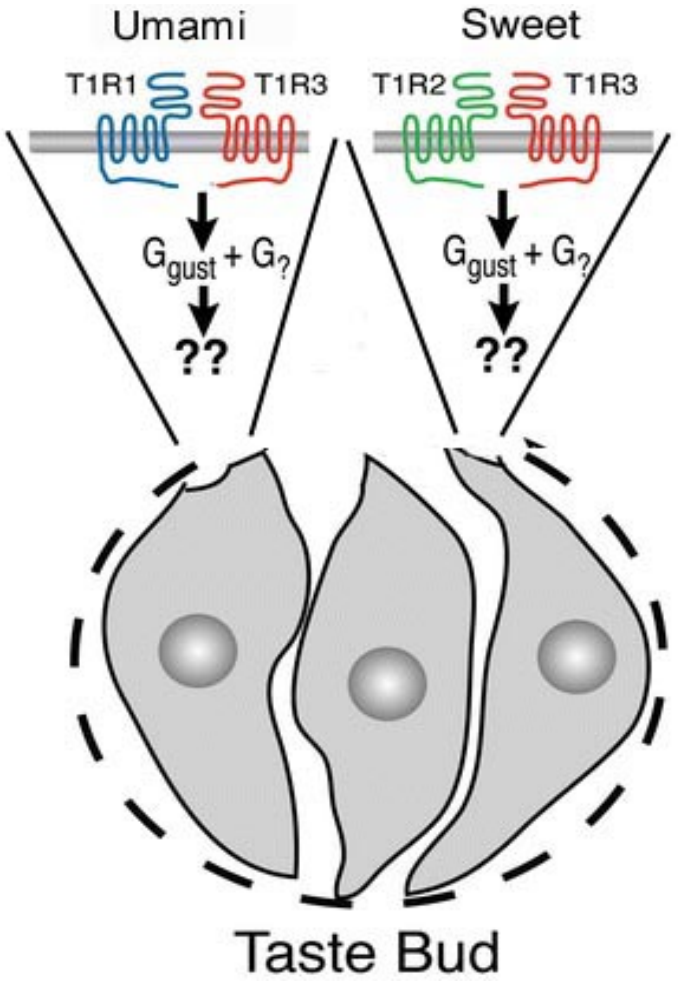
Umami: GPCRs – heterodimer T1R1+T1R3

Bitter GPCRs - ~25 in humans; dimerize?

Sour: Ion channel(s) – PDK, ASIC, others?

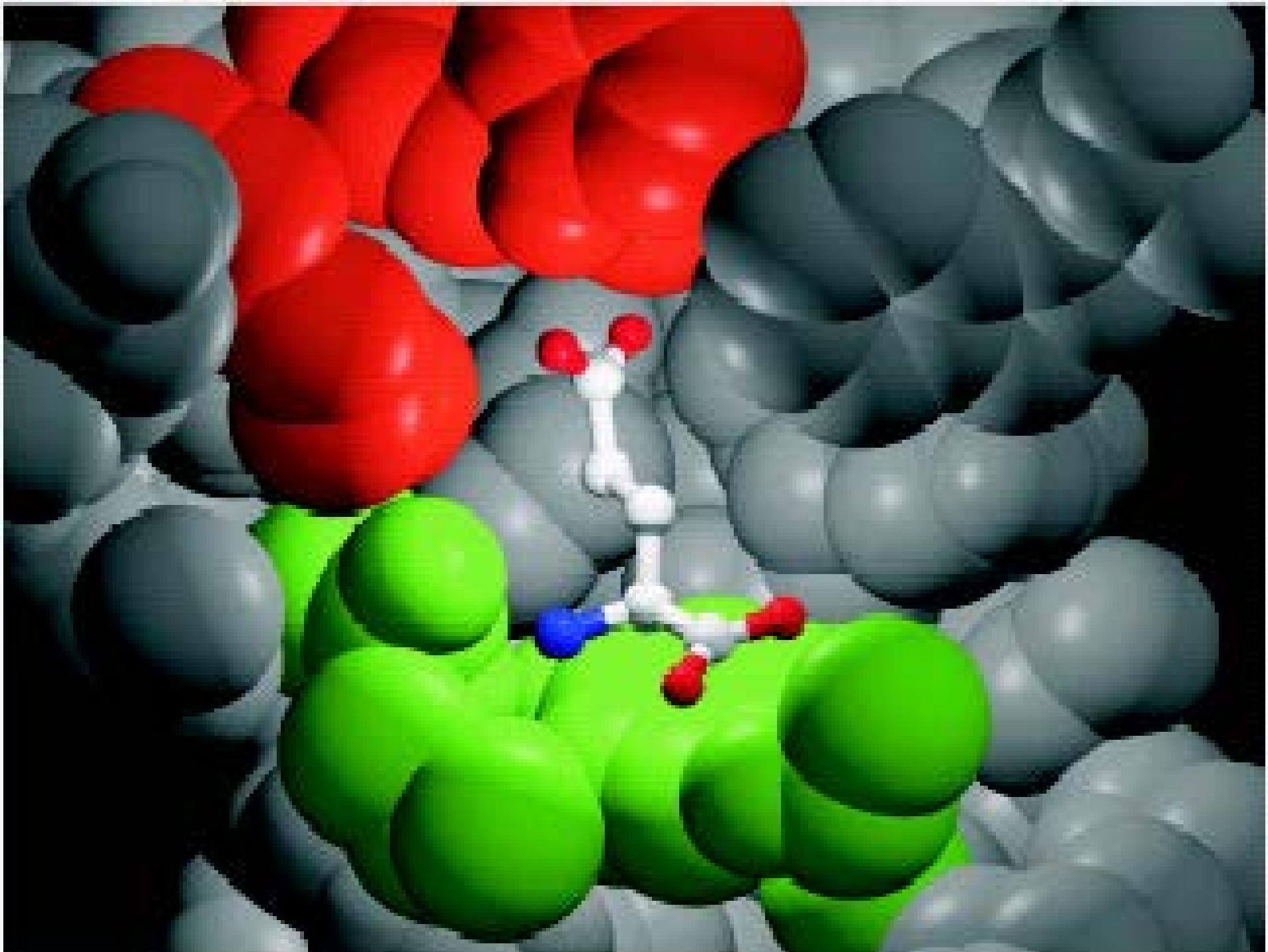
Salt: Ion channel(s) – ENaC, TRP, others?

Major Discoveries in Taste Receptors



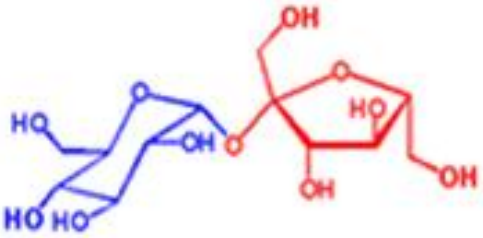
Li et al, 2002;

Nelson et al., 2002.

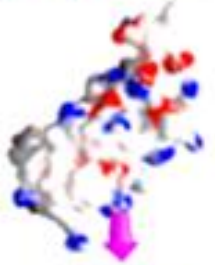


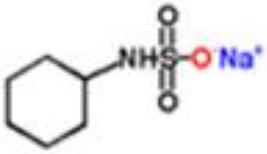
Diverse Compounds are Sweet

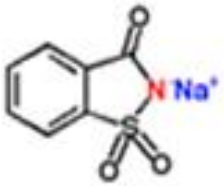
How can one receptor respond to so many chemically diverse compounds?

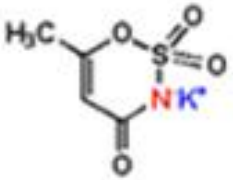


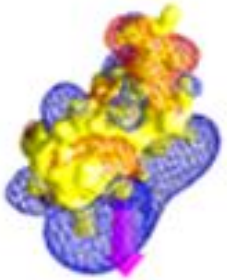
Sucrose









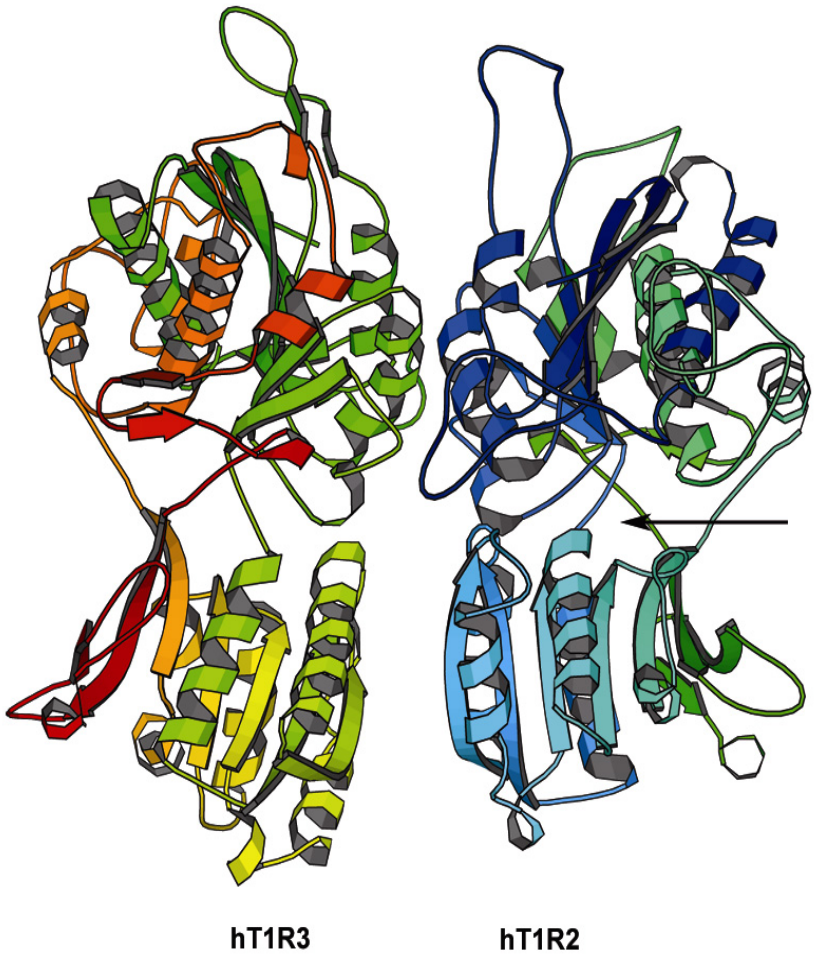


Cyclamate | Saccharin | Acesulfame K | Brazzein | Monellin

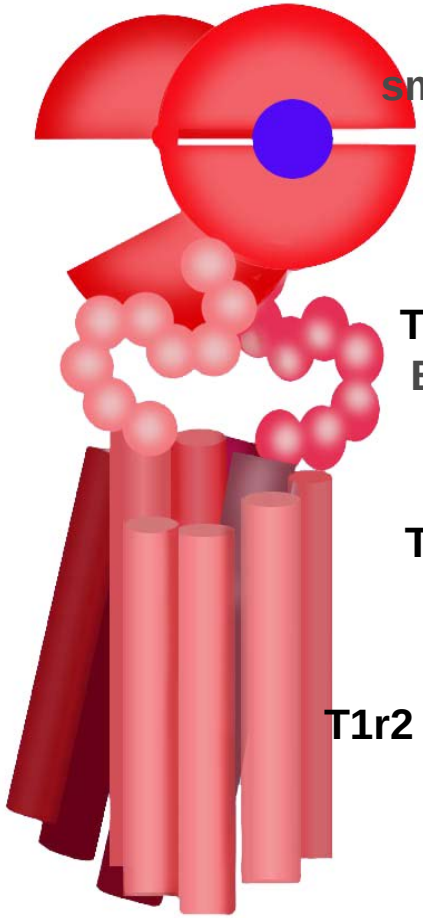
R. Margolskee

Multiple Regions of T1R2+T1R3 are Required for Effective Interaction with Different Sweet Compounds

The sweet receptor has six distinct ligand binding sites



ATDs



T1r2 & T1r3 Amino Terminal Domains
Sugars, aspartame,
small molecule sweeteners

T1r3 C-Rich Region
Brazzein, monellin

T1r3 Transmembrane Region
cyclamate, lactisole

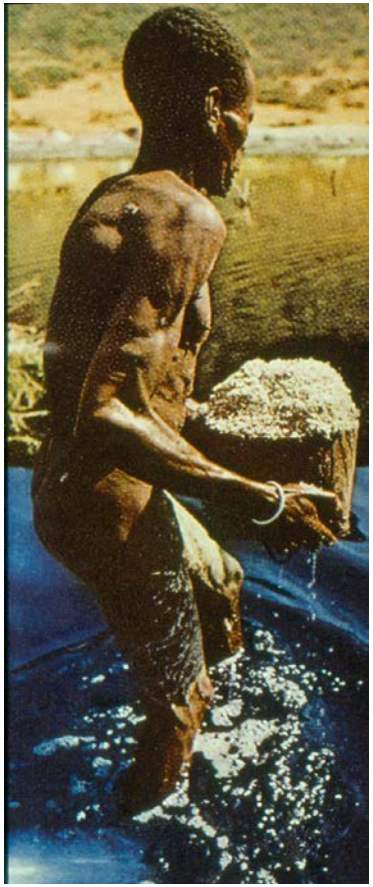
T1r2 Transmembrane Region
perillartine

T1r2+T1r3 Heterodimer

R. Margolskee

Salt

Salt, … the primordial narcotic*



***Multhauf, RP, *Neptune's Gift*, Baltimore: The Johns Hopkins University Press, 1978, p. 4.**

Too much?


CENTER CITY SOFT PRETZEL CO.
TRANS FATS
816 Washington Ave., Philadelphia PA 19147
Ph: (215) 463-5664 ✦ Fax: (215) 463-5949

The Problem: Once Americans reach their fifties, the risk of developing high blood pressure over the remainder of the lifespan is estimated to be 90% even for those with healthy blood pressures. It has been estimated that reducing sodium intakes could prevent more than 100,000 deaths annually and save billions in medical costs.

Recommendations in the past:

1969: The first statement from the U.S. government:

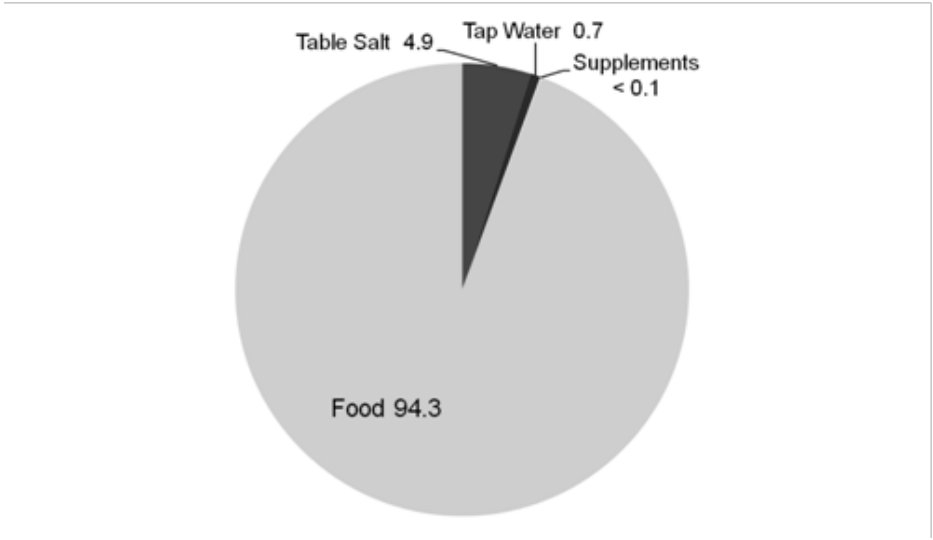
First: at risk populations

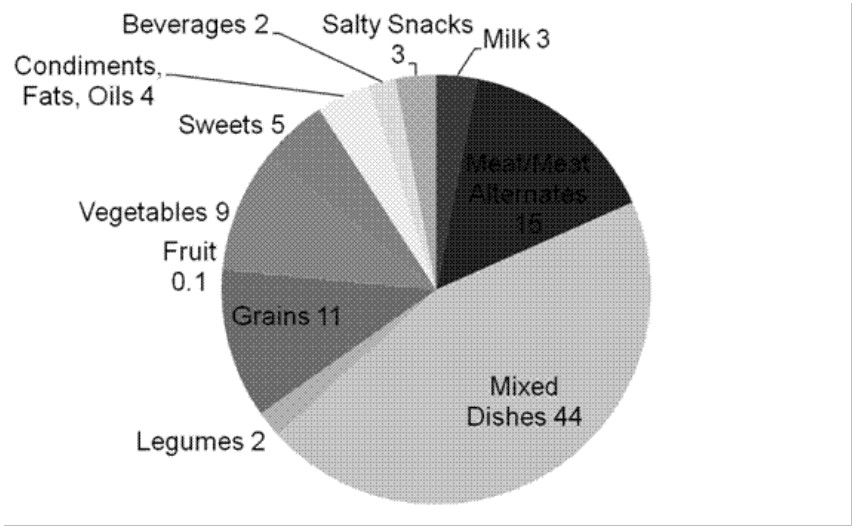
Later: all U.S. population

Since 1968, more than 18 national and international government and medical bodies have concurred.

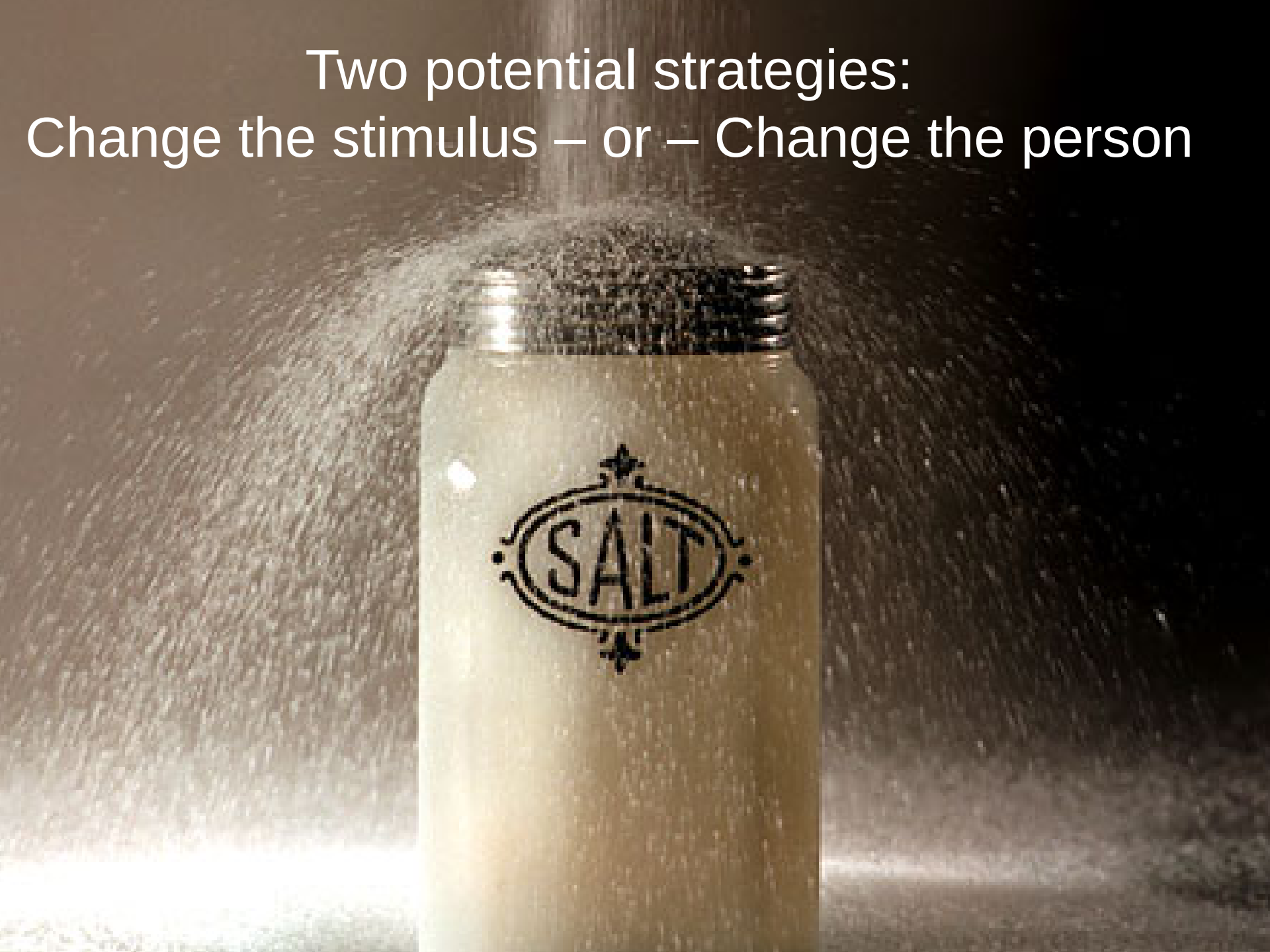
Results to date: NO EFFECT!

Salt is everywhere in the U.S. food supply and most is added by others





Two potential strategies:
Change the stimulus – or – Change the person



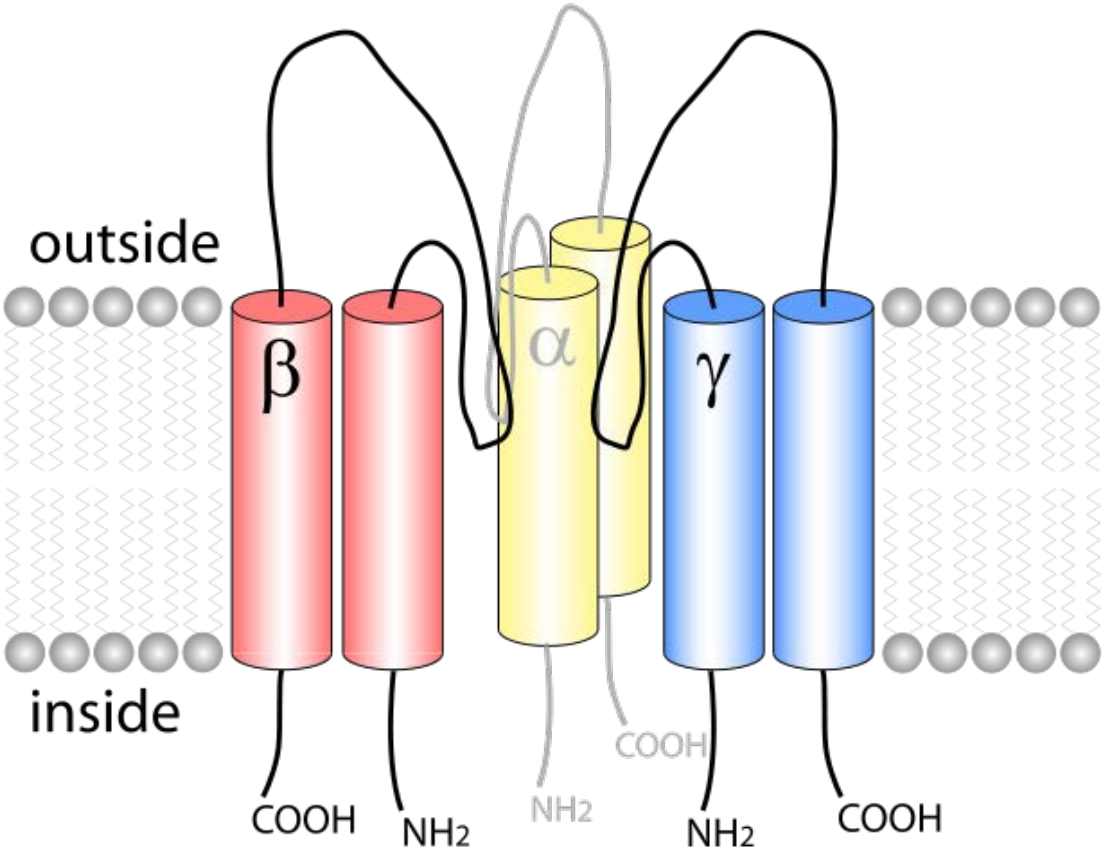
Salt taste mechanisms

The identity of the human salt receptor - new information and remaining puzzles

- Stimulus specificity:
  - NaCl and LiCl only purely salty substances known.
  - This suggests a very specific mechanism.

- Animal models:
  - Neural responses to NaCl are inhibited by the diuretic amiloride.
  - In 2010 two research groups proved that one component of the salt receptor mechanism involves an epithelial Na channel (ENaC).

Epithelial Na channel (ENaC)



Salt taste mechanisms

- One component is an ENaC*
- Implications:
  - Salt taste substitute through this mechanism unlikely due to specificity
  - Salt taste enhancer possible

***Bosak et al., 2010; Chandrashekar et al., 2010**

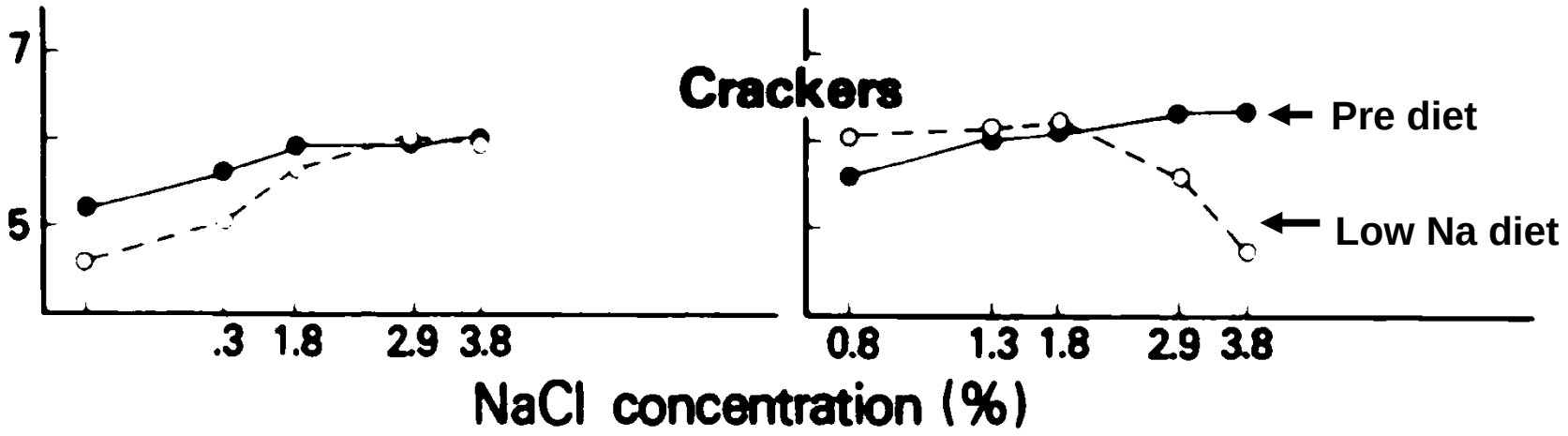
Salt taste mechanisms

- An ENaC is not the entire answer.
- A second less specific salt taste mechanism also exists.
- This may account for several of the other taste attributes of salt such as mouthfeel, fullness, lowered bitterness and overall balance.
- This mechanism is unknown.

Vilhjalmur Stefansson

Decreasing Na intake is followed by decreased salt preference

Experimental



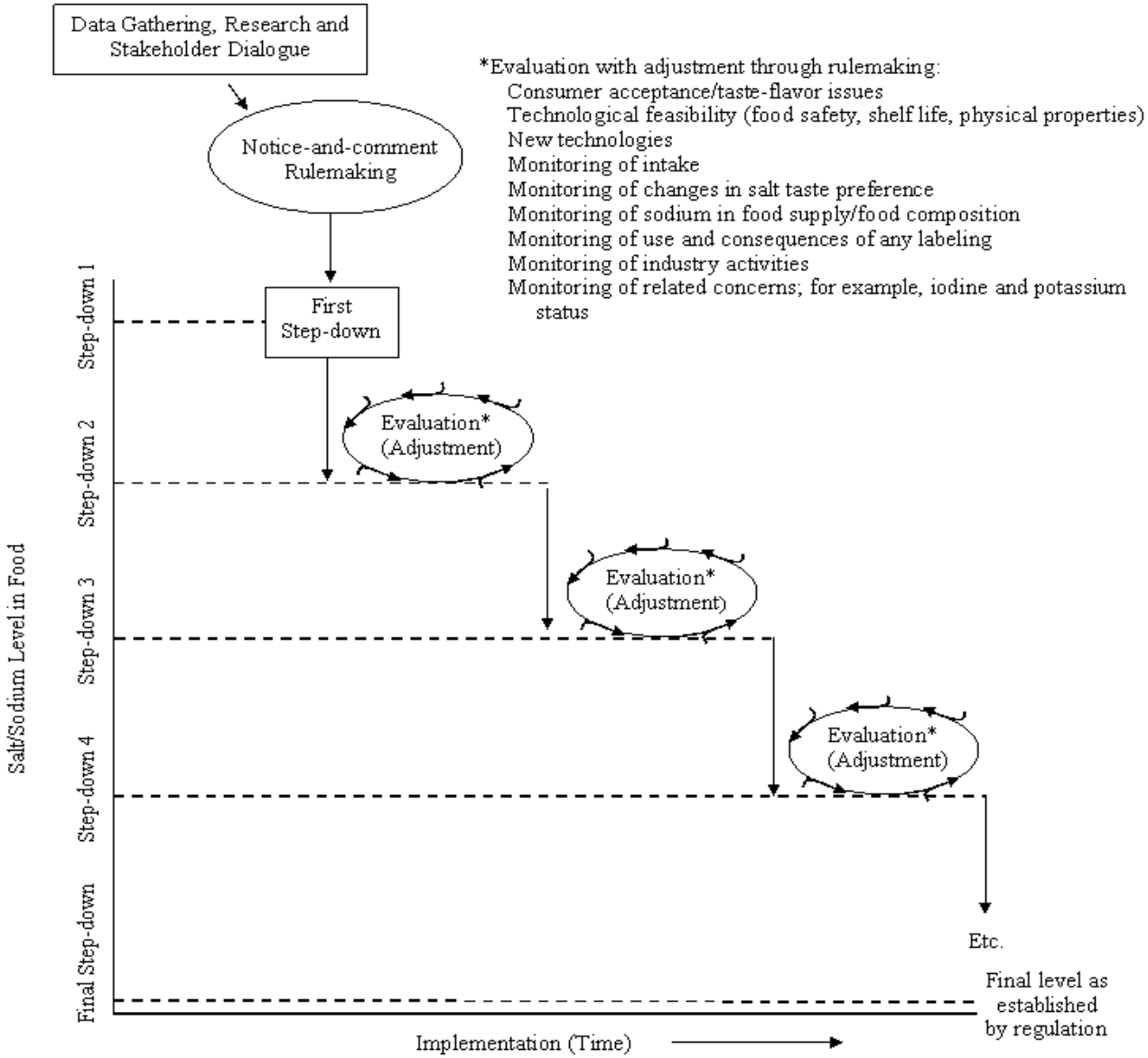
NaCl Concentration in crackers (%)

Bertino , Beauchamp & Engelman, AJCN

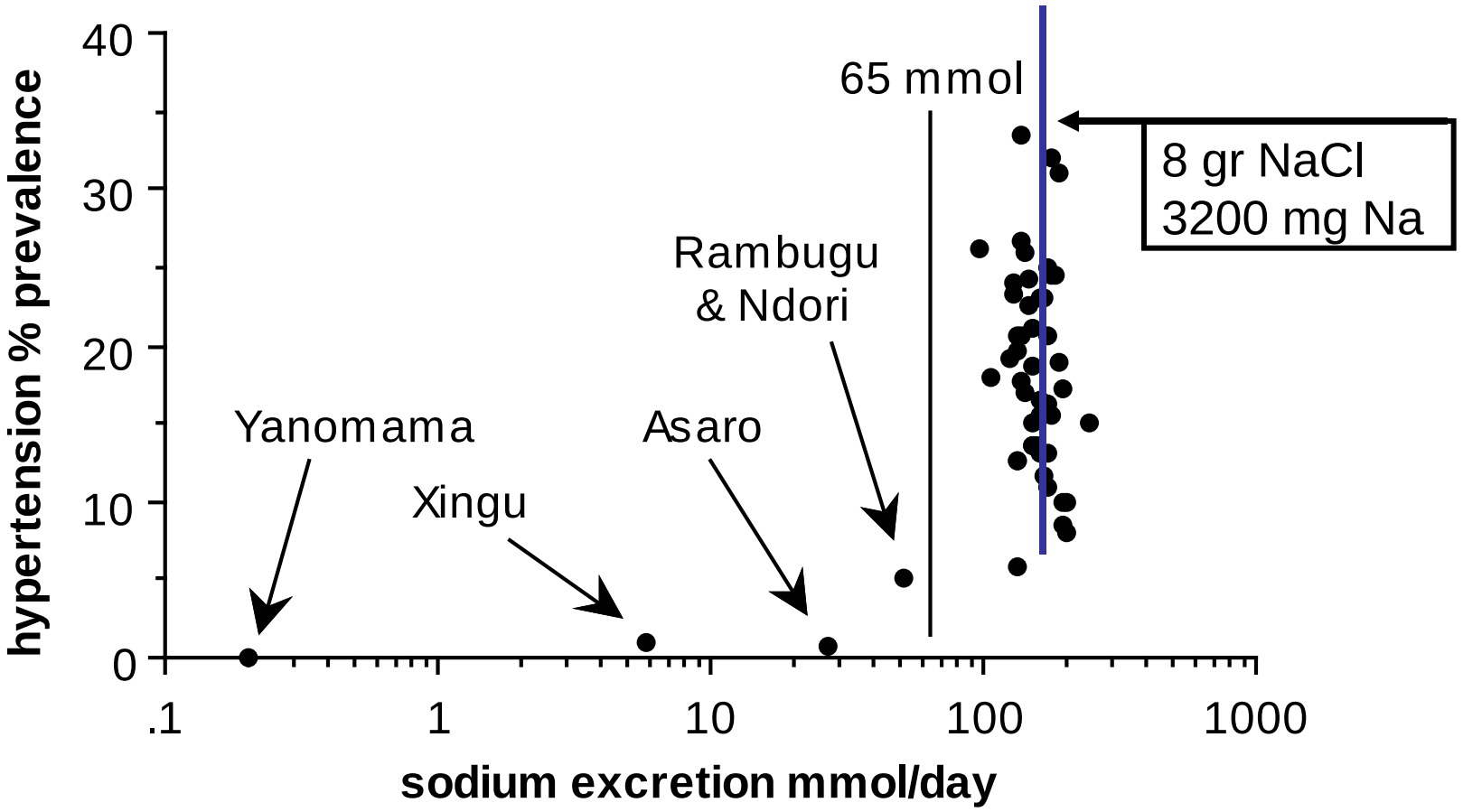
Recommendation of the IOM Committee on Strategies to Reduce Sodium Intake:

FDA set mandatory standards to require food and restaurant industries to gradually reduce the salt content of their products.

Stepwise process for achieving final standards for the addition of salt to foods

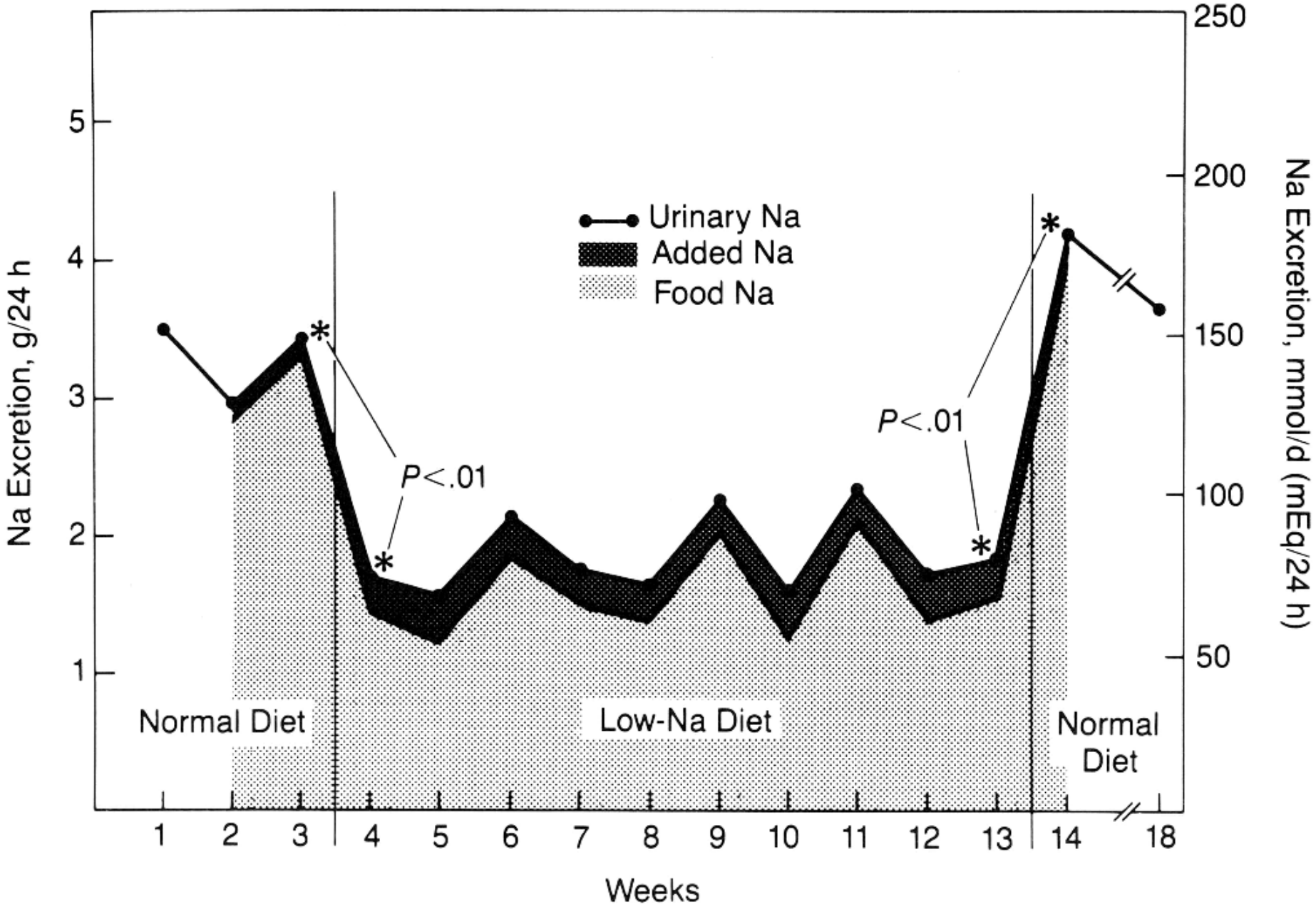


Salt intake across cultures

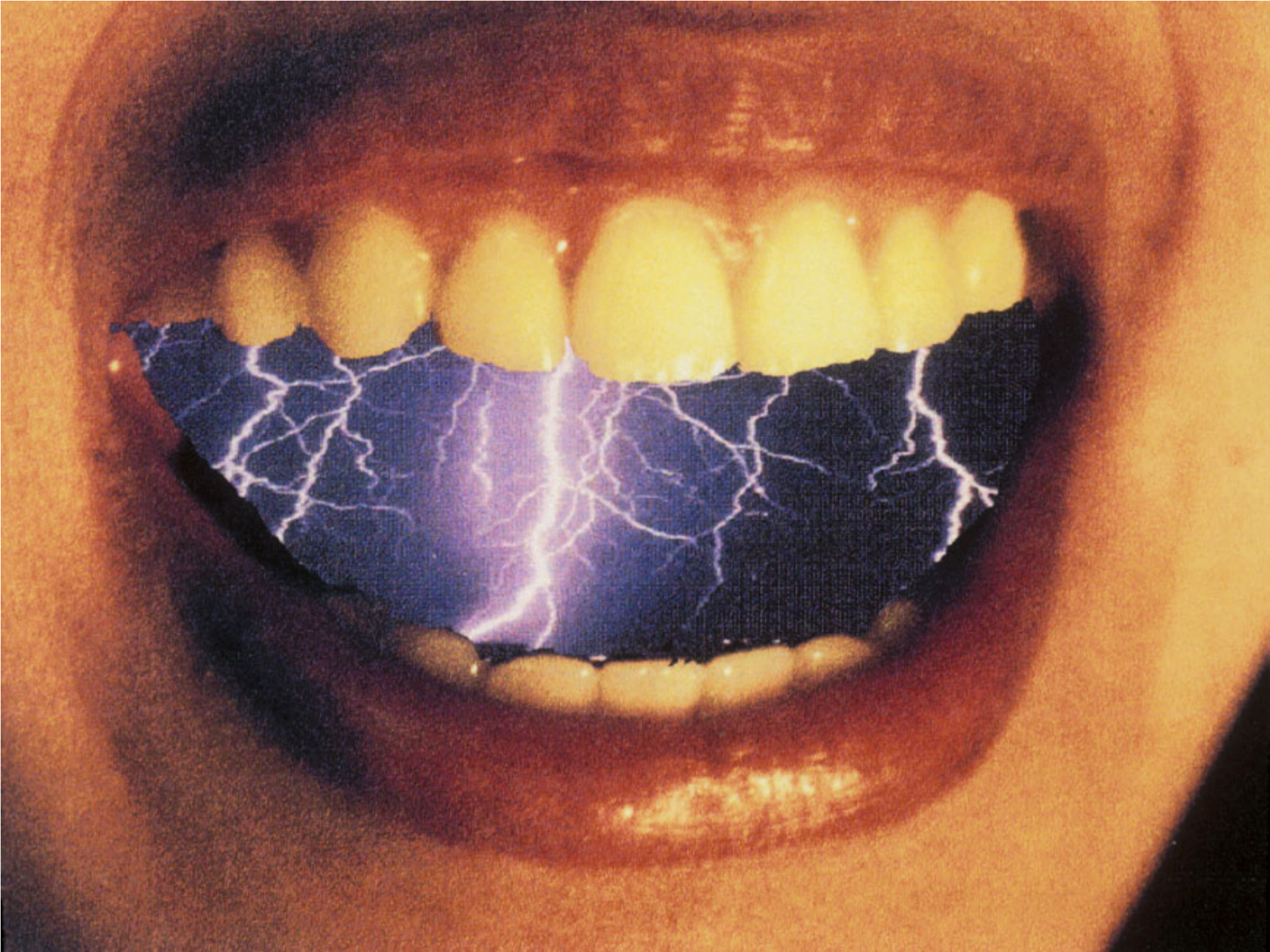


From Beard, 2004

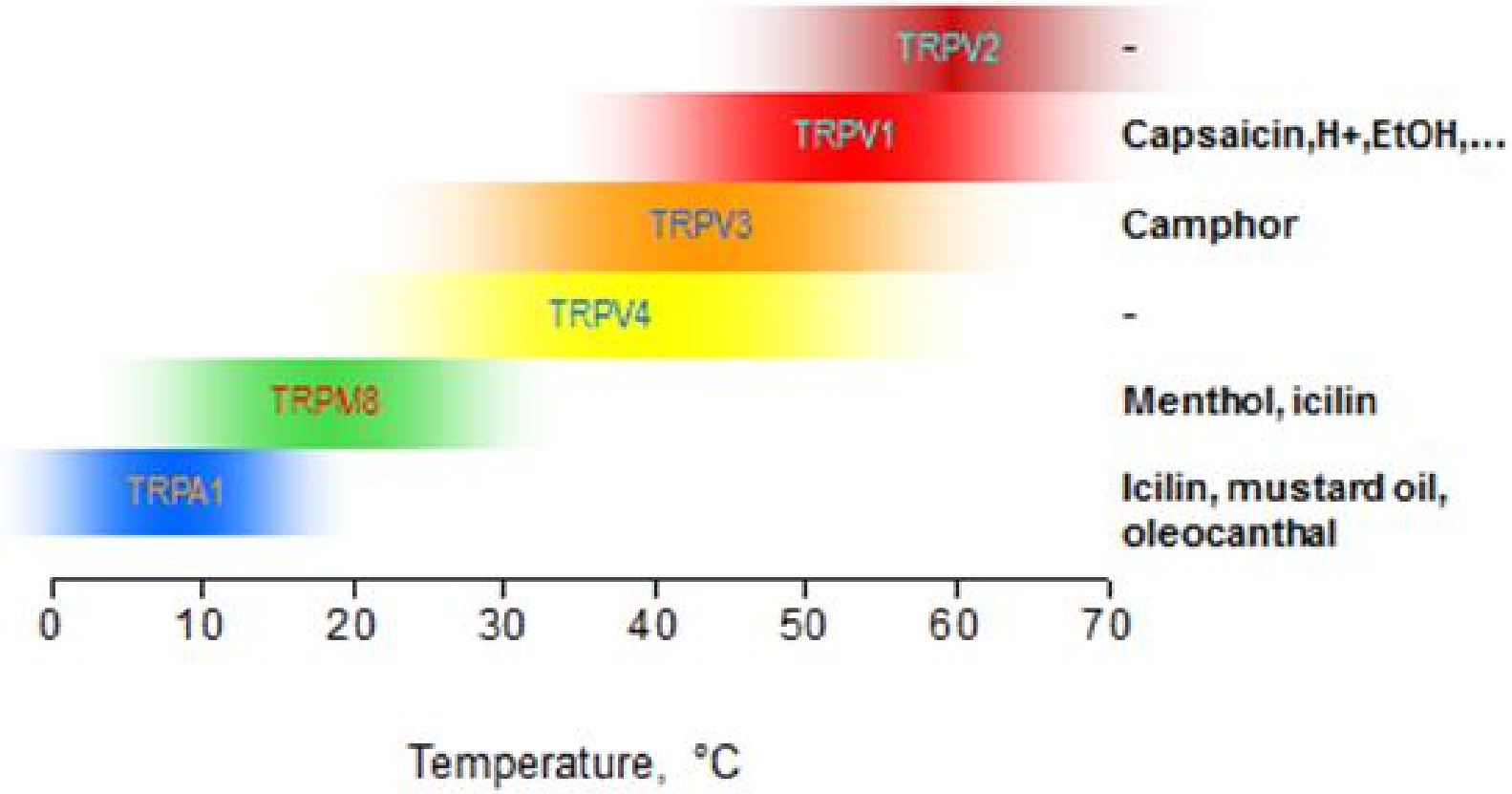
Human adults do not compensate



Beauchamp et al., JAMA



TRP family thermoreceptors are also chemosensitive



Chemesthesis/Irritation

Chemical skin sense

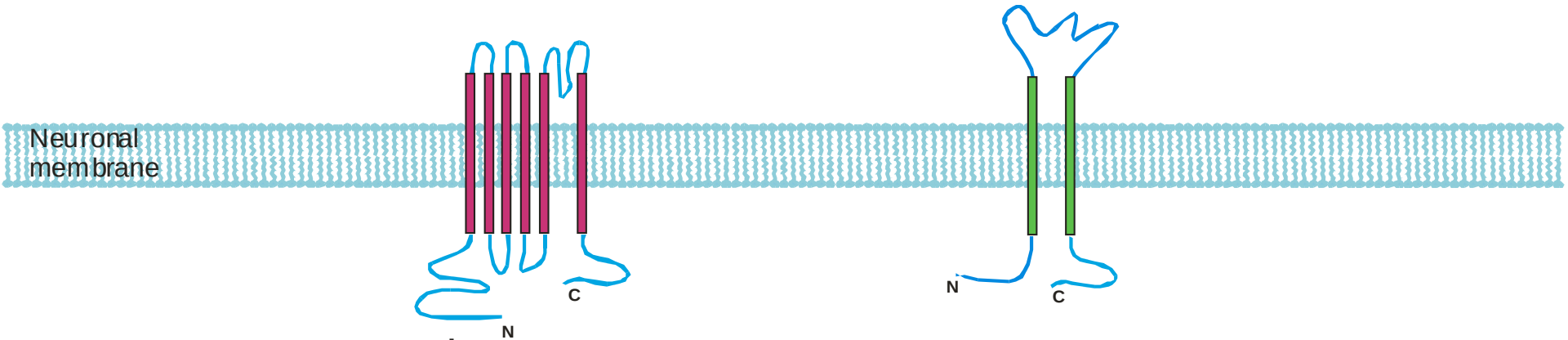
Stimuli: CO_2, menthol, hot peppers

Pain, heat, cooling, tingle, itch etc

Receptors: TRP ion channels - originally discovered as temperature sensitive

Why do people like these in foods and beverages?

The Ion Channels of Nociception



Transient Receptor Potential Channels (TRPs)

Acid - TRPV1
Heat - TRPV1, TRPV2
Cold - TRPA1
Capsaicin - TRPV1
Mustard oil - TRPA1
Membrane stretch - TRPV2

Acid Sensing Ion Channels (ASICs)

Acid - DRASIC

Oleocanthal

Ibuprofen

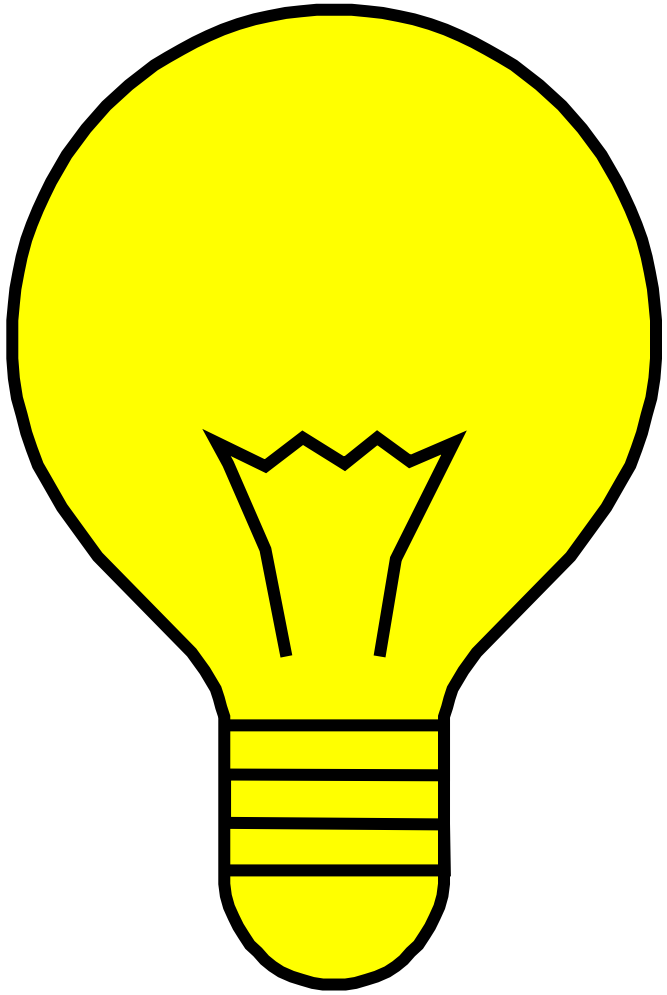
A widely used anti-inflammatory drug

Relieves pain

In some ways mimics aspirin without all of the side effects

Long-term consumption has been reported to reduce the risk of heart disease and some forms of cancer and to delay the onset of Alzheimer's disease

"Tastes bad" – Exclusive throat irritant



Profile sheet used for sensory assessment of olive oil

INTENSITY

PERCEPTION OF DEFECTS:

Fusty ——————————➡

Musty ——————————➡

Winey - Vinegary - Acid - Sour ——————————➡

Muddy sediment ——————————➡

Metallic ——————————➡

Rancid ——————————➡

Others (specify) ——————————➡

PERCEPTION OF POSITIVE ATTRIBUTES:

Fruity ——————————➡

Bitter ——————————➡

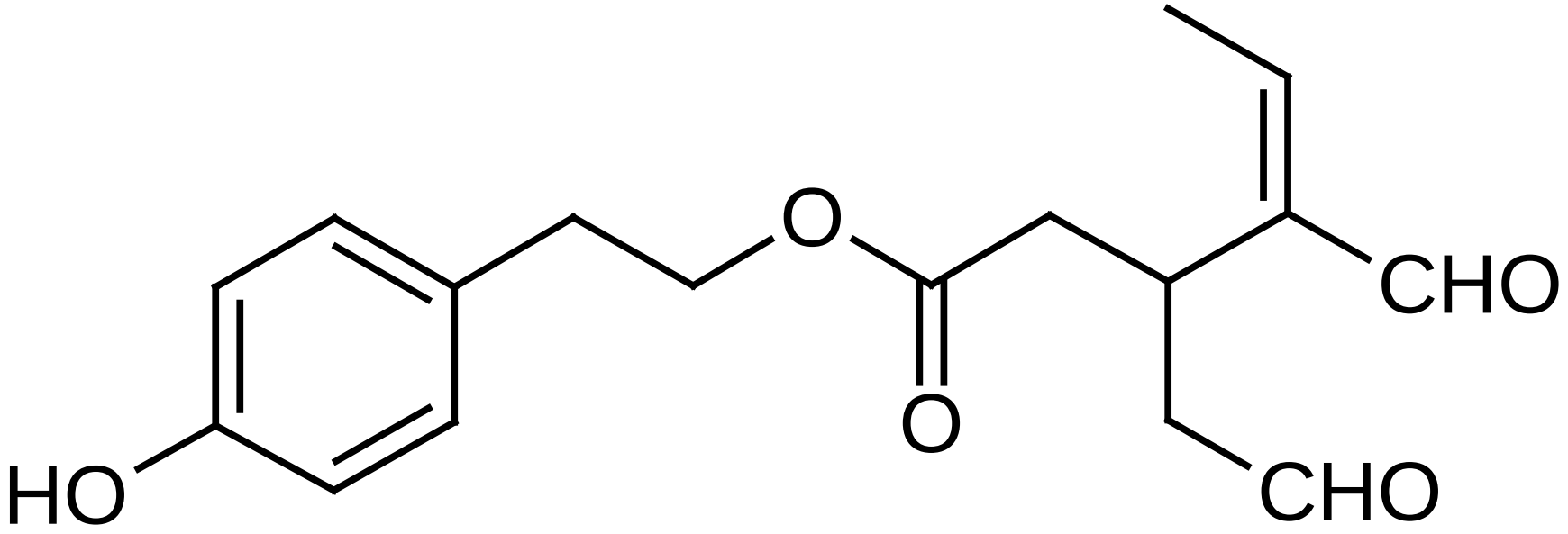
Pungent ——————————➡

Name of taster:

Sample code:
Date:

Throat stinging compound

(-)-decarbomethoxy-dialdehydic ligstroside aglycone



1

Oleocanthal

(oleo = olive; canth = sting; al = aldehyde)

Oleocanthal

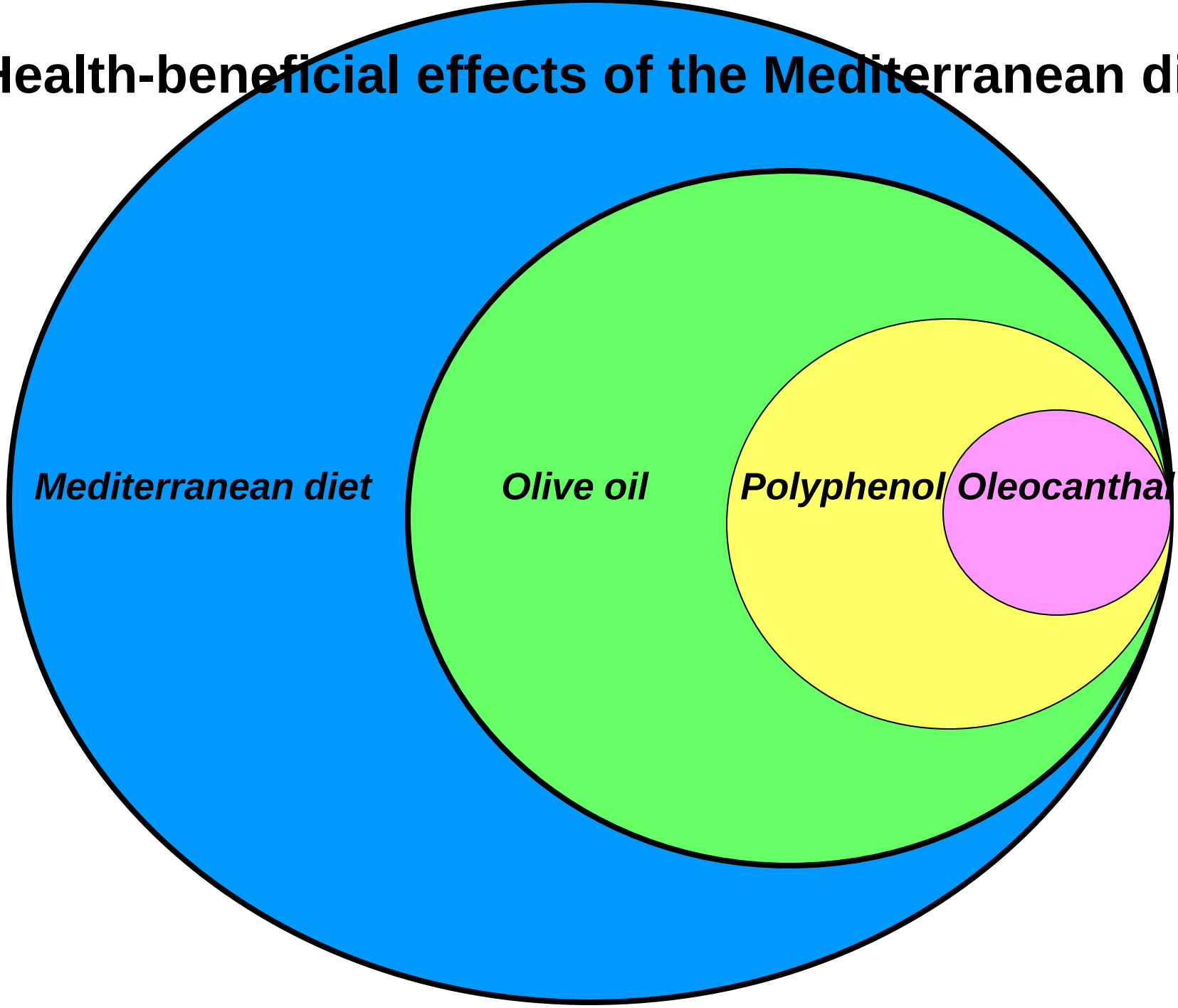
A potent anti-inflammatory compound found in many extra virgin olive oils

Activates receptors in throat only through TRPA1; very specific.

In humans TRPA1 is expressed in throat but not the mouth, hence the specificity

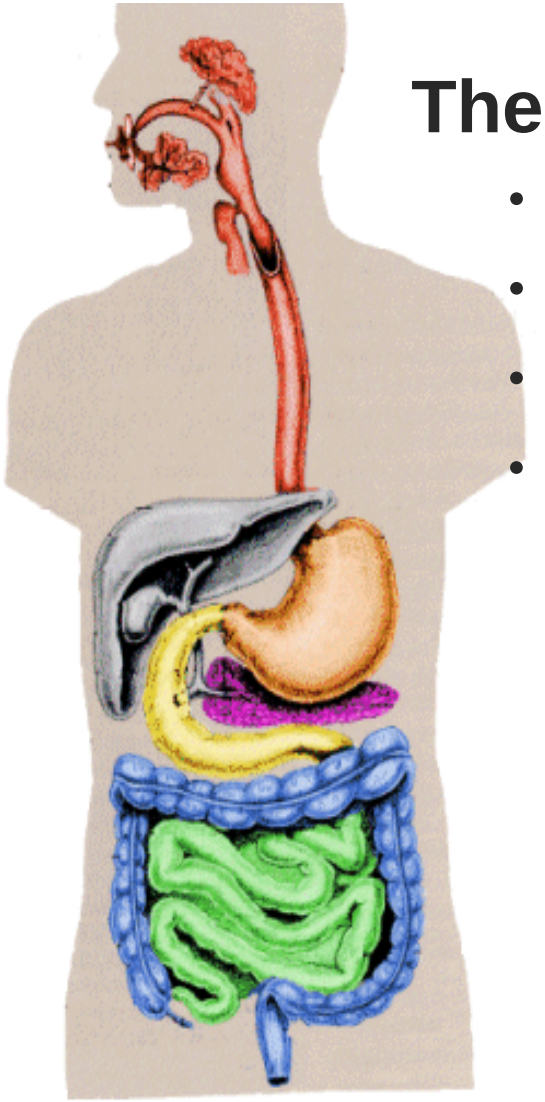
In vitro, is effective against several cancer cell models and pathways involved in Alzheimer’s disease

Health-beneficial effects of the Mediterranean diet



Flavor Expanded: “Taste” throughout the body

The Tongue's Taste Cells are the Initial Chemosensors of the Alimentary Tract

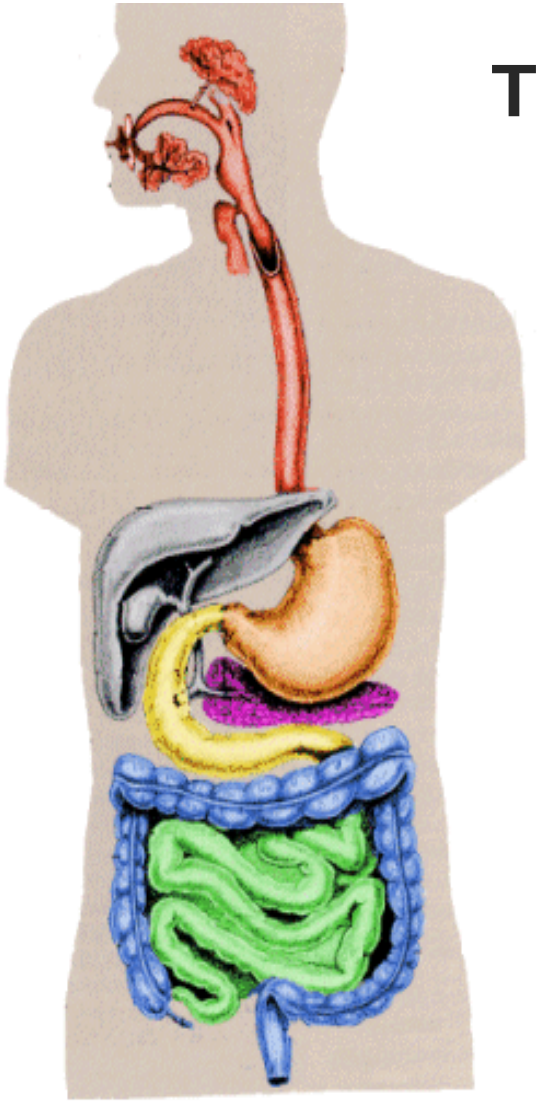


There are also *Taste Cells* in the Gut!

- **Multiple taste signaling proteins are found in the gut**
- **And the pancreas**
- **In specific gut endocrine cells and brush cells**
- **Integrate physiological responses to digestion**

R. Margolskee

The Tongue's Taste Cells are the Initial Chemosensors of the Alimentary Tract



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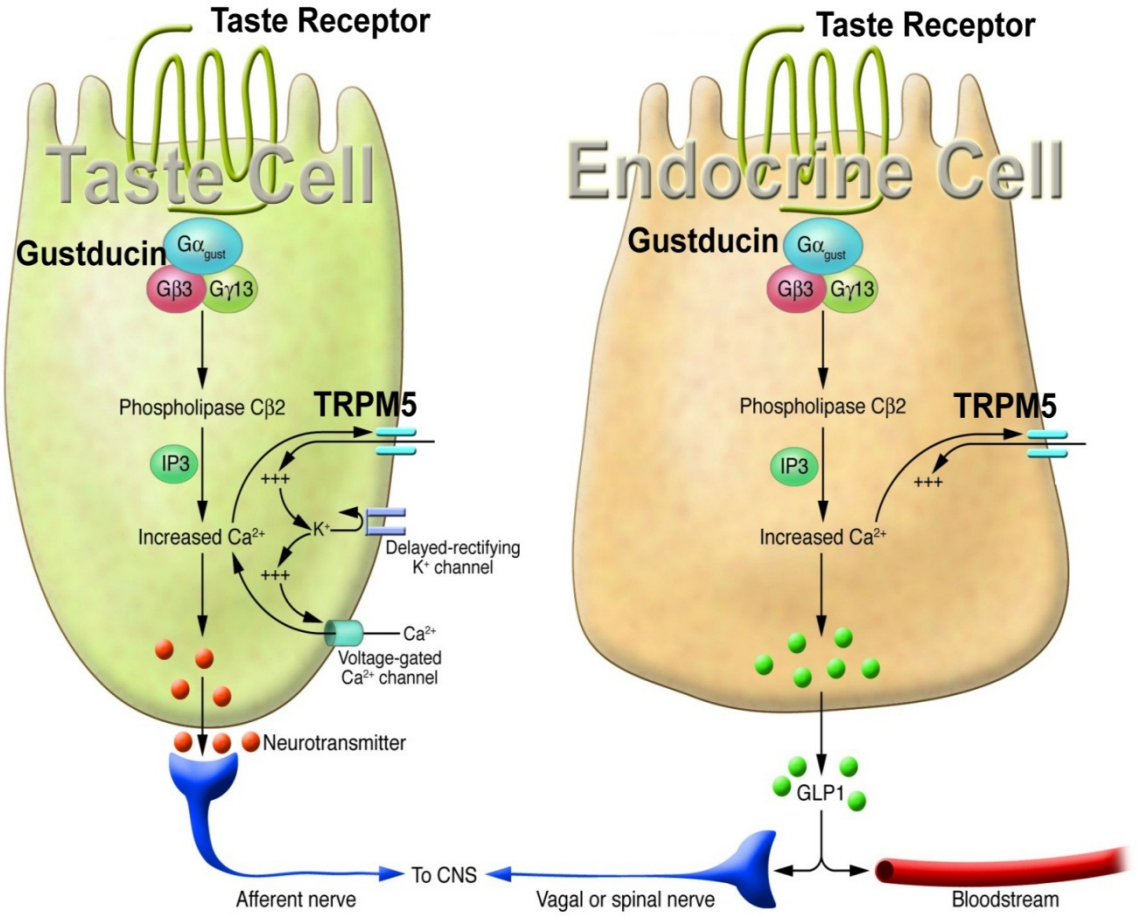
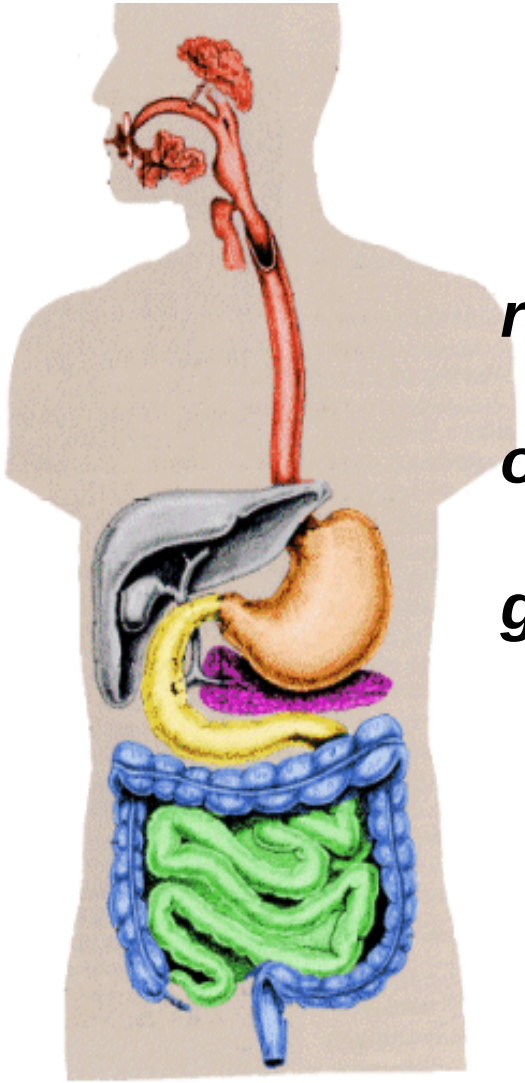


R. Margolskee

Prospects



Targeting gut taste cells

New secretagogues to promote GLP-1 release

Potential new targets for treatment of obesity

Potential new targets for modulating gut motility

Flavor Receptors Elsewhere: Functions?

Bitter taste receptors in the upper nose
Bitter taste receptors in the smooth muscle of the lung
Sweet taste receptors in the brain and pituitary gland

Flavor Receptors Elsewhere: Functions?

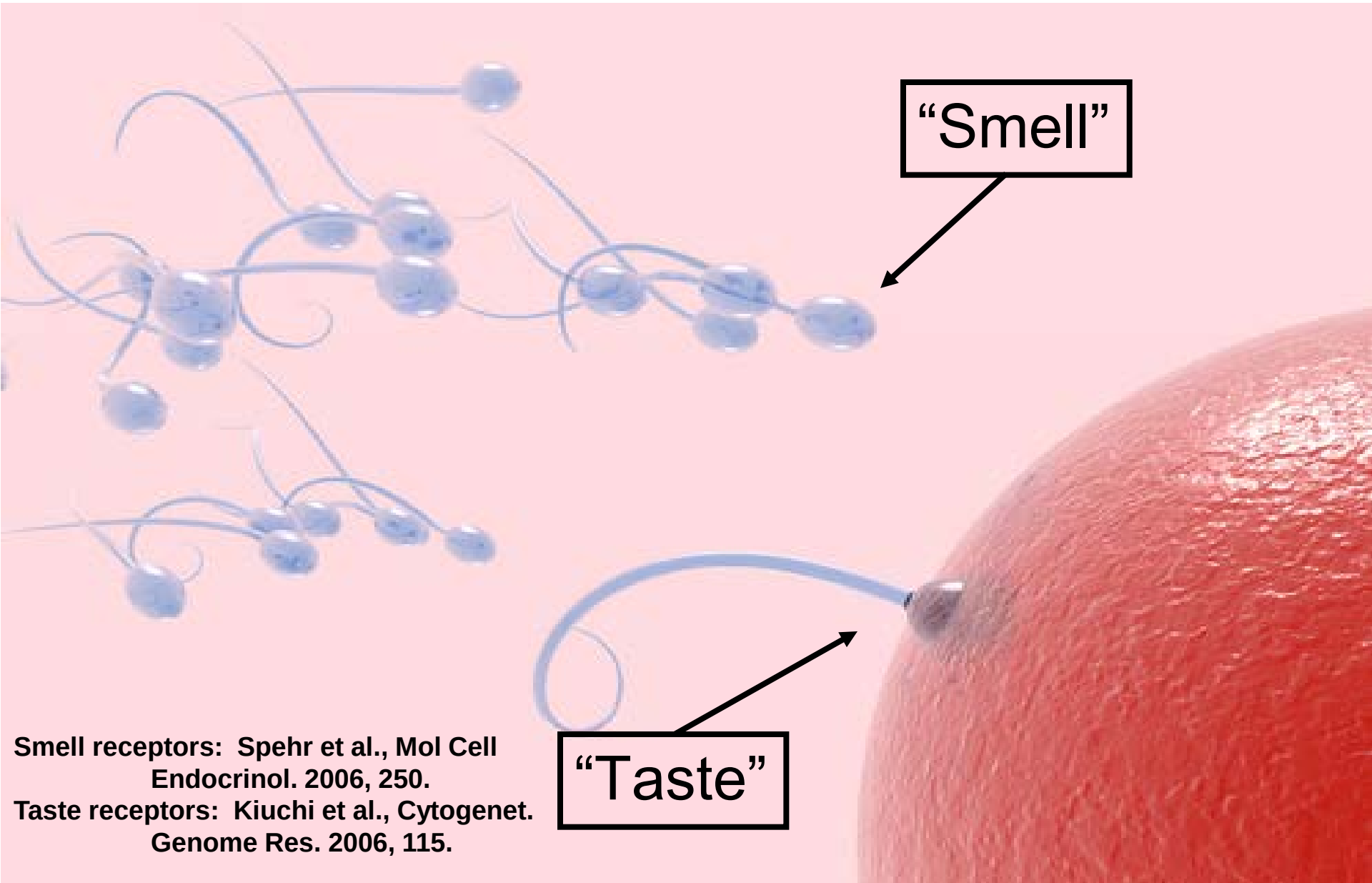
Bitter taste receptors in the upper nose

Bitter taste receptors in the smooth muscle of the lung

Sweet taste receptors in the brain and pituitary gland

Sweet taste and olfactory receptors in sperm

Sperm and egg meet



Smell receptors: Spehr et al., Mol Cell Endocrinol. 2006, 250.
Taste receptors: Kiuchi et al., Cytogenet. Genome Res. 2006, 115.

Some Research Needs

- What is the nutritional importance of genetic variation in flavor receptors?
- What nutritional roles are played by flavor receptors outside the nasal and oral cavities?
- How does genetic variation interact with environmental variation to influence nutritional phenotyes?
- Are epigenetic modifications in flavor receptors of nutritional significance?
- How can our new and growing knowledge of flavor perception mechanisms and functions be translated into practical applications to reduce incidence and consequence of human diseases?

Thank you

Monell Chemical Senses Center

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