The Shake on Salt

What We Know About Salty Taste and What We Don't

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Monell Chemical Senses Center

AMSA 66th RMC

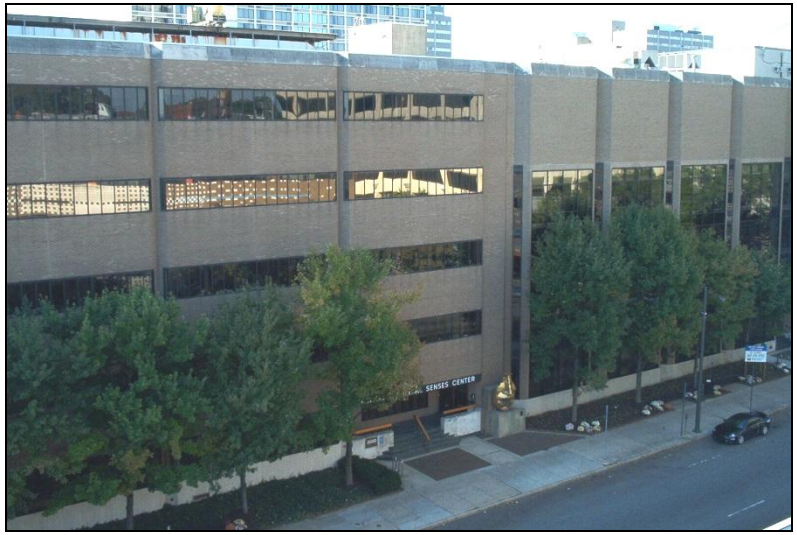
June 17, 2013

Monell Center

Monell is the world's only independent, non-profit scientific institute dedicated to basic research on taste and smell.

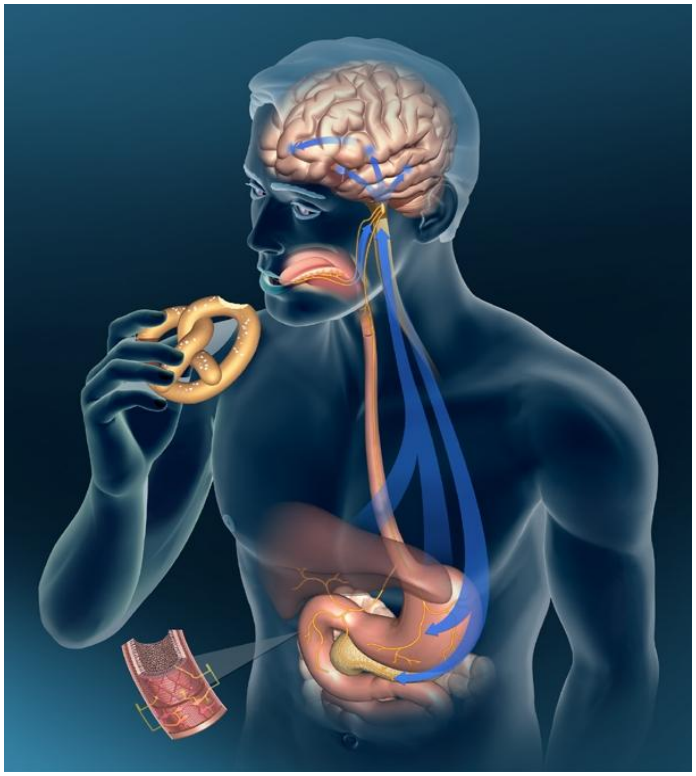
Located in Philadelphia, Monellr was founded in 1968.

Scientists from many disciplines work together to focus on understanding the mechanisms and functions of taste, smell and chemisthesis.




MONELL CHEMICAL SENSES CENTER
3500

Chemical Sense: Taste



Receptors for conscious taste perception

are located in the oral cavity:

Salt (NaCl), sweet, sour, bitter, umami, others?

Sodium is Necessary for Life

- Blood volume
- Blood pressure regulation
- Nerve transmission
- Digestion
- pH regulation

HotForWords

SALARY

Today, it seems crazy to pay someone in salt.

But what if we told you that **SALT** is very closely related to the word **"SALARY"**?

In Latin, the word "sal" means salt, which was a widely used and **extremely valuable food preservative** in ancient Rome. Remember: This is before there were refrigerators.

It was so valuable that wars were fought over it, and Roman soldiers were actually paid in salt.

Over time, the system changed, and soldiers were instead given a *"salarium,"* which meant an allowance for buying salt.

The word took on a more general meaning of **"regular fixed payment for work done"** and evolved into the Anglo-French word **"salarie"** in the late 13th century. Eventually, this turned into the English word **"salary."**

13TH

Bankrate.com

Too much?

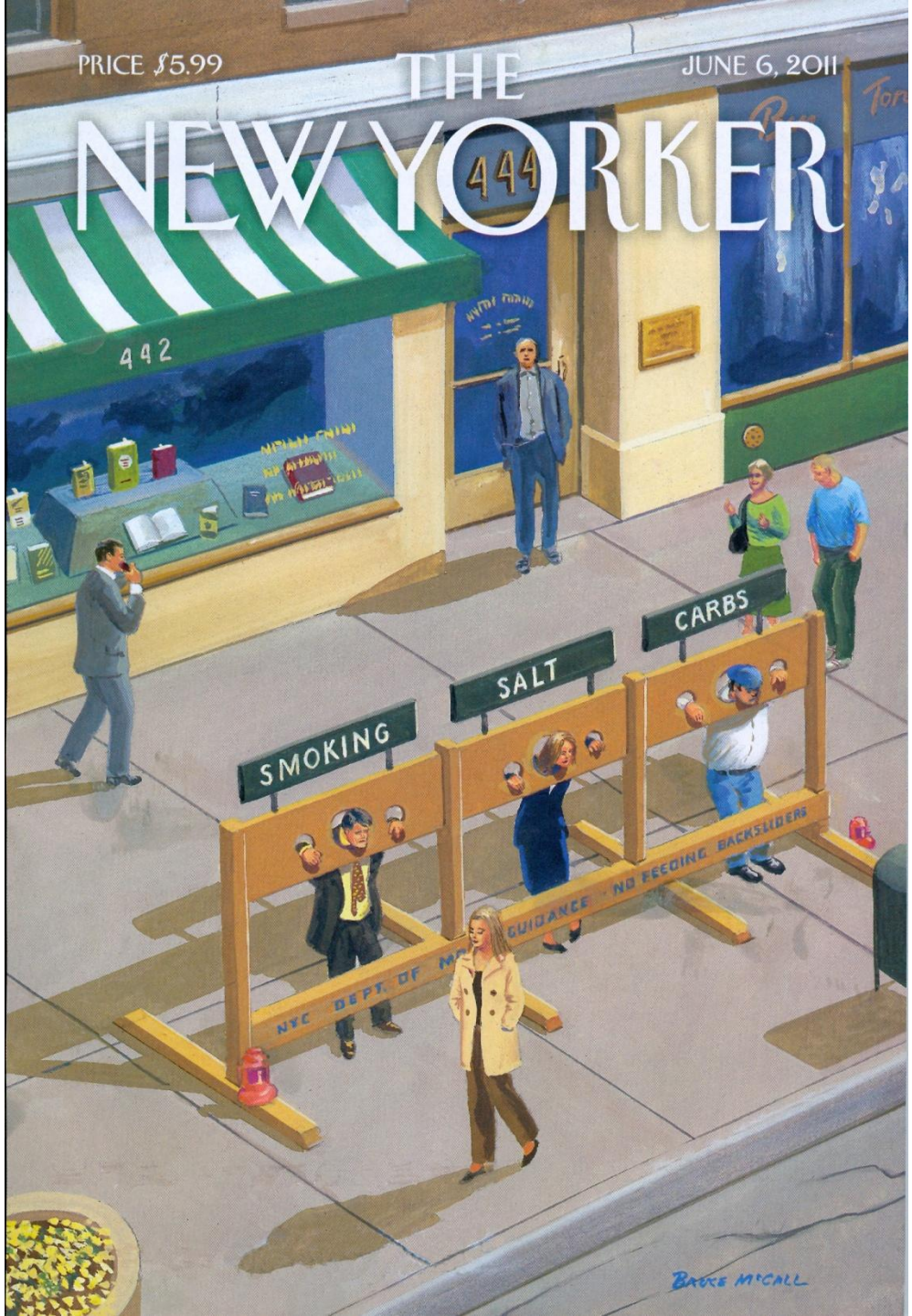
The Problem: Public Health

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.

PRICE $5.99

THE NEW YORKER

JUNE 6, 2011



RECOMMENDATIONS TO REDUCE SALT INTAKE

- 1969: Initial statement from US government

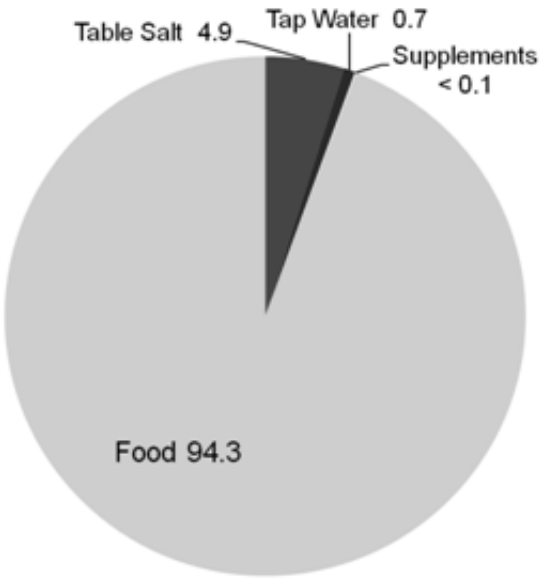
  First: at risk populations

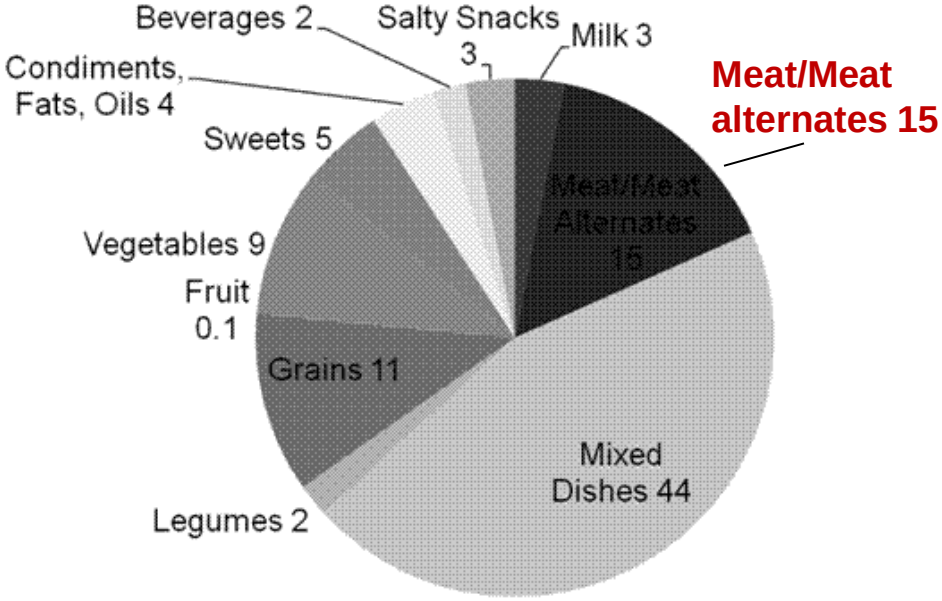
  Later: all U.S. population

- 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





SALT IS A *MAGIC INGREDIENT* IN FOOD

** Statistically significant at the 99% level of confidence.

M. Gillette

APPROACHES & KNOWLEDGE NEEDED TO REDUCE SALT INTAKE

1. <u>Change the Receptor</u>

   Physiology: How does salty taste work?

   Don't Know, but We're Getting Closer…

2. <u>Change the Person</u>

   Psychology: Why do we like salty taste?

   It Tastes GOOD!!!

TASTE PHYSIOLOGY:

1) How Does Taste Work?

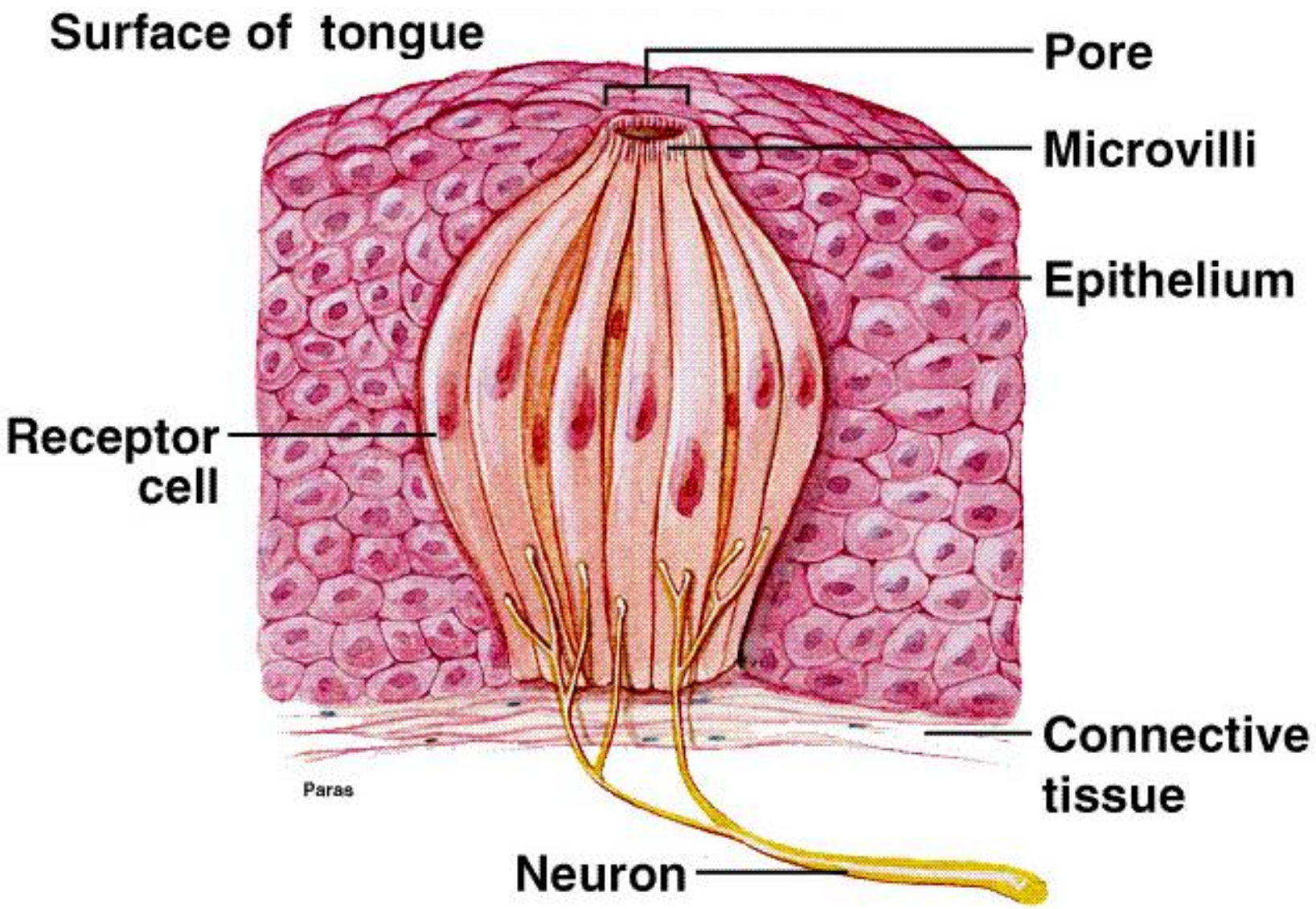
An Overview: Taste Physiology 101

TASTE: Last stop before ingestion

Taste qualities evolved for fundamental nutritional reasons

- **POSITIVE**
  - **Sweet** - sugars, high intensity sweeteners: **Calories?**
  - **Salty** - NaCl, LiCl: **Sodium, minerals?**
  - **Umami** - Glutamate, aspartate, nucleotides: **Protein?**
- **NEGATIVE**
  - **Sour** - acids: **Ripeness?**
  - **Bitter** - Alkaloids, peptides, toxins: **Poison avoidance?**
- **OTHERS?**

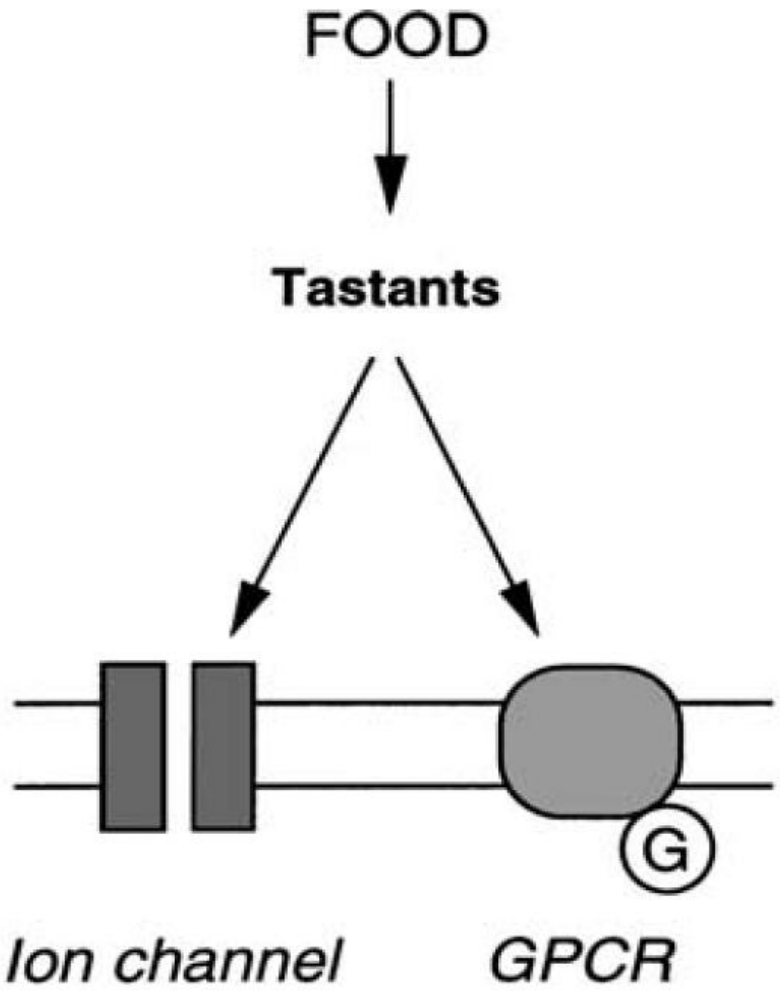
TASTE BUD


Surface of tongue
Pore
Microvilli
Epithelium
Receptor cell
Connective tissue
Neuron
Paras

TASTE QUALITIES & TASTE RECEPTORS

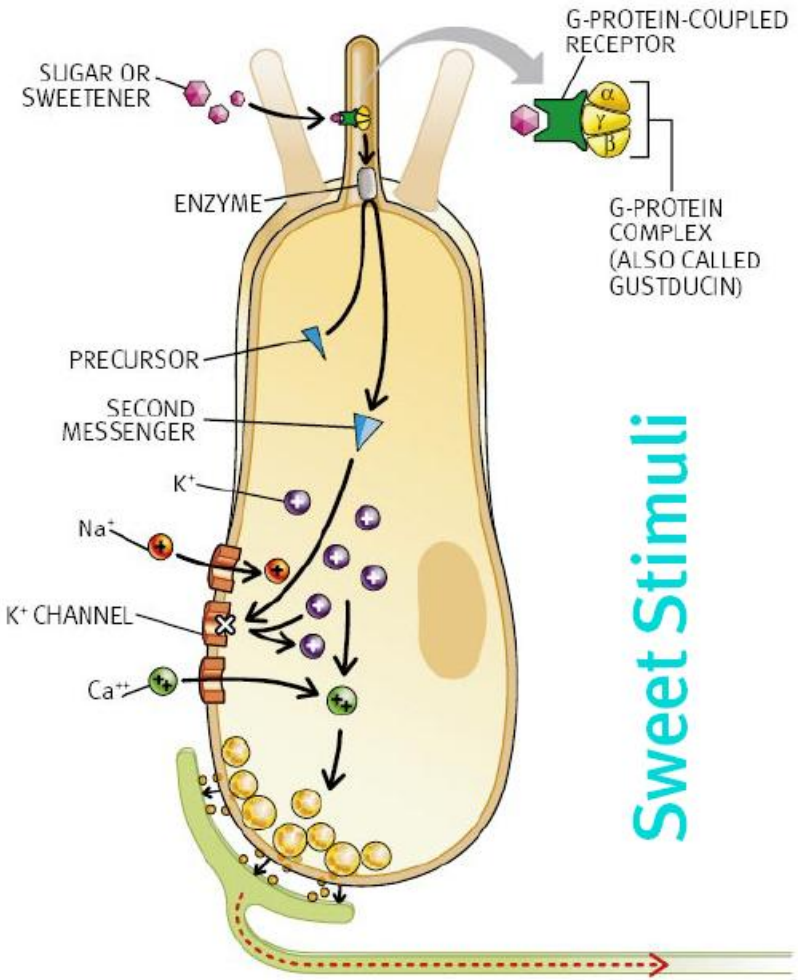
Taste qualities:	Taste ligands:	Taste receptors:	Taste nerves	Brain
Sweet	Sweeteners	Sweet receptor		
Umami	MSG, nucleotides	Umami receptor		
Bitter	Bitter compounds	Bitter receptor		
Salty	Sodium	Salty receptor		
Sour	Acid	Sour receptor		

TWO MAJOR TYPES OF TASTE RECEPTORS



Bigiani et al., 2003

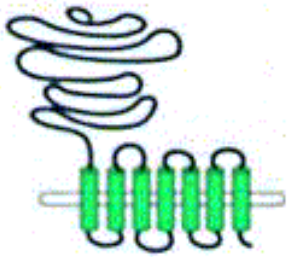
GPCR RECEPTOR ACTIVATES G-PROTEIN & INTRACELLULAR CASCADE



Smith and Margolskee, 2001

G PROTEIN-COUPLED TASTE RECEPTORS

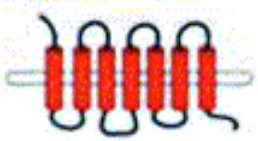
T1R: Sweet, umami



1 sweet receptor (T1R2 + T1R3)

1 umami receptor (T1R1 + T1R3)

T2R : Bitter



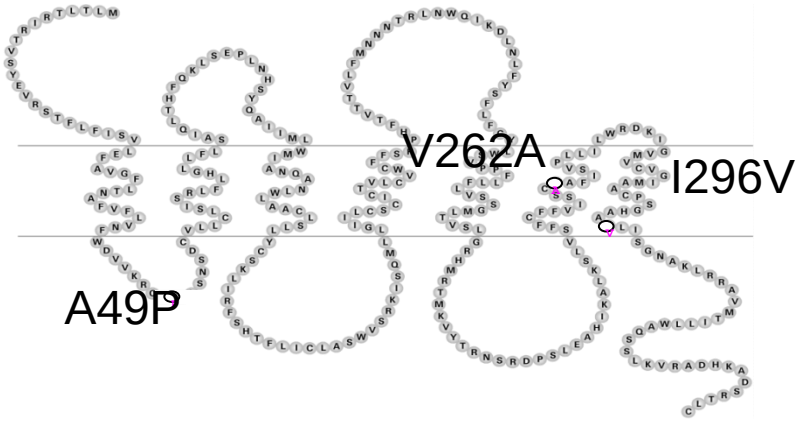
~25 bitter receptors

GPCR: RECEPTOR VARIATION UNDERLIES DIFFERENCES IN BITTER TASTE PERCEPTION

- ~ 25 different bitter receptor genes
- variations in a single bitter receptor gene can code for different taste receptors
- each receptor is differentially sensitive to distinct bitter taste compounds
- because each gene can code for multiple receptors with differing sensitivities
- there may be hundreds of different bitter taste receptors in the human population as a whole

- leading to <u>wide individual variation</u> in perception of bitterness

Alleles Of Tas2r38 Are Associated With Sensitivity To Bitter Compounds (PTC And PROP)



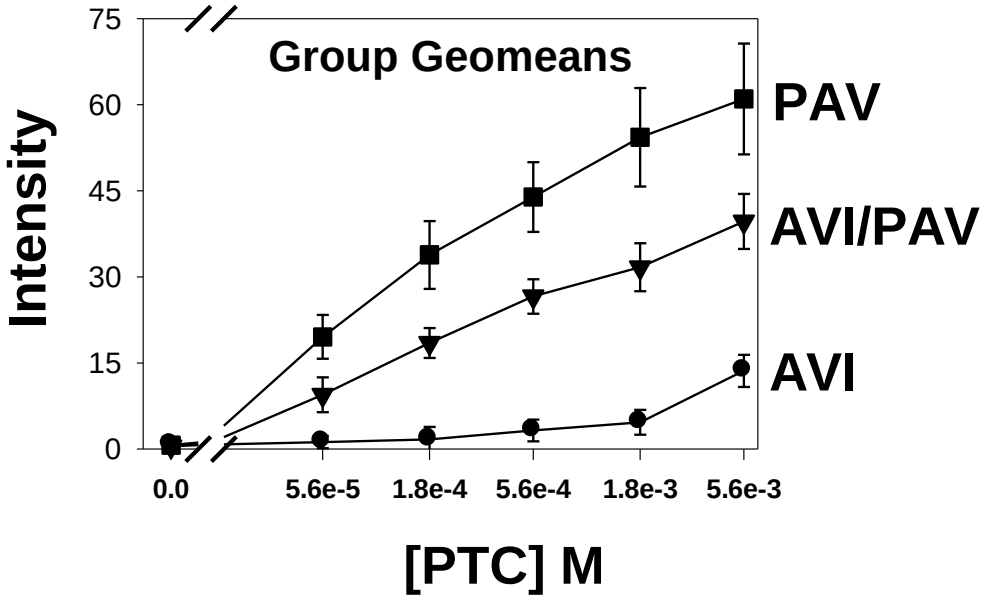
A	A	P	A	P	P
V	V	A	V	A	A
I	I	V	I	V	V

Human TAS2R38 haplotypes

P-A-V	**Tasters**
A-V-I	**Non-tasters**

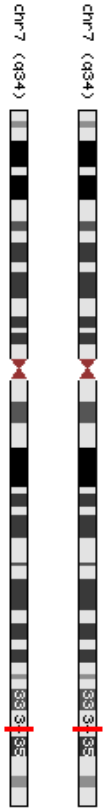
We use the terms *tasters* and *non-tasters* as a short-hand term. Most non-tasters can taste PTC or PROP if the concentration is high enough.

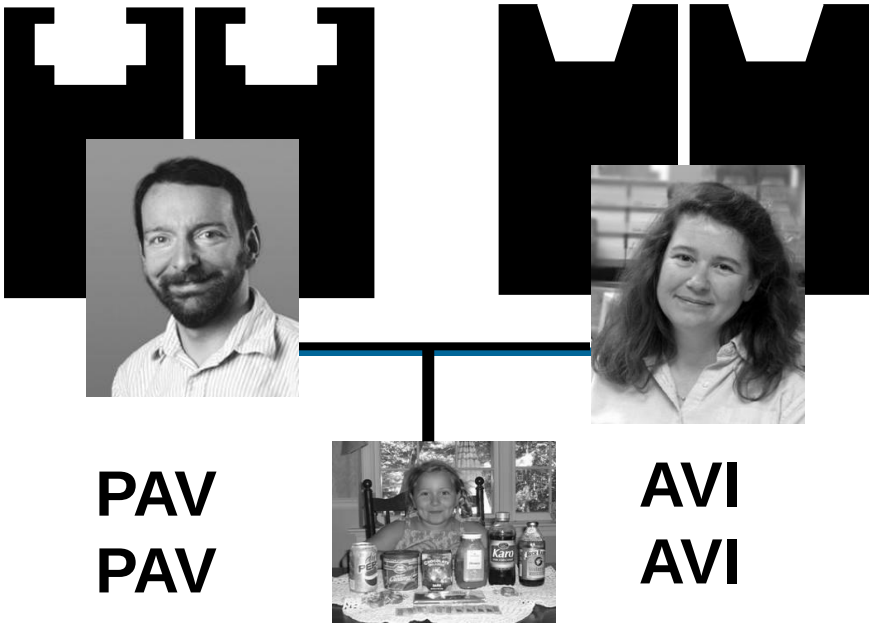
Bitter Taste Perception Is A Function Of Tas2r38 Alleles



Bitter Taste Sensitivity Is Genetically-Transmitted:

Family Inheritance





PAV=taster, AVI non-taster; PAV is dominant

TASTE QUALITIES AND TASTE RECEPTORS

Taste qualities:	Taste ligands:	Taste receptors:	Taste nerves	Brain
Sweet	Sweeteners	**T1R2+T1R3**		
Umami	MSG, nucleotides	**T1R1+T1R3**		
Bitter	Bitter compounds	**Multiple T2Rs**		
Salty	Sodium	Salty receptor??		
Sour	Acid	Sour receptor		

TASTE PHYSIOLOGY

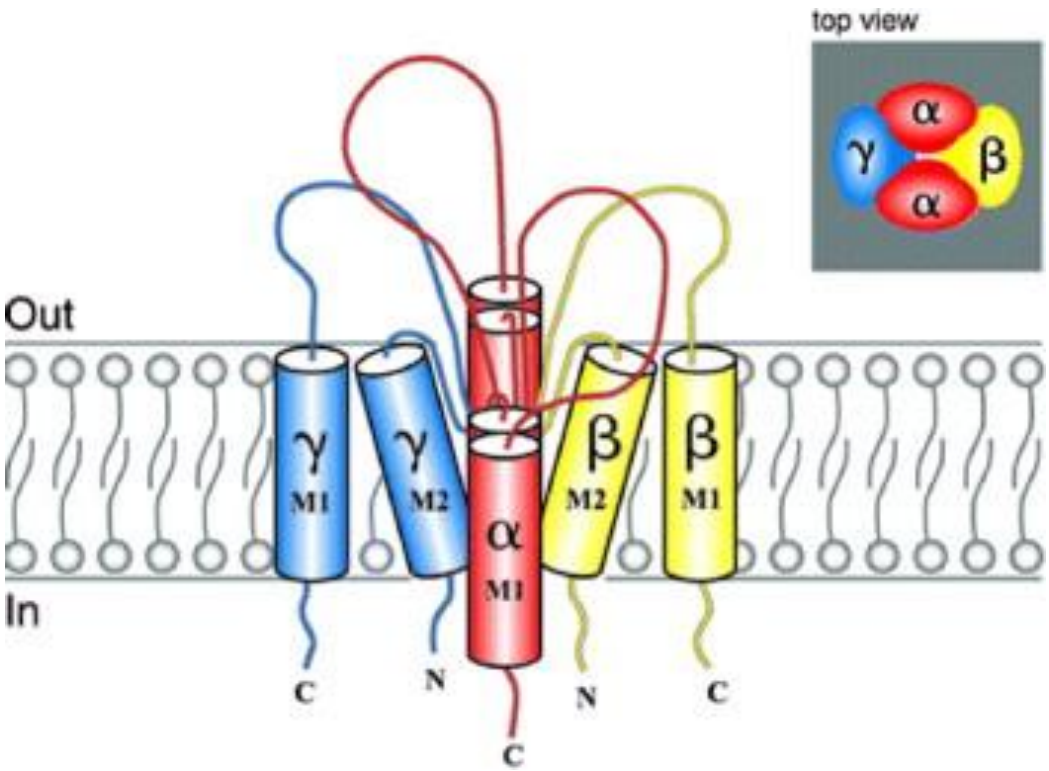
2) How Does Salty Taste Work?

Salty Taste Mechanisms
New Information and Remaining Puzzles

- Stimulus specificity:
  - NaCl and LiCl only purely salty substances known
  - Suggests a highly specific mechanism

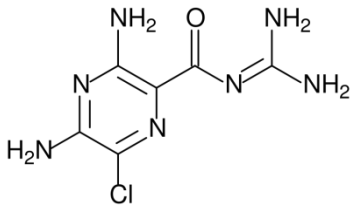
- Animal models:
  - In 2010, two research groups (Chandrashekar et al., Bosak et al) proved that one component of the salt receptor mechanism involves an epithelial Na channel (**ENaC**)

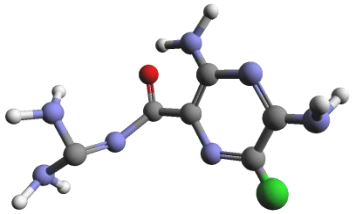
ENaC



- Heteromer consisting of several different subunits
- Each subunit has two transmembrane domains and is encoded by a separate gene

Amiloride





- Potassium-sparing diuretic, used in management of hypertension and congestive heart failure
- Partially inhibits the response to salty taste
- Primary target is ENaC, but also interacts with other biological molecules

ENaC hypothesis

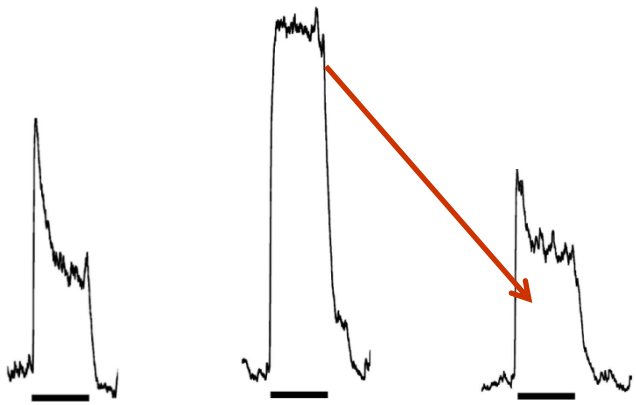
Facts: Amiloride blocks ENaC Amiloride blocks NaCl taste

Hypothesis: ENaC is a NaCl taste receptor

Proof: ENaC disruption must block NaCl taste

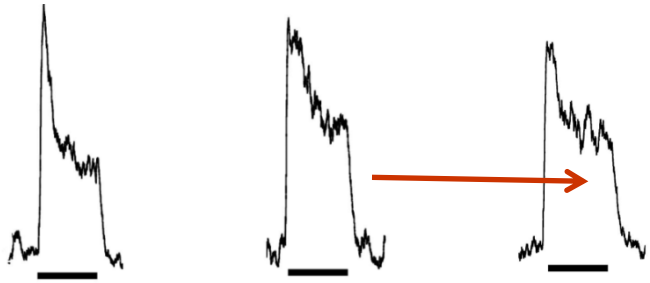
Taste nerve electrophysiology
NaCl: Sample chorda tympani recordings

Control



0.1 M NH4Cl 300 mM NaCl 300 mM NaCl+Amiloride

ENaC-KO



0.1 M NH4Cl 300 mM NaCl 300 mM NaCl+Amiloride

1. ENaC knockout mice have diminished neural taste responses to NaCl
2. Amiloride inhibits NaCl response in control but not in ENaC knockout mice

Bosak et al, 2010

Taste Nerve Electrophysiology Summary: Effects of ENaC Deletion

- Removing ENaC from the tongue selectively affects the amiloride-sensitive component of taste nerve responses to sodium.

- Without ENaC - response to sodium blunted, <u>but</u> not abolished

- ENaC responsible for a portion of salty taste transmission

Bosak et al, 2010

IMPLICATIONS FOR SALT SUBSTITUTE

Fact:

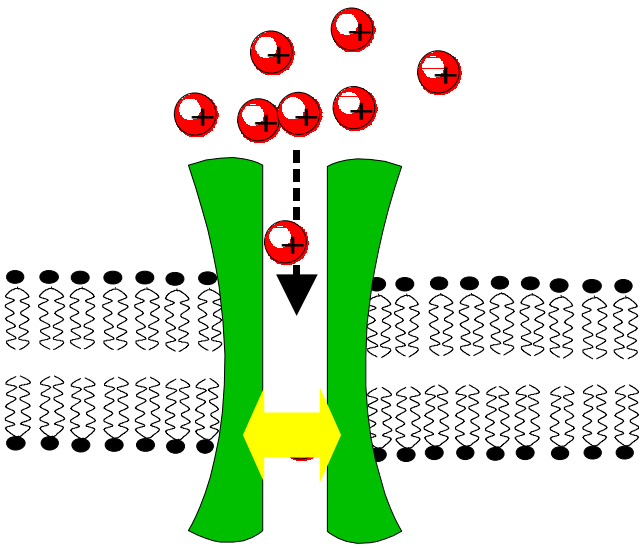
- One component of salt receptor is an ENaC

Problem:

- Specificity of Na+ channel

A potential alternative:

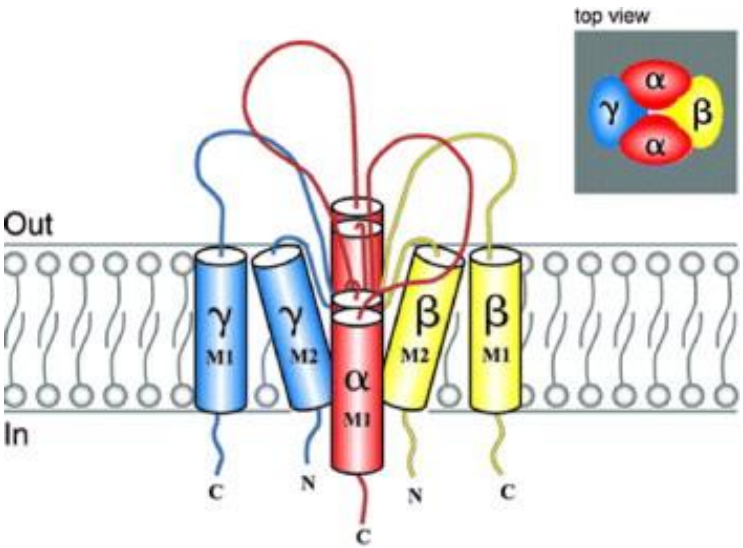
- Salt enhancers – many examples described in the literature



Major Problem to ENaC Hypothesis: Humans Not Sensitive to Amiloride

- Could humans have a different salt taste mechanism than rodents?
- How can this species difference be explained?
- Active area of study at Monell, one of few institutions in the world with the ability to work with human taste tissue.

ENaC Subunits: Species Differences



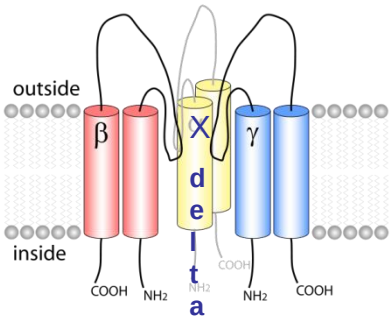
- α, β, γ (rodents)
- δ, β, γ (humans)

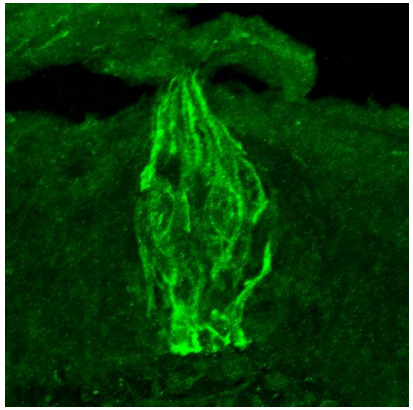
Salty Taste Enhancers: Things to Ponder

- If an ENaC is part of the salty taste transduction process, how do we enhance its activity without enhancing activity of other ENaC's in the body?

- A potential clue: The ENaC of human fungiform taste bud are composed of the heterotrimer delta: beta: gamma, whereas most epithelial tissues use alpha: beta: gamma.

- Hence: Design an enhancer that selectively targets only the delta component of the taste bud ENaC.





Human taste bud labeled by an antibody to human ENaC delta

-- Courtesy of Joe Brand

Beyond ENaC: Implications for programs seeking to reduce salt intake

1. A second less specific salt taste mechanism also exists. Candidate salty taste receptors currently being explored include other ion channels: TRPV1, TRPML3 and Kv3.2

2. May account for several of the other taste attributes of salt such as mouthfeel, body, and “enhanced flavor”

3. We must identify this mechanism to help develop fully functional salt replacers or enhancers

PSYCHOLOGY

Why Do We Like Salty Taste?

Can We Decrease Liking for Salt?

Why Do We Like Salty Taste?

Innate factors

Genes?

Individual experiences

- Early development: Pre- and early post-natal events
- Learning during development: the role of context
- Habit

Sensory enhancement

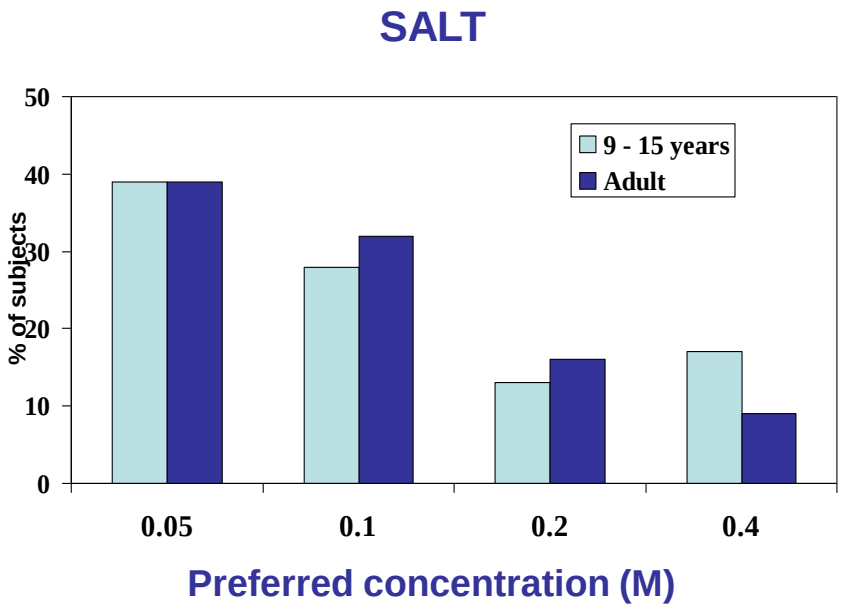
A Biological Imperative:
SALT TASTES GOOD

- Sodium essential for life
- Positive hedonic response ensures adequate consumption
- *Variability* in hedonic response

KIDS AND ADULTS LIVE IN DIFFERENT SENSORY WORLDS

Sweet, salt and savory tastes:

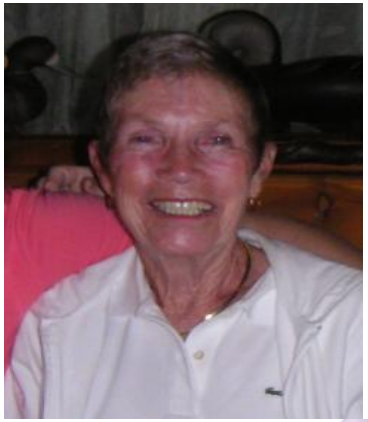
- Children prefer higher levels than adults
- Evident in food selection (eg,cereals & candies)
- Declines evident in late adolescence



Desor et al, 1975

Case History:
How The Stein Girls Like Their Margaritas…

MOM



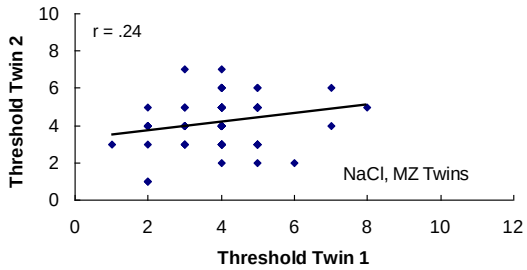
DAUGHTER #1

DAUGHTER #2

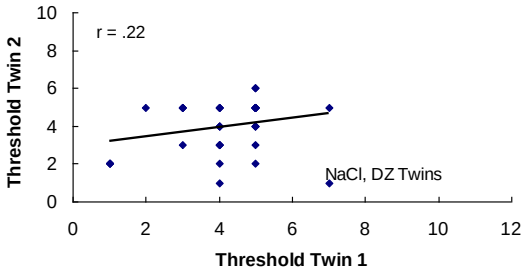
What accounts for individual differences in salty taste perception?

- Genetics???

IDENTICAL



FRATERNAL

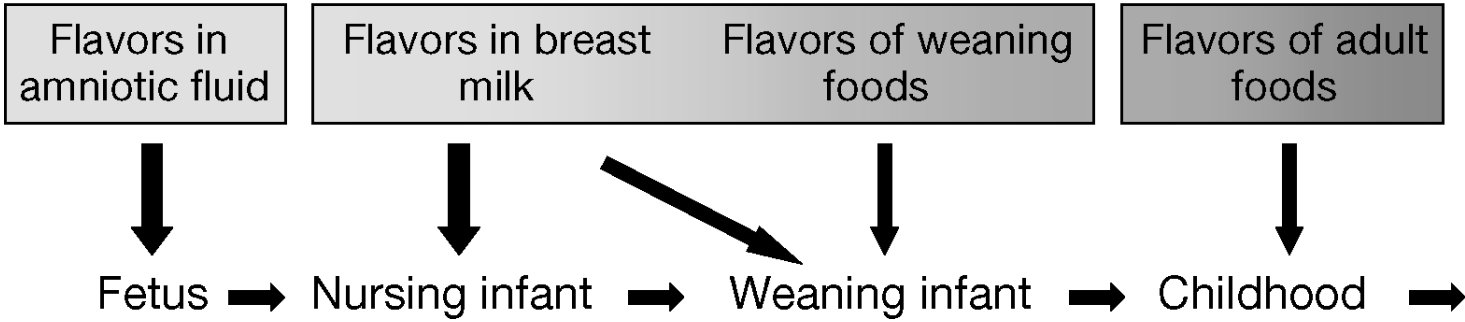


Wise et al., 2007

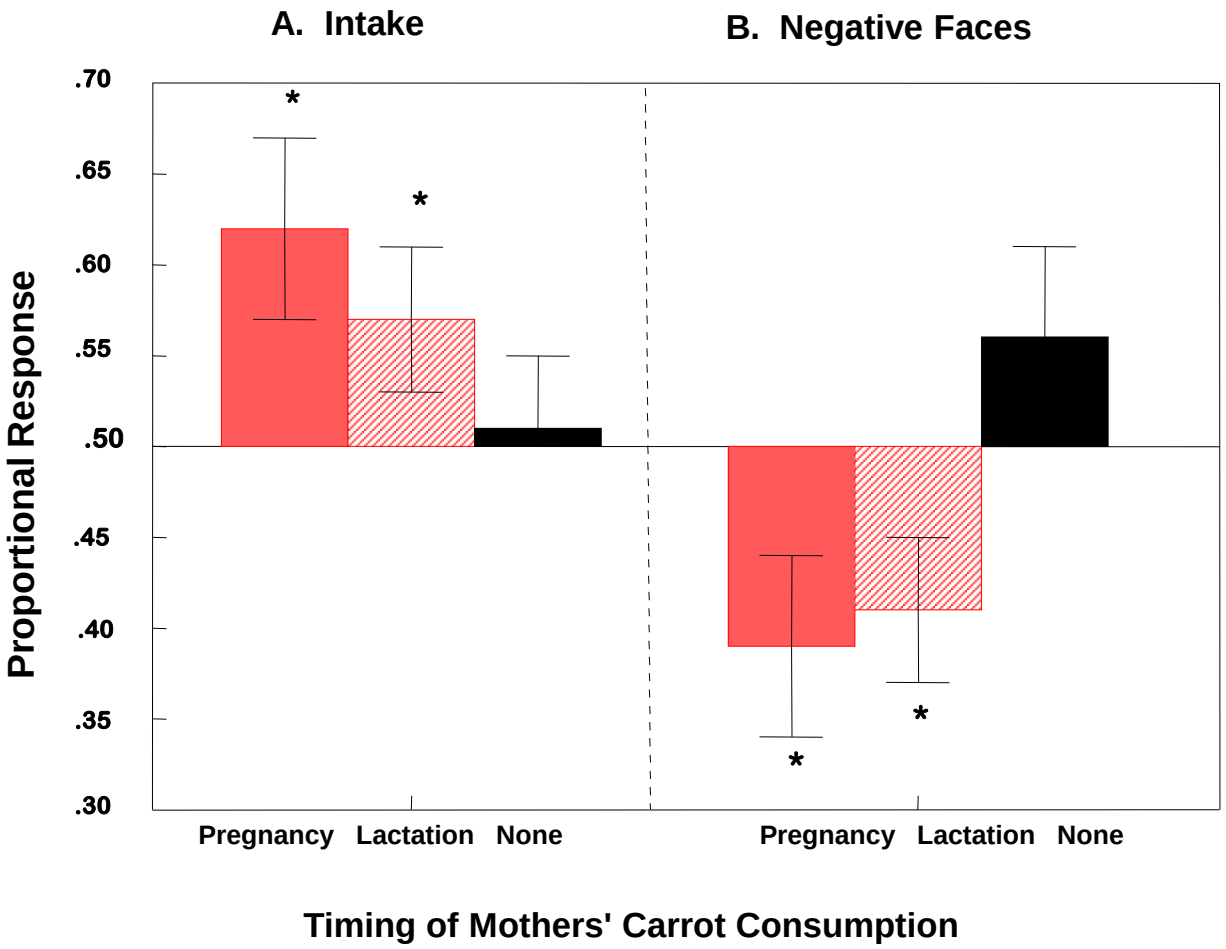
- Environmental/Experiential differences -- may start before birth

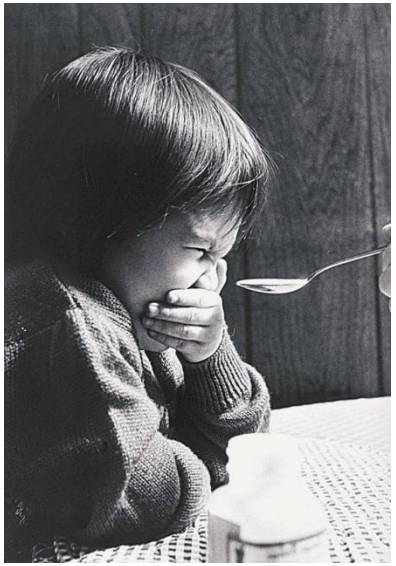
Salt Preferences

Impact points of early experience in development of flavor preferences



Sensitive Periods for Flavor Learning





Mennella, Jagnow, Beauchamp. *Pediatrics*. 2001;107: e88.

Developmental Appearance of Salty Taste Acceptance

- Newborns indifferent to salty taste
- Contrast to innate responses to sweet, bitter, and sour
- Reflect immature development of sensory mechanisms?
- Postnatal developmental shift: Hedonic response to salt appears between 4 and 6 months (?)
- Significance unclear – plasticity of salty taste system?
- Perinatal period may represent a window for nutritional or physiological modulation of developing salty taste system

Salt

Sour

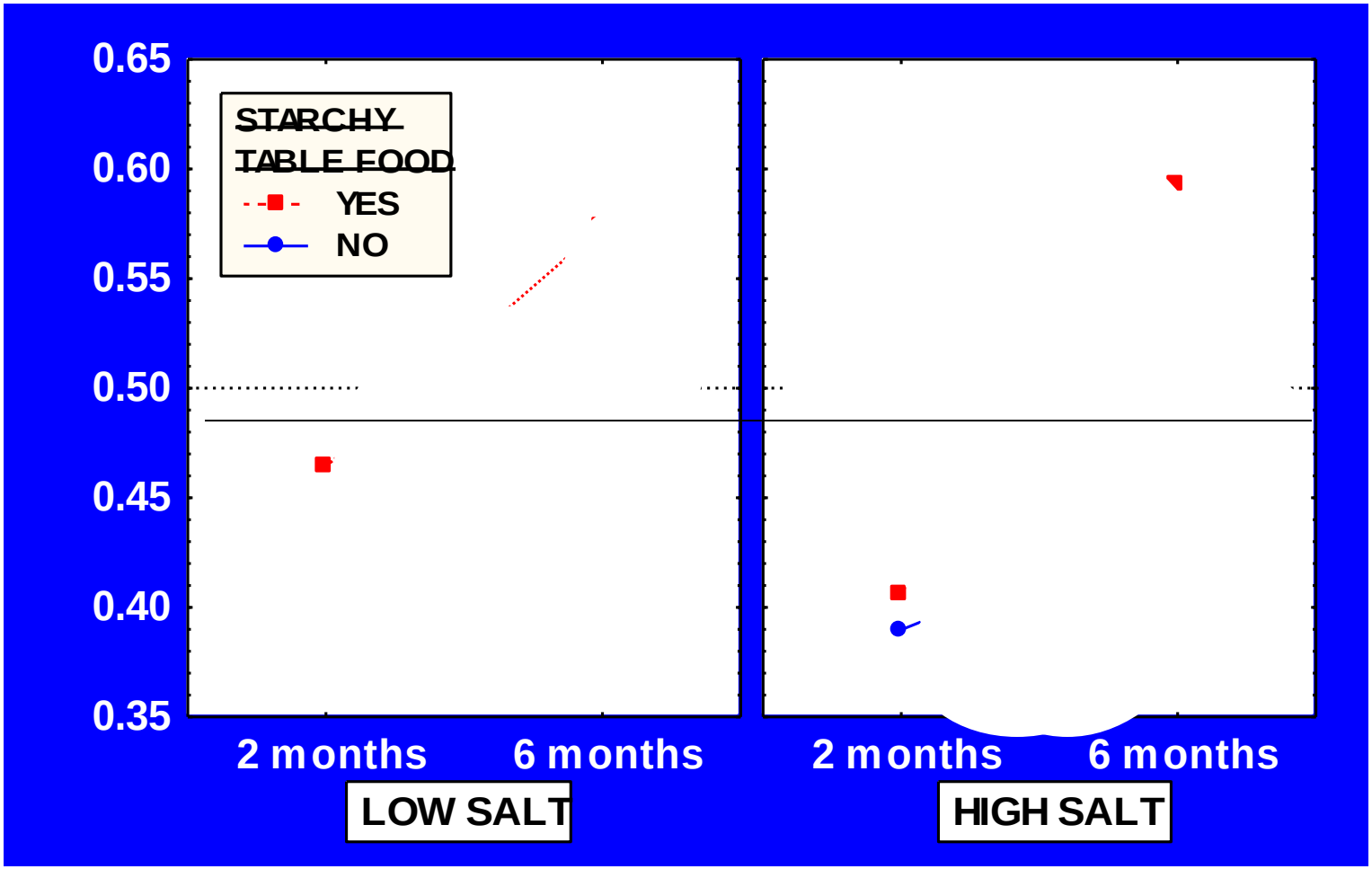
POTENTIAL SOURCES OF SODIUM IN WEANLING INFANT DIET: TABLE FOOD

- ***Breakfast cereal:*** **273 mg**
- ***Toaster waffle:*** **260 mg**
- ***Bagel*:** **245 mg**
- ***American cheese:*** **300 mg**
- ***Yogurt:*** **114 mg**
- ***Chicken noodle soup:*** **1100 mg**
- ***Cheese curls:*** **300 mg**

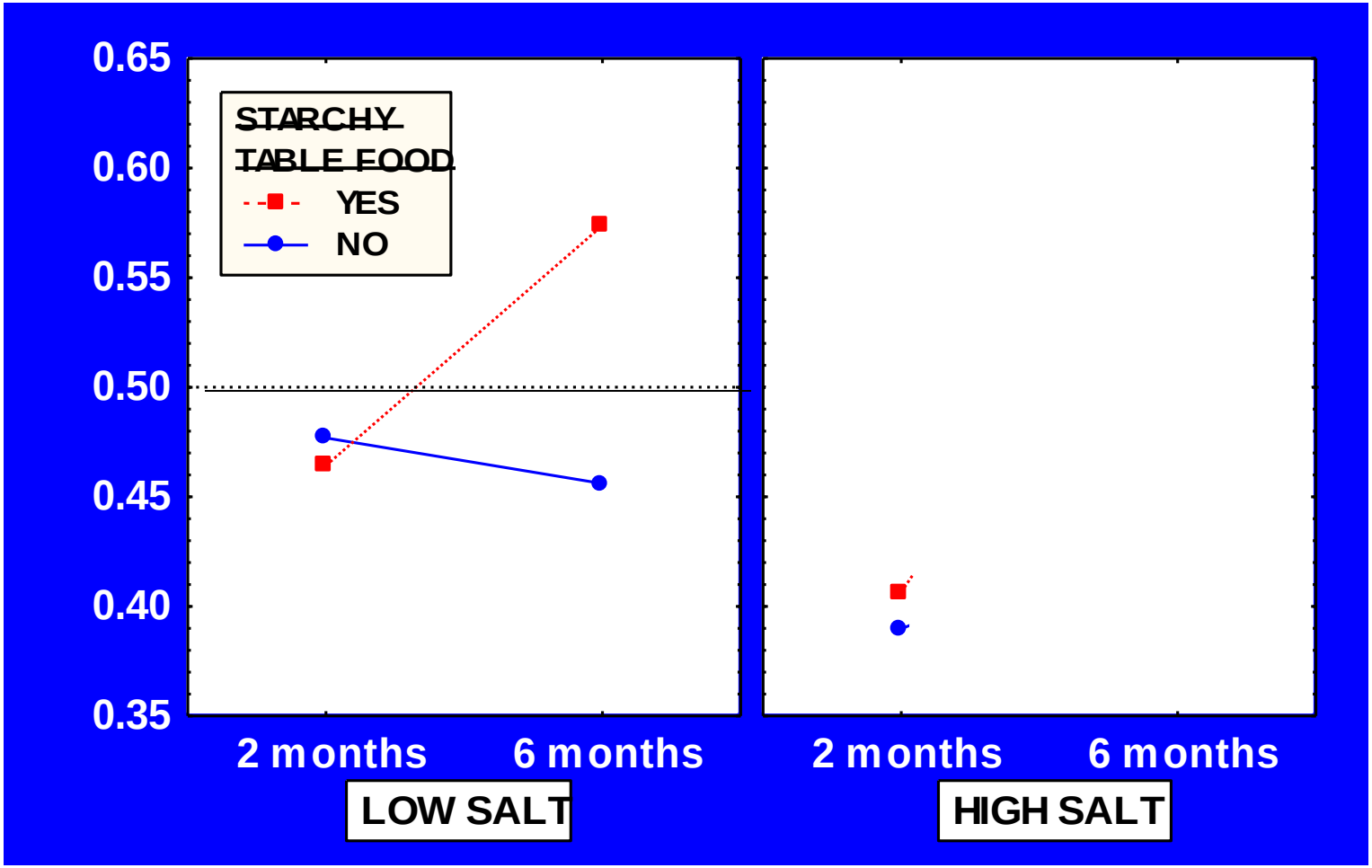
National Academy of Sciences
Estimated Minimum Requirement

< 6 months:	**120 mg/day**
12 months:	**225 mg/day**

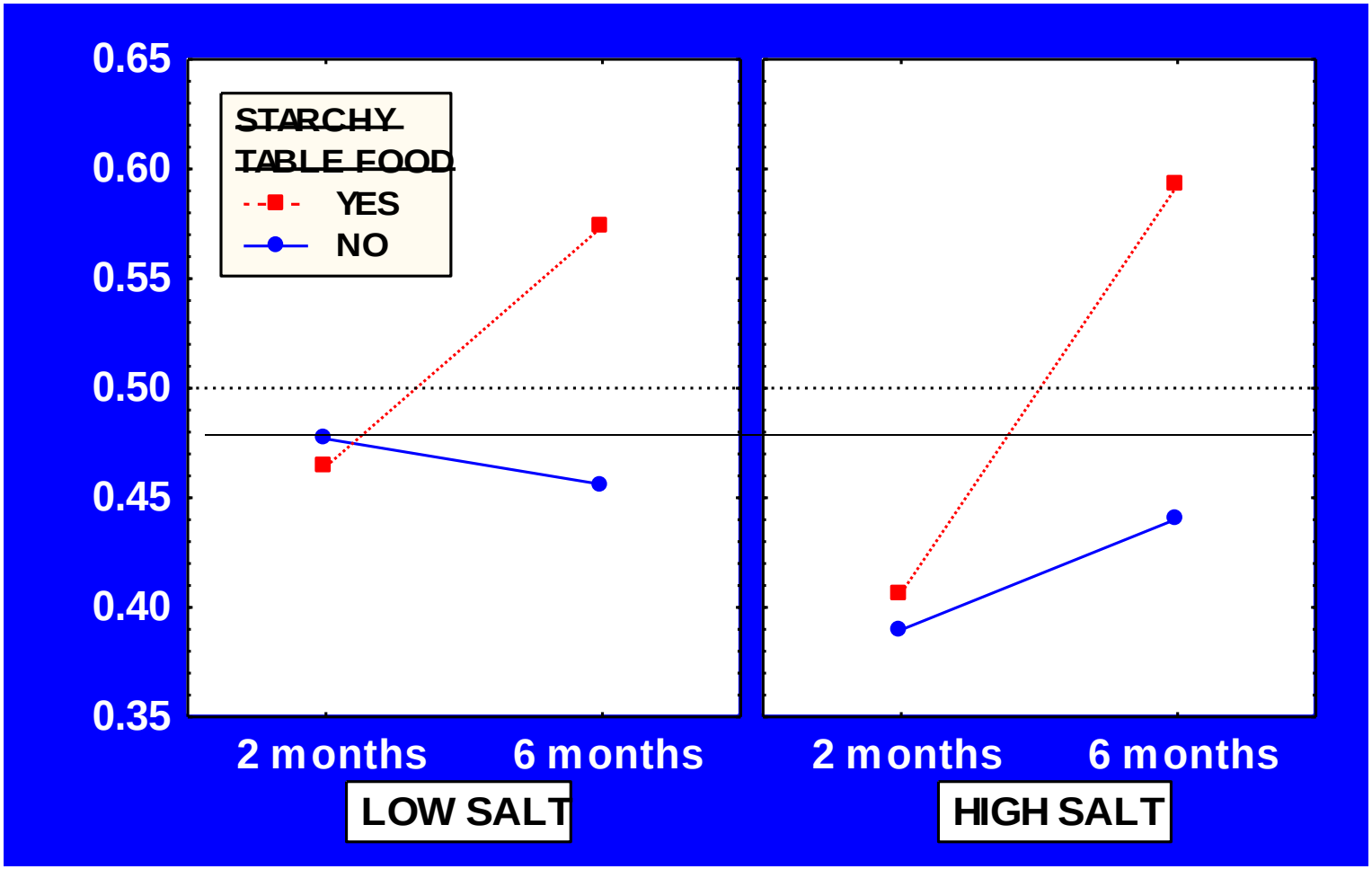
DIET-RELATED DEVELOPMENTAL PLASTICITY
Age-related shift: Interaction with diet exposure



DIET-RELATED DEVELOPMENTAL PLASTICITY
Age-related shift: Relationship with dietary practices



DIET-RELATED DEVELOPMENTAL PLASTICITY
Age-related shift: Relationship with dietary practices



Stein et al, AJCN, 2012

Salt Preference Summary

- A preference for NaCl is likely innate
- Experience, especially prenatal and early dietary experience, may shape the set point for what is considered normal salty taste
- The critical period of childhood in shaping life-long dietary habits is likely to become a larger focus of public policy discussions

Sensory Considerations

Mixture Perception

- Foods are complex mixtures and the sensory interactions between ingredients can occur at the receptor level and in the brain where sensory information relays occur

- We know from human fMRI and sensory research that commonly encountered taste-taste and taste-odor mixtures become integrated into one flavor percept at higher centers in the brain

- Today we capitalize on these learned associations to boost the perception of one ingredient/quality with others

Taste-Odor Mixtures

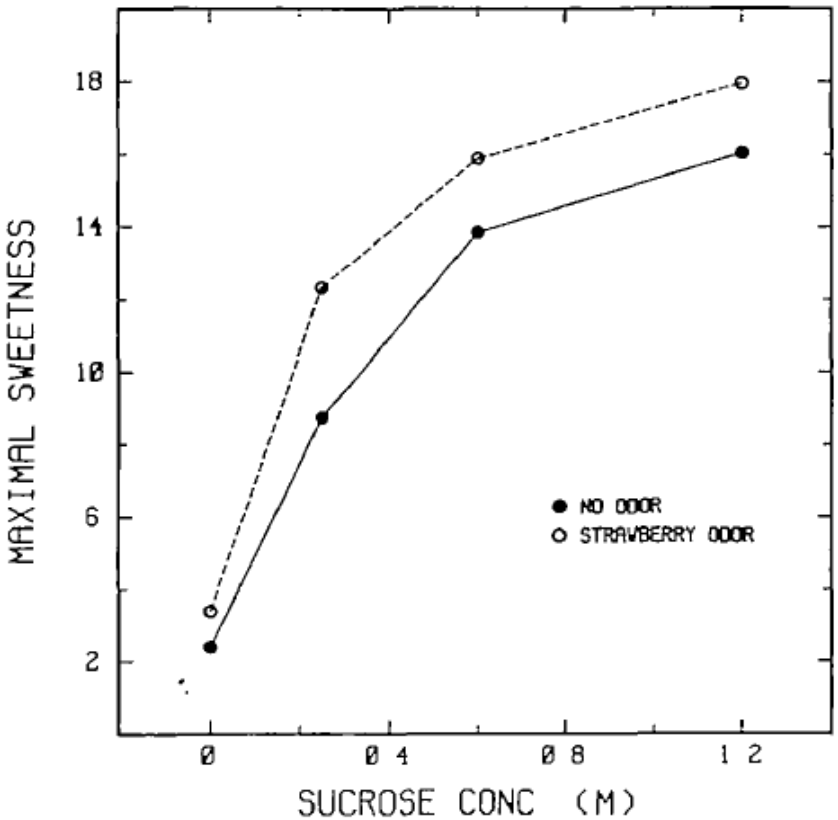
- Generally, one taste quality will suppress the intensity but not the quality of another taste

- Generally an odor and taste mix with some small suppression of intensity of each quality

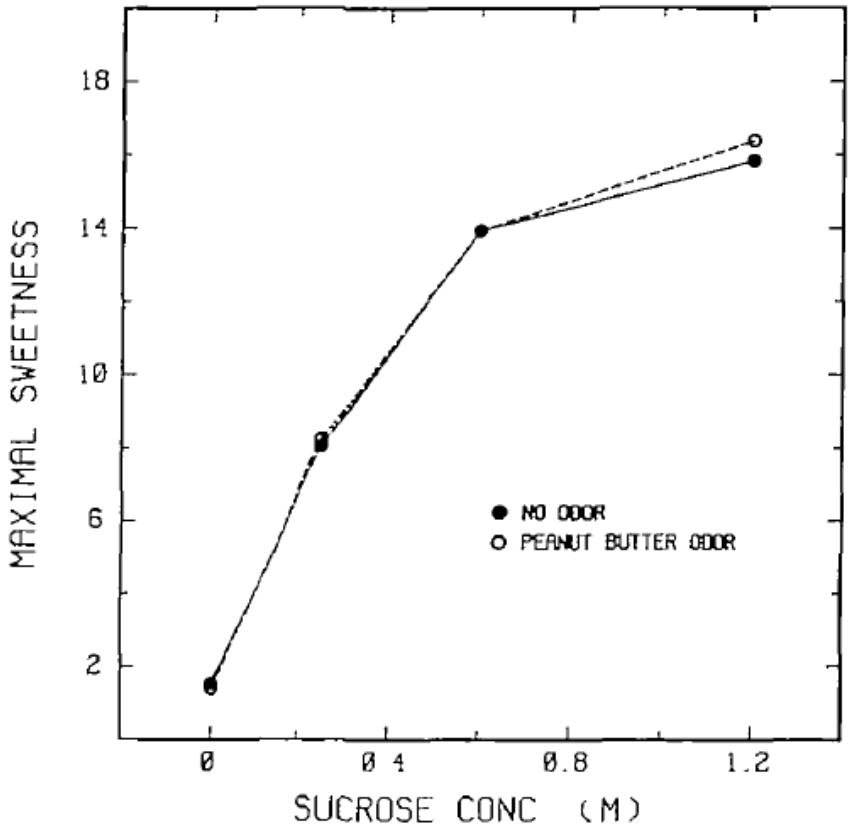
- Enhancement can occur in taste-taste, taste-odor interactions and appears to be related to learned congruency and/or sensory similarity
  - E.g. citric acid and NaCl are rated as more similar than other taste mixtures and each is able to enhance the other (Breslin et. al., 2002 & 2011)

Context-specific Enhancement of Sweetness

Strawberry Odor



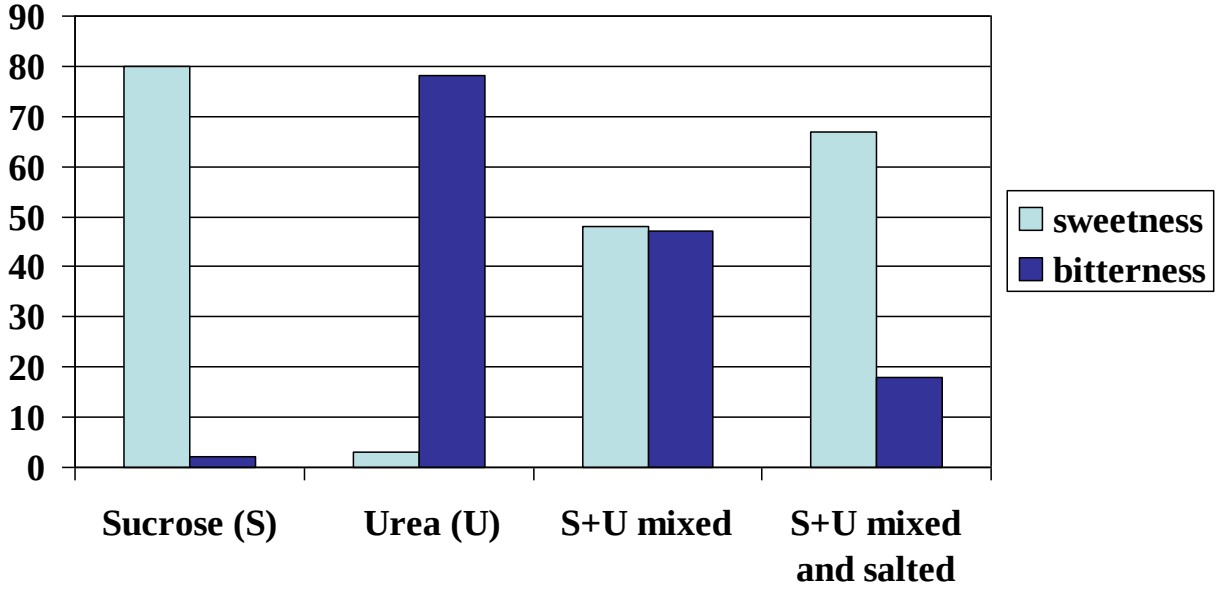
Peanut Butter Odor



Frank and Byram, 1988

Taste-Taste Mixtures

NaCl is especially effective at suppressing the bitterness of many types of bitter compounds

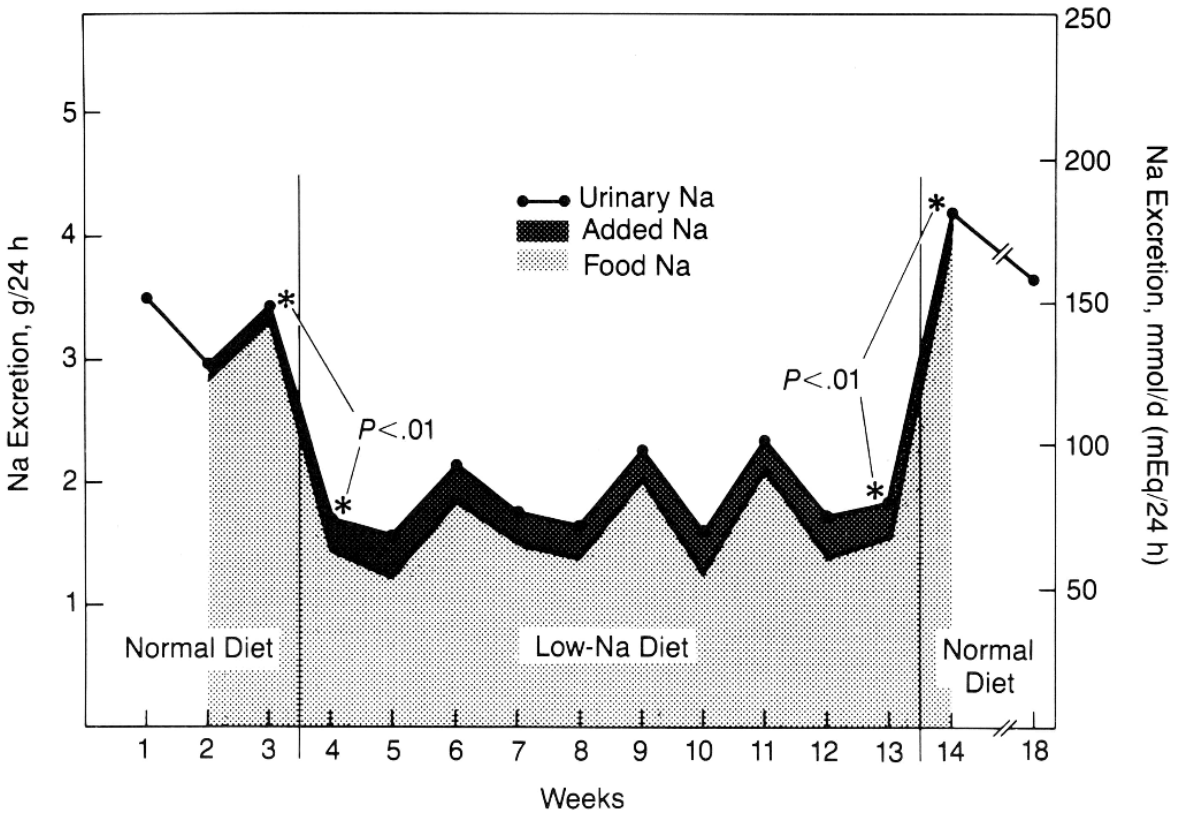


Beauchamp & Breslin, Nature

Enhancement by In vs On

Humans regulate salty taste not sodium level

(when sodium is sufficient in the diet)



Beauchamp et al., JAMA

Perception Summary

- One strategy for reducing sodium in foods is to find other ingredients that perceptually enhance the saltiness of food
  - The enhancement may not be dramatic but can be part of a broader program to reduce sodium in foods.

- Strategies that make sodium physically more available to taste receptors should enhance the salty taste experience

WHAT ABOUT POTASSIUM

Only NaCl is Purely Salty

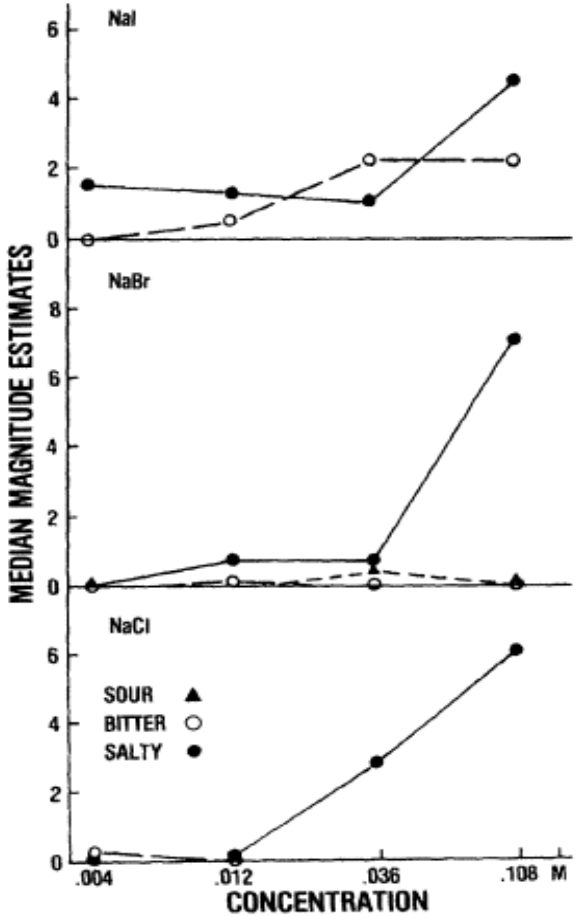


FIG. 7. Median magnitude estimates of the four gustatory qualities as a function of concentration of NaI (upper graph), NaBr (middle graph), and NaCl (lower graph).

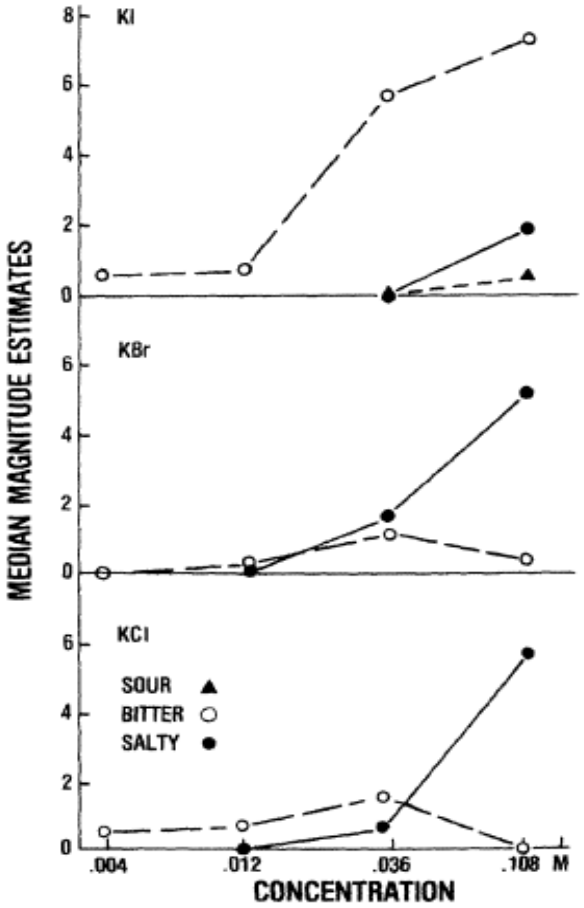
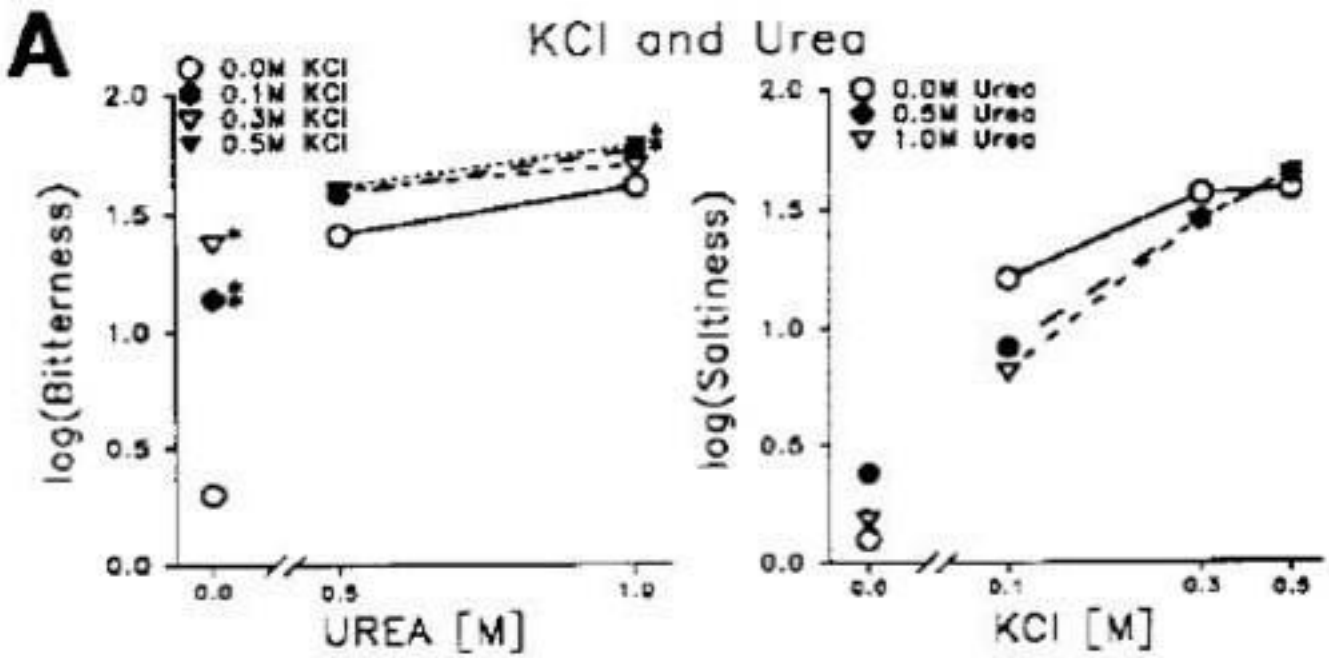


FIG. 8. Median magnitude estimates of the four gustatory qualities as a function of concentration of KI (upper graph), KBr (middle graph), and KCl (lower graph).

Murphy, Cardello & Brand
Physiol & Behav, 1981

Potassium Does Not Suppress Bitterness



Breslin and Beauchamp, 1995

WHAT ABOUT POTASSIUM???

- Not purely salty – has bitter taste component
- Does not interact with leading salt receptor candidate
- Does not modify flavor like sodium to increase sweetness and suppress bitterness

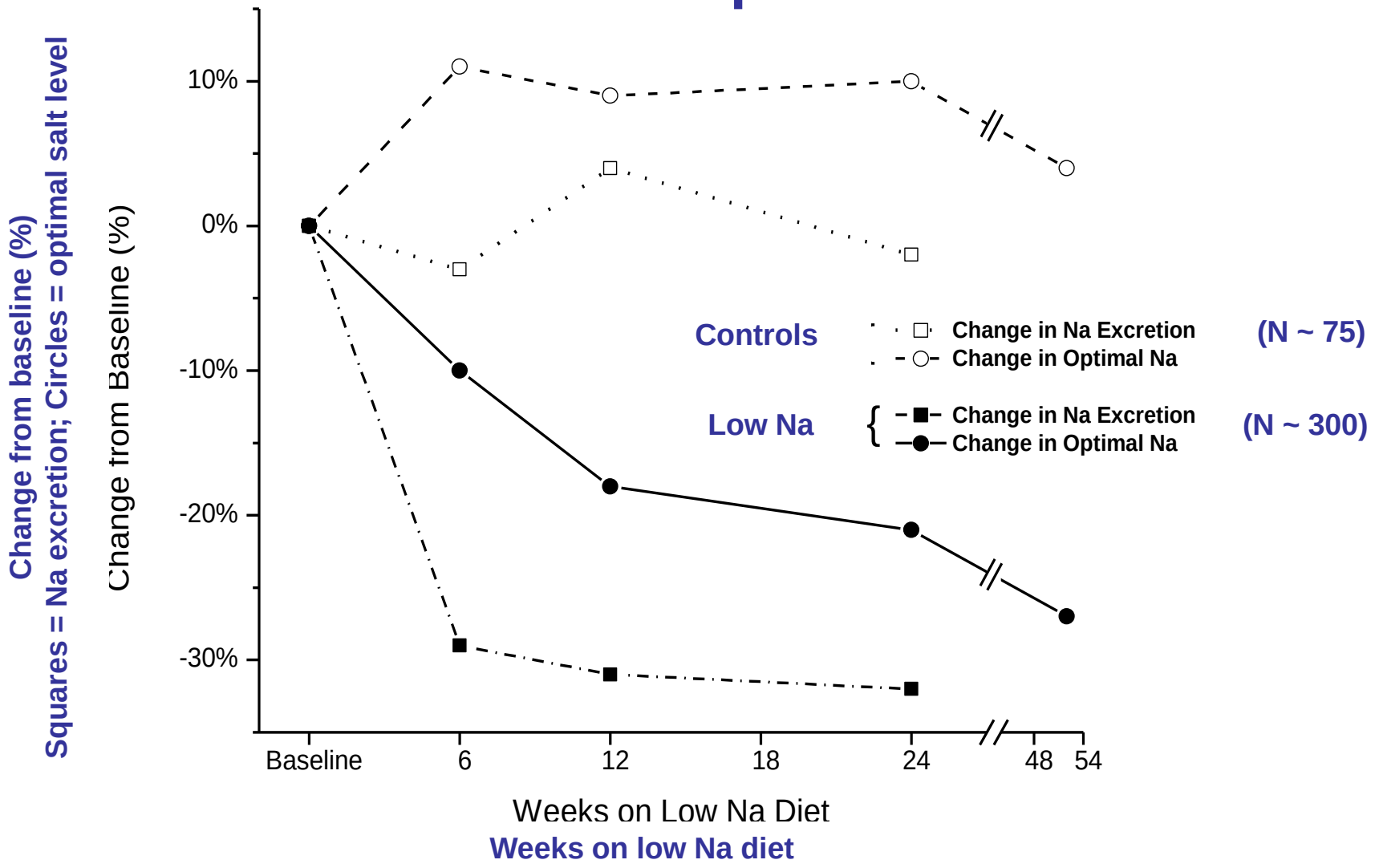
- Unlikely to be widely accepted as a salt substitute

Flavor-based Considerations When Developing Strategies To Reduce Na Intake On A Population Wide Basis

- Must deal with sodium added during manufacture and processing.
- Must recognize inherent pleasantness of the taste of salt.
- Must recognize the multiple functions of salt in food.

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

Decreasing Na intake is followed by decreased salt preference



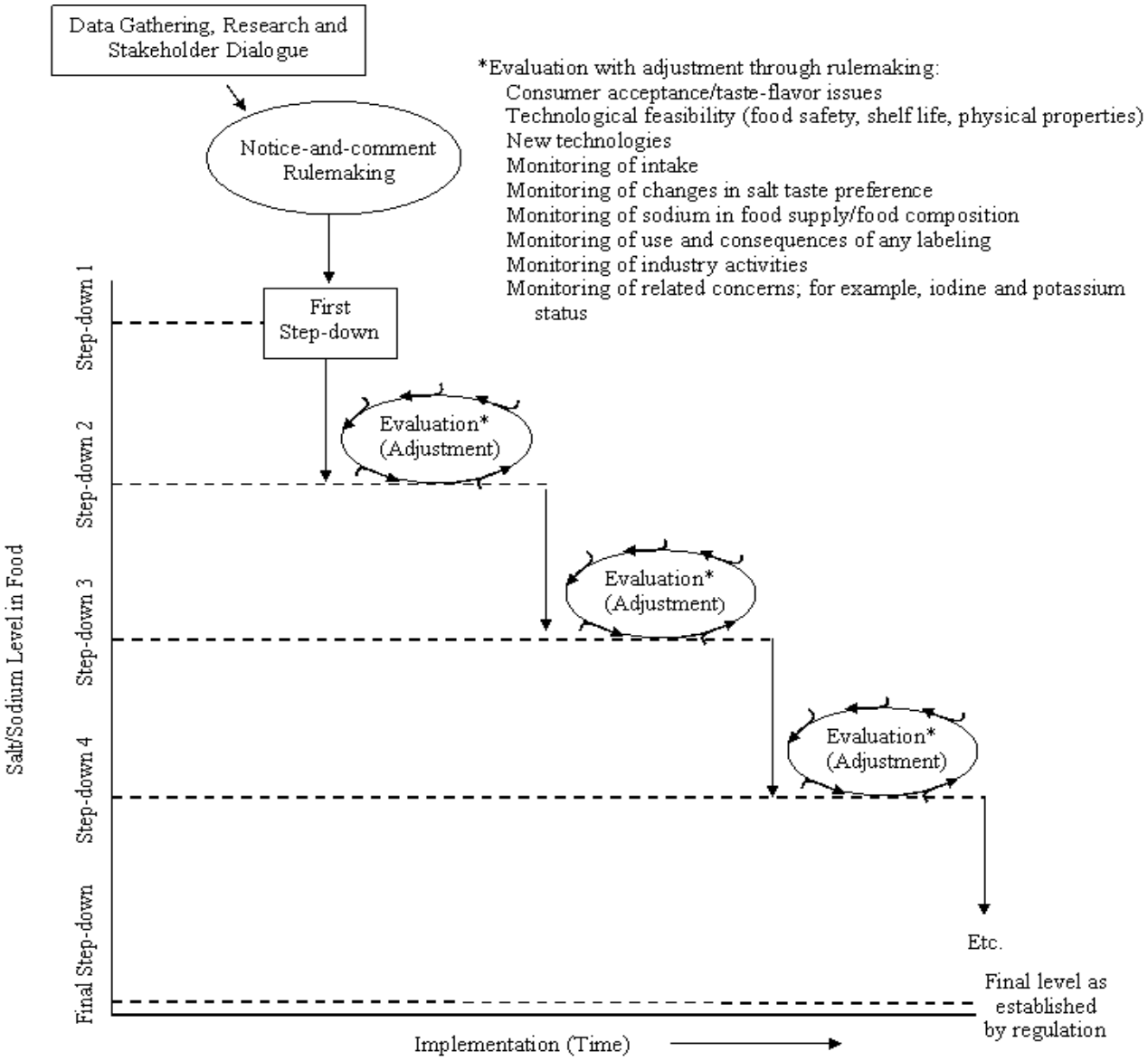
Adapted from: P. Elmer, unpublished PhD thesis, University of Minnesota in Henney et al., Institute of Medicine, *2010*

Acknowledging the Power of Taste

- An Institute of Medicine panel was convened in 2009 to recommend strategies to reduce sodium intake in the US diet
  - "Activities to reduce sodium intake of the U.S. population have been ongoing for more than 40 years, but they have not succeeded"

    IOM report, 2010
- The final recommendation of the panel in 2010 called for regulation of sodium levels in food using a gradual, stepwise reduction in sodium
  - This recommendation has at its root the acknowledgement that humans have a powerful avidity for salt and that preferred levels of salt in food is shaped by experience

Stepwise process for reducing salt intake



Institute of Medicine, 2010

jnd

- Weber's Law says that the size of the *just noticeable difference* is a constant proportion of the original stimulus value

- Thus, with each reduction in sodium levels in food, consumers will be sensitive to smaller changes in sodium

Behavior Summary

- Though we have an avidity for salt, the preferred level of salt can be manipulated by experience
- Taking advantage of the jnd, it is possible over time to reduce salt in food with little sacrifice to the palatability of the saltiness of food
- A cautionary note is that the level of salt must drop rather widely across the dietary experience
  - Hence the IOM recommendation to mandate reductions in Na industry-wide

Research needs identified by IOM

- Understanding salt taste reception and salt taste development throughout the lifespan.
  - Mechanisms of salt taste reception
  - Importance of childhood exposure

- Develop innovative methods to reduce sodium in foods while maintaining palatability, physical properties and safety.

- Enhance current understanding of factors that impact consumer awareness and behavior relative to sodium reduction.

- Monitoring sodium intake and salt taste preference.
  - How can consumers know how much they are consuming?
  - Has the reduction in salt in the food supply reduced preference and/or altered taste function?

Institute of Medicine, 2010

Overall Summary

- Reducing sodium in food requires a multi-pronged approach and time since there is no “magic bullet”

- Large reductions in dietary sodium will require better understanding of the biology of salt taste
  - Salt enhancers will be found!

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ADVANCING DISCOVERY IN TASTE AND SMELL

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Joe Brand

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