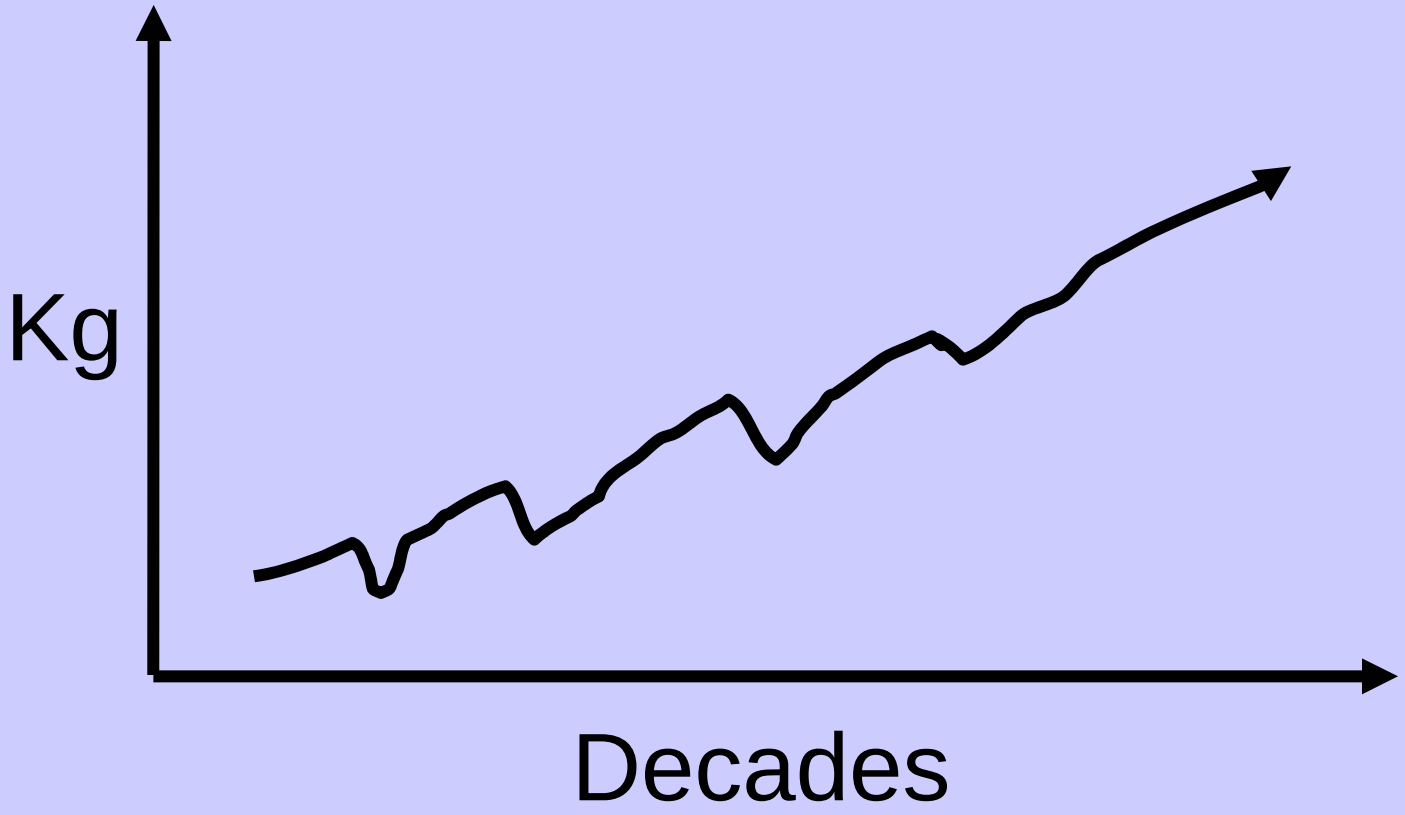
OBESITY CONUNDRUM 1: Is There Evidence That a Food Solution Can Impact Overweight Through Biological Mechanisms: Appetite, Satiety and Energy Balance

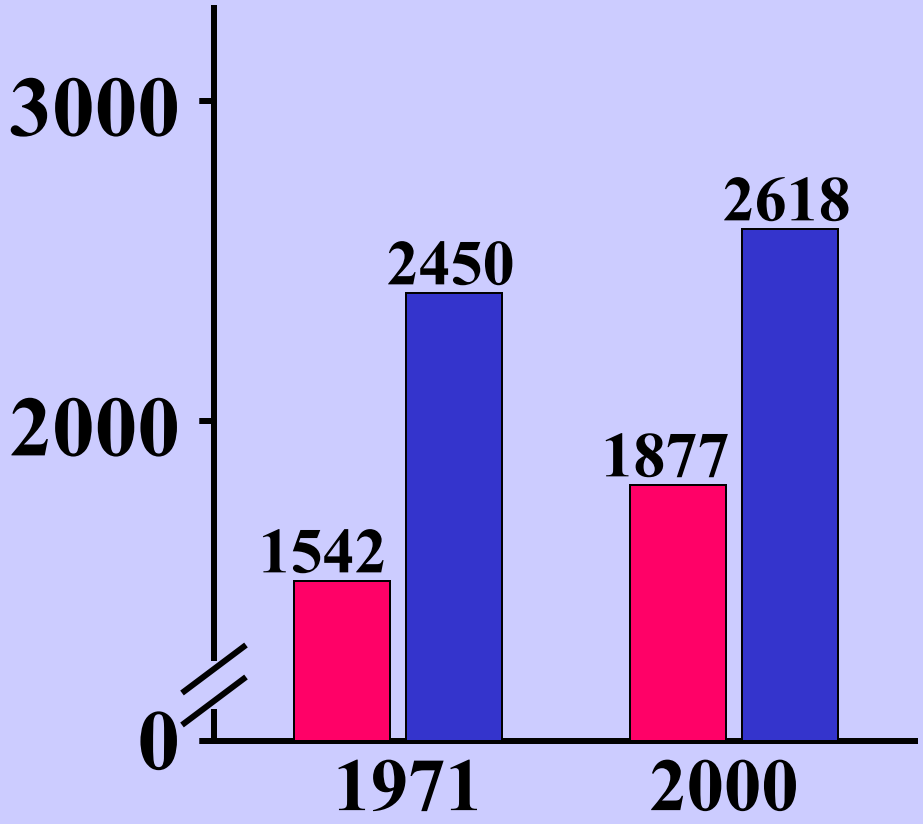
Stephen C. Woods
University of Cincinnati

IFT Summit, New Orleans, 2004

The Dilemma



Mean Daily Consumption (Calories)



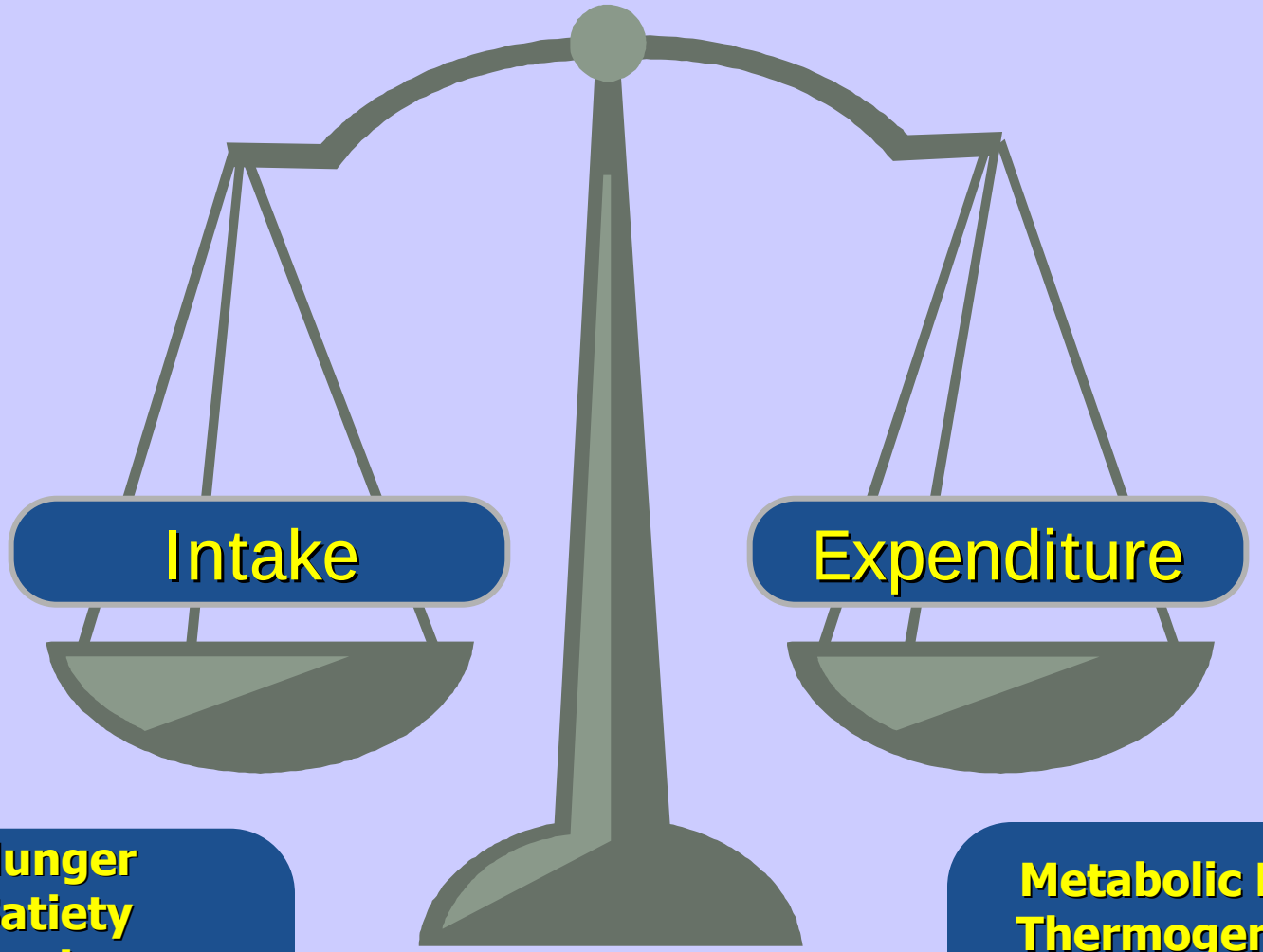
In the last three decades, American men increased their caloric intake by 7% and American women by 22%.

Women

Men

CDC Morbidity and Mortality Weekly Report, Feb 05, 2004

Energy Balance Equation



Hunger
Satiety
Nutrient Absorption

Metabolic Rate
Thermogenesis
Activity

Accuracy!

Energy Intake in a Year

955,570 calories

Gaining 1 pound (0.45 kg) in a year

~4000 calories

Error of 0.4%,

or

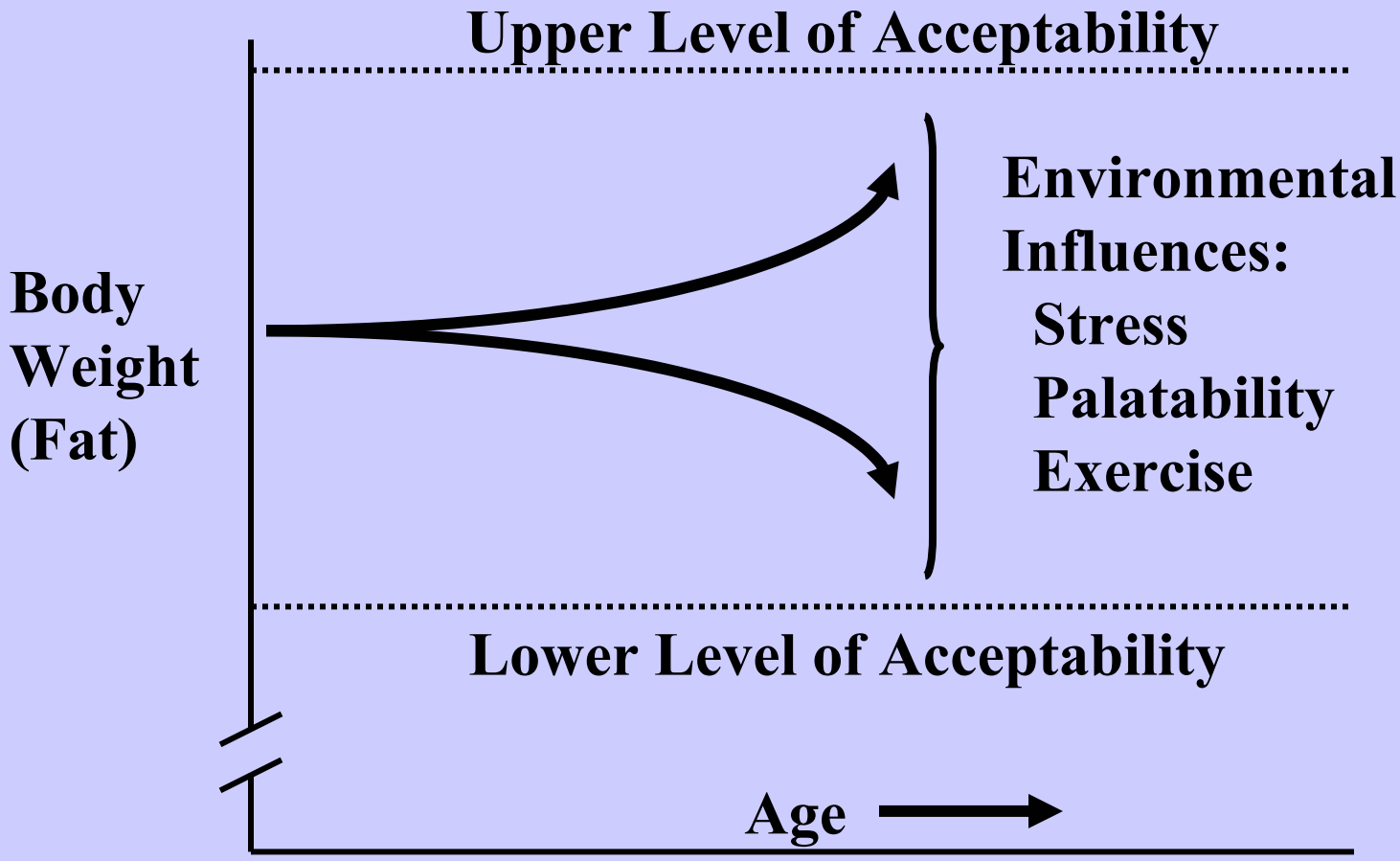
11 calories/day

THE PUZZLE

If energy homeostasis is regulated so precisely,

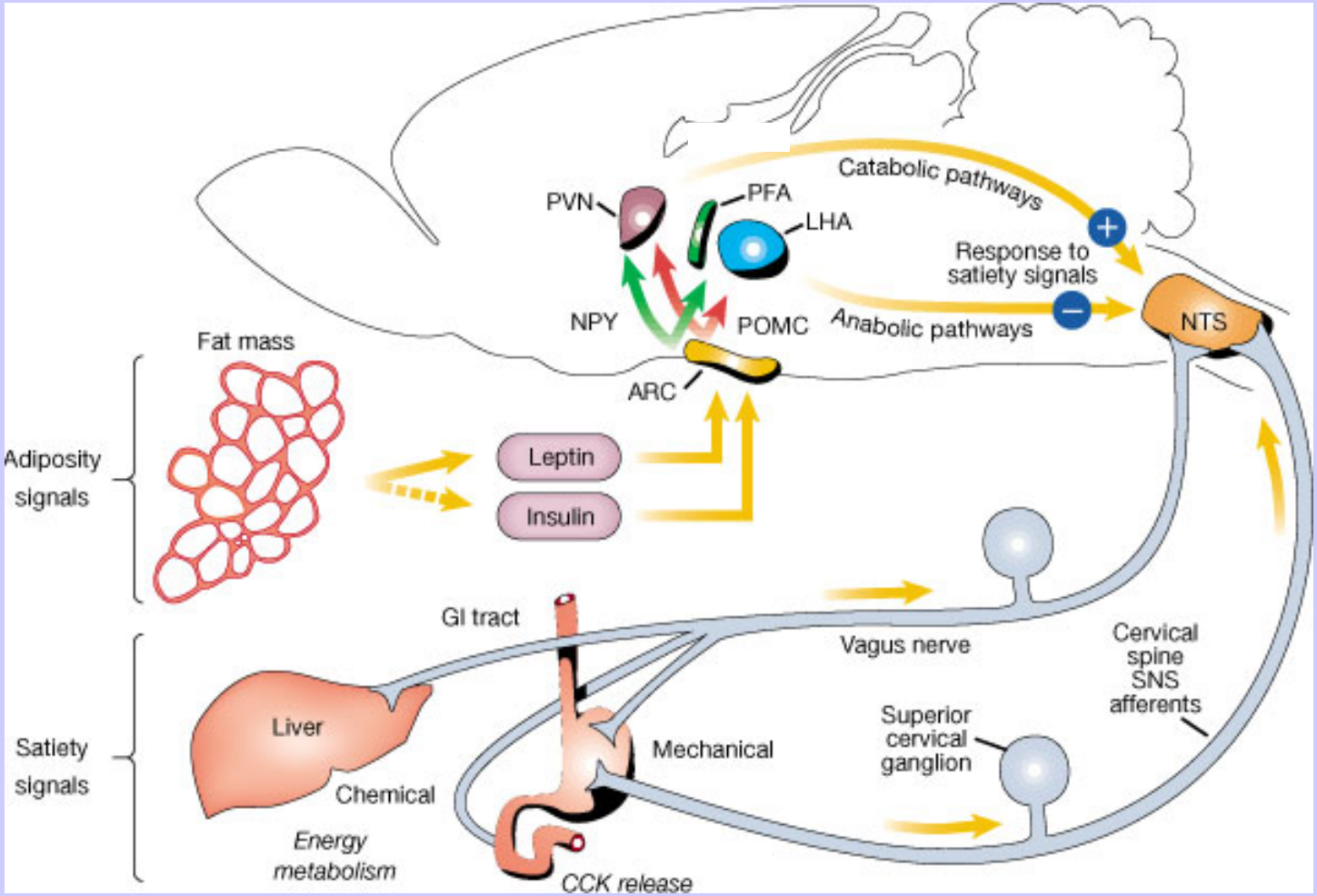
- **Does this imply the existence of a "set point?"**
- **Is the control system overwhelmed by environmental factors?**

Evidence suggests that there is a body weight range rather than a body weight set point.



Upper and lower boundaries are genetically and ontogenetically determined.

The control system over energy homeostasis is complex, relying upon several types of signals.



MW Schwartz, SC Woods et al., *Nature*, 2000

MEALS

“Meals are the fundamental unit of food intake.”

GP Smith

MEALS

"Meals are the fundamental unit of food intake."

GP Smith

- **Factors that control when meals will occur are distinct from factors that control when meals will end;**
- **i.e., different signals control meal initiation and meal size.**

CONTROL OF MEALS

- **There is scant evidence that meal initiation is controlled by metabolic or hormonal signals.**

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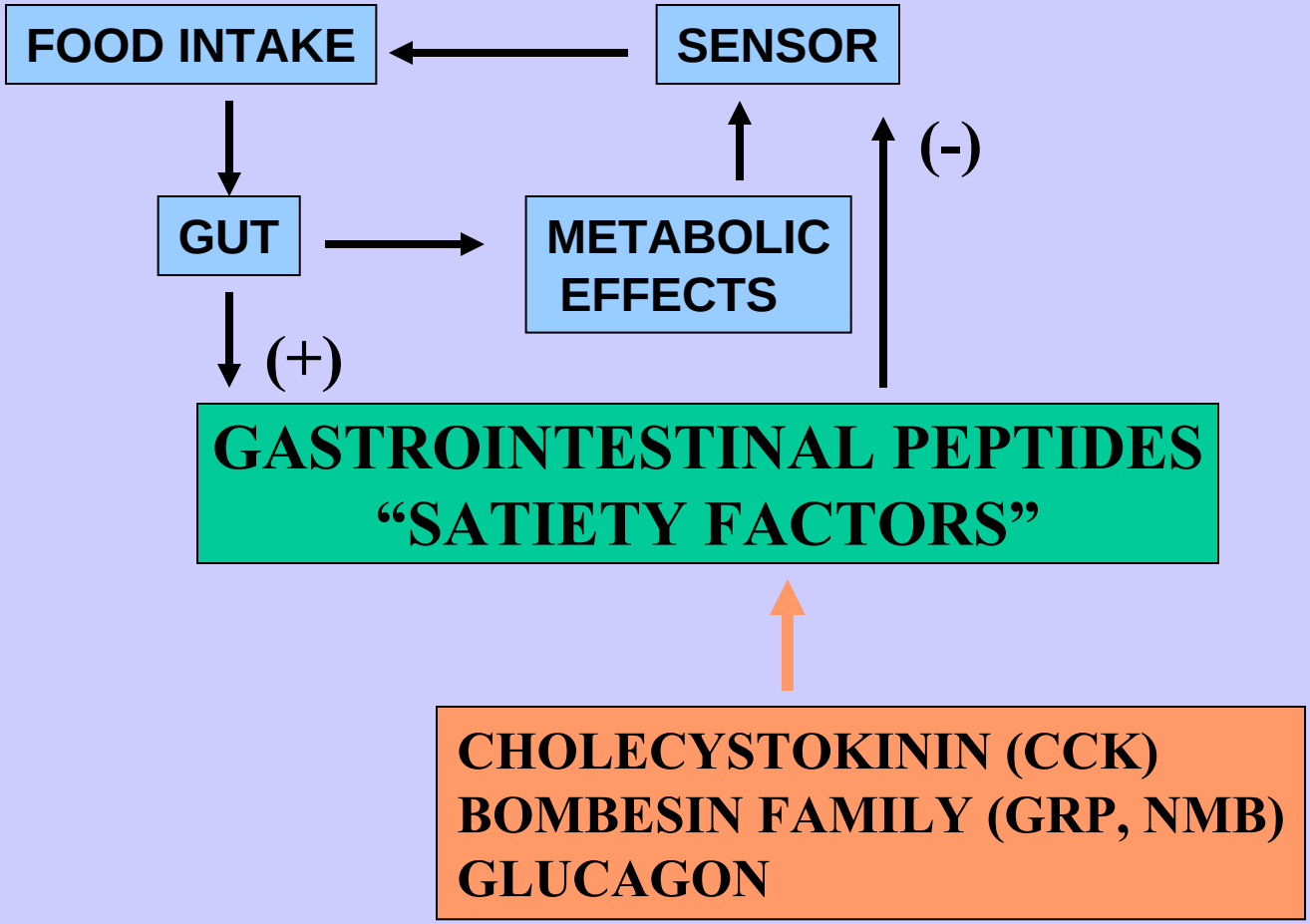
The best evidence is that under normal circumstances, meal initiation is based upon learned associations, convenience or the social situation.

CONTROL OF MEALS

- There is scant evidence that meal initiation is controlled by metabolic or hormonal signals.

- **There is compelling evidence that meal cessation (meal size) is controlled by preabsorptive signals from the gastrointestinal system.**

CONTROL OF MEAL SIZE



Putative Satiety Factors:

- Cholecystokinin (CCK)
- Peptides in the bombesin family
  Bombesin, GRP, Neuromedin B
- Apolipoprotein A-IV (apo A-IV)
- Peptide YY (PYY)
- GLP-1, enterostatin, amylin, glucagon, somatostatin

- Ghrelin

Reduction of Meal Size by CCK

From: J Gibbs & GP Smith, 1976

Satiety Signals:

- **Secreted during meals, create a sensation of fullness or satiety**
- **Reduce meal size without causing malaise**
- **Interact with other controllers of meal size**

Features of satiety signals:

- **Most are made in both the GI tract and the brain.**

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  This includes CCK, bombesin peptides, somatostatin, PYY, apo-A-IV and GLP-1, as well as ghrelin.

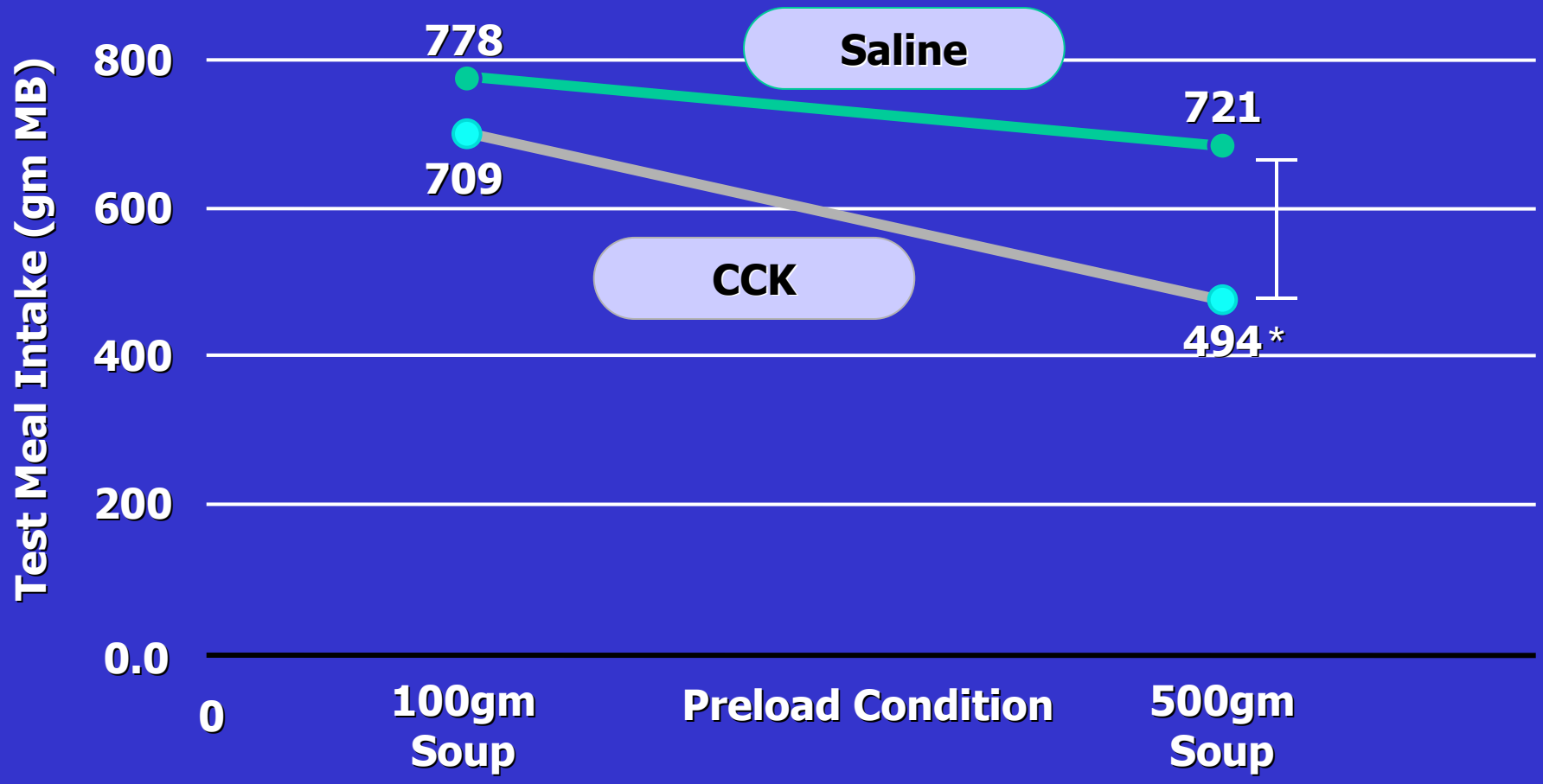
Features of satiety signals:

- **Most are made in both the GI tract and the brain.**
- **They are efficacious in humans.**

Reductions of Meal Size in Humans Administered IV CCK

Subjects	Δ from Control	Reference
Men	-3%	Kissileff, AJCN, 1981
Obese Men	-24%	Pi-Sunyer, PB, 1982
Men	-39%	Muurahainen, PB, 1988
Men, Women	-32%	Muurahainen, AJP, 1991
Men, Women	-8%	Geary, AJP, 1992
	-6%	Geary, AJP, 1992
	-32%	Geary, AJP, 1992
Obese Women	-31%	Geary, AJP, 1992
Men, Women	-20%	Lieverse, Gut, 1995
Men	-21%	Ballinger, Clin Sci, 1995
Men	-7%	Gutzwiller, AJP, 2000

IV CCK is More Effective at Reducing Meal Size in Men and Women After Eating a Standard Preload

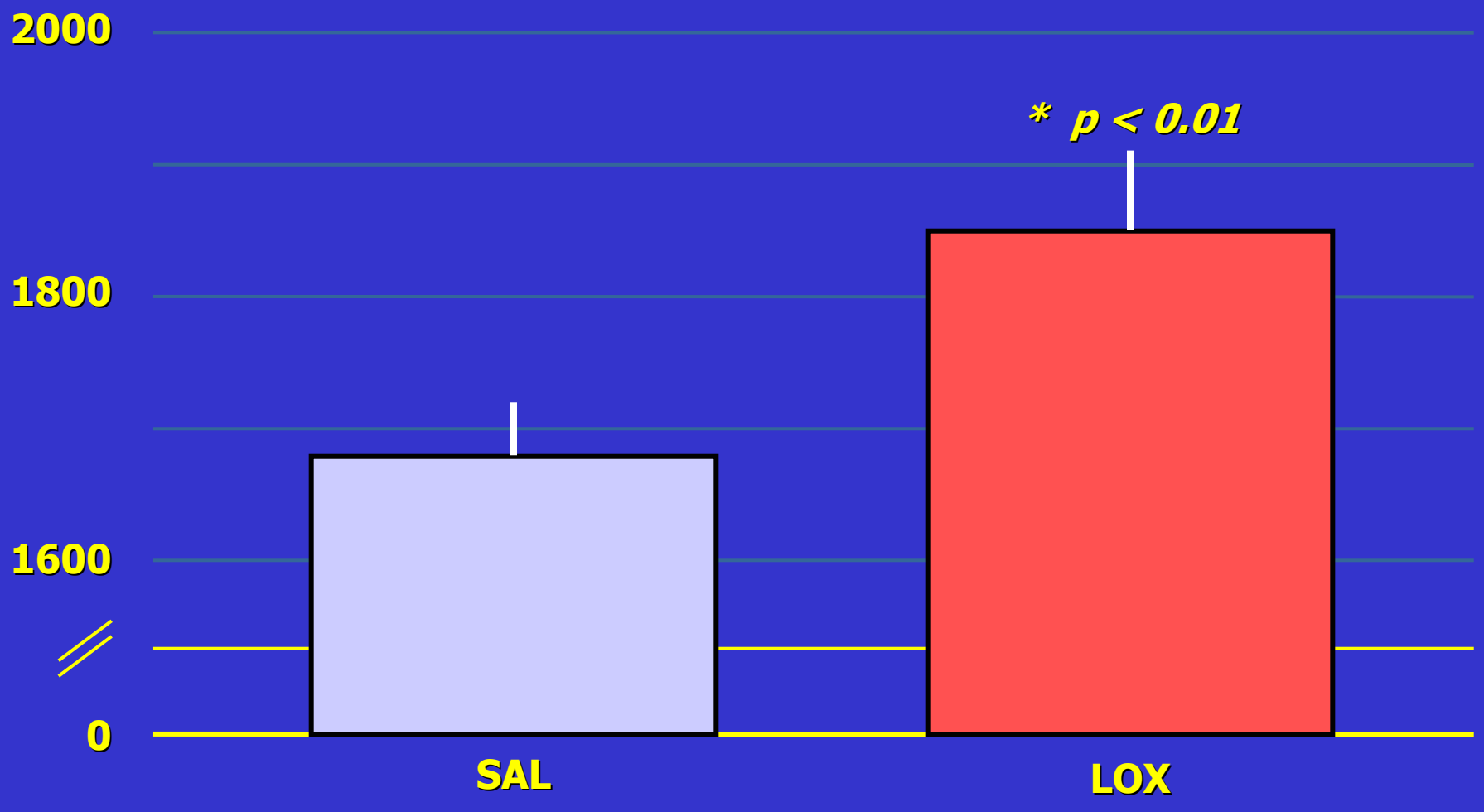


Muurahainen NE, Am J Physiol 1991;260:R672-80

Features of satiety signals:

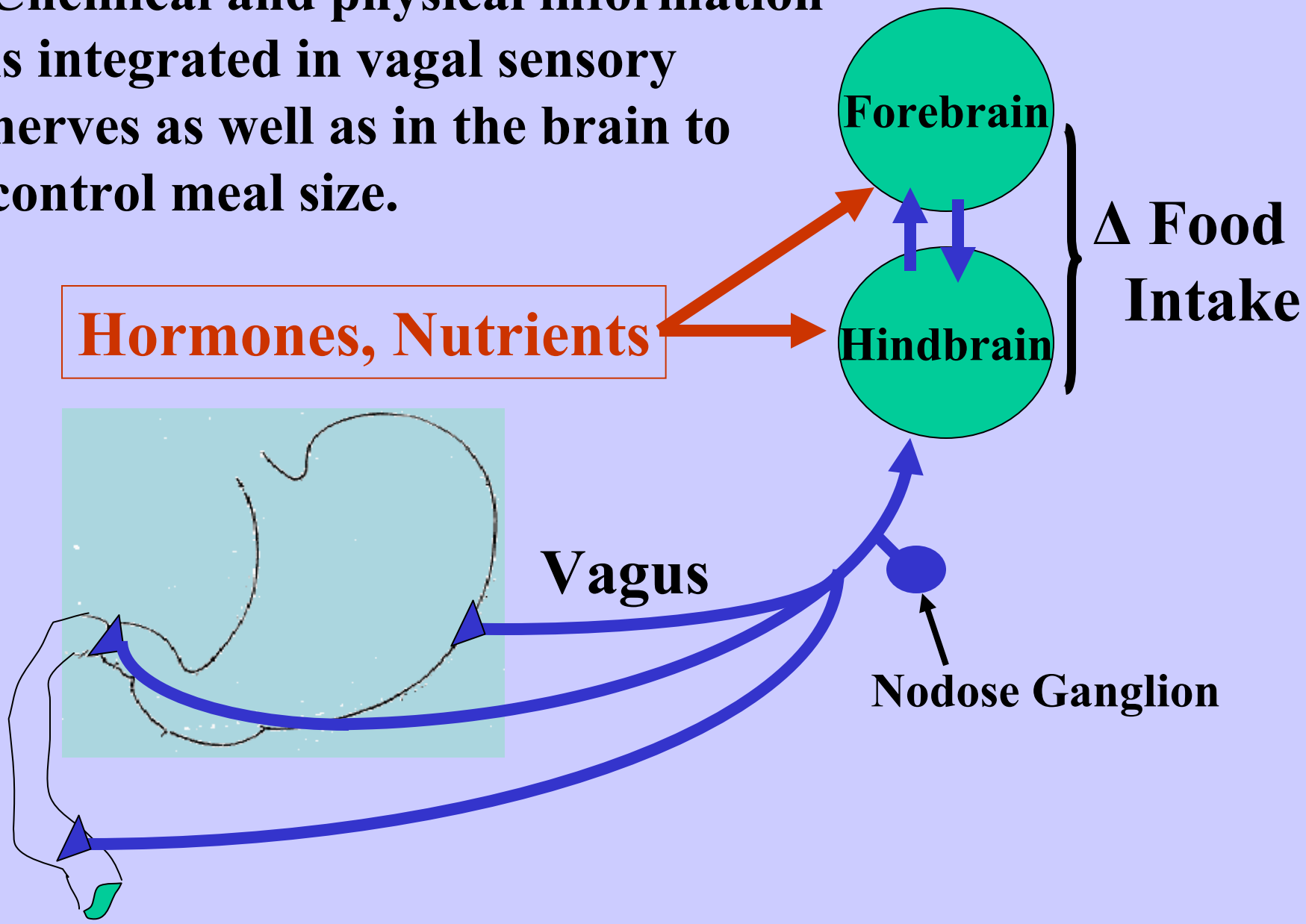
- Most are made in both the GI tract and the brain.
- They are efficacious in humans.
- Blocking their action leads to increased meal size.

The CCK-A Receptor Antagonist, Loxiglumide (22 µMol/kg, iv), increases Caloric Intake in Men

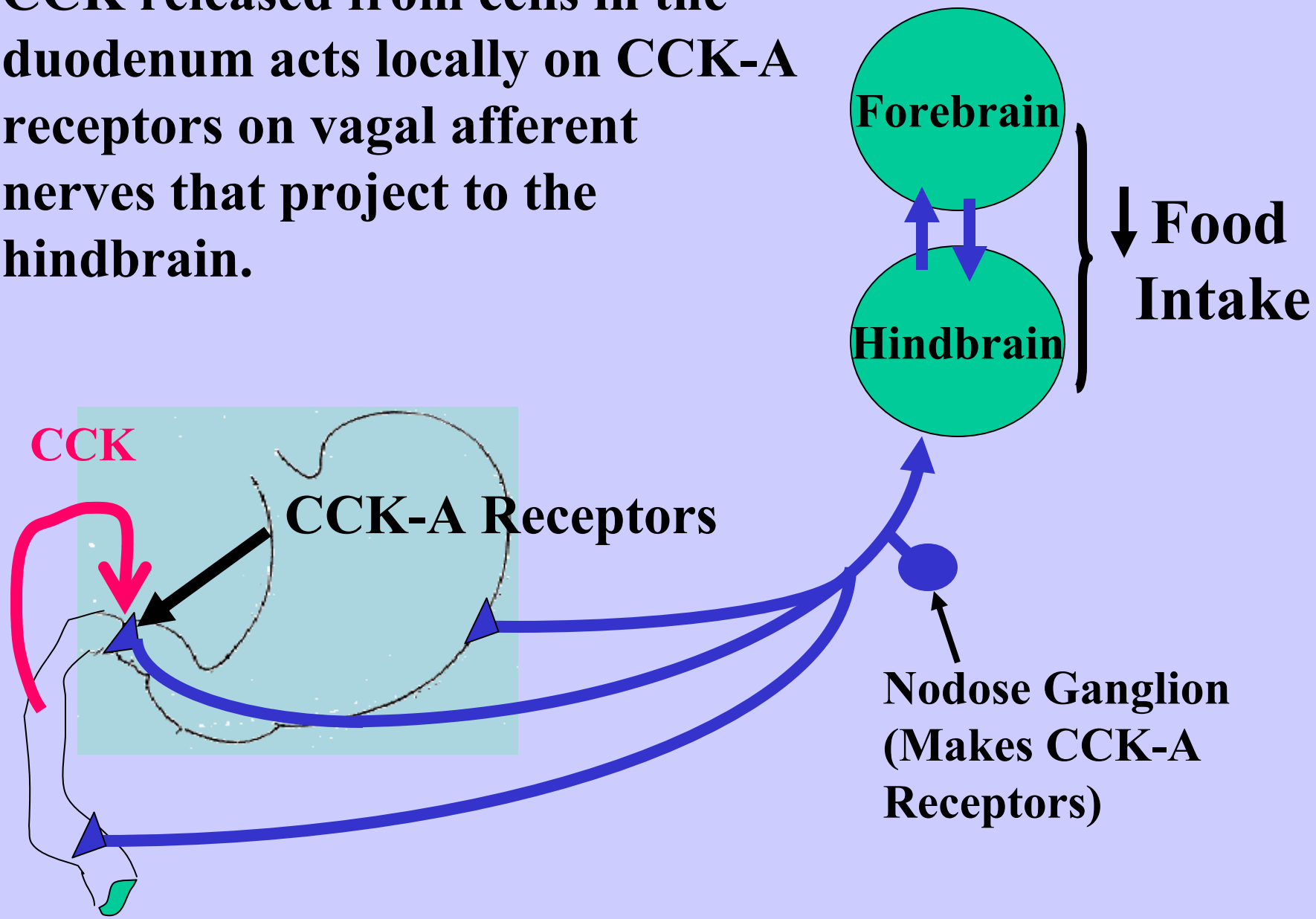


Adapted from Beglinger C, Am J Physiol Regul Integr Comp Physiol 2001;280:R1149-54

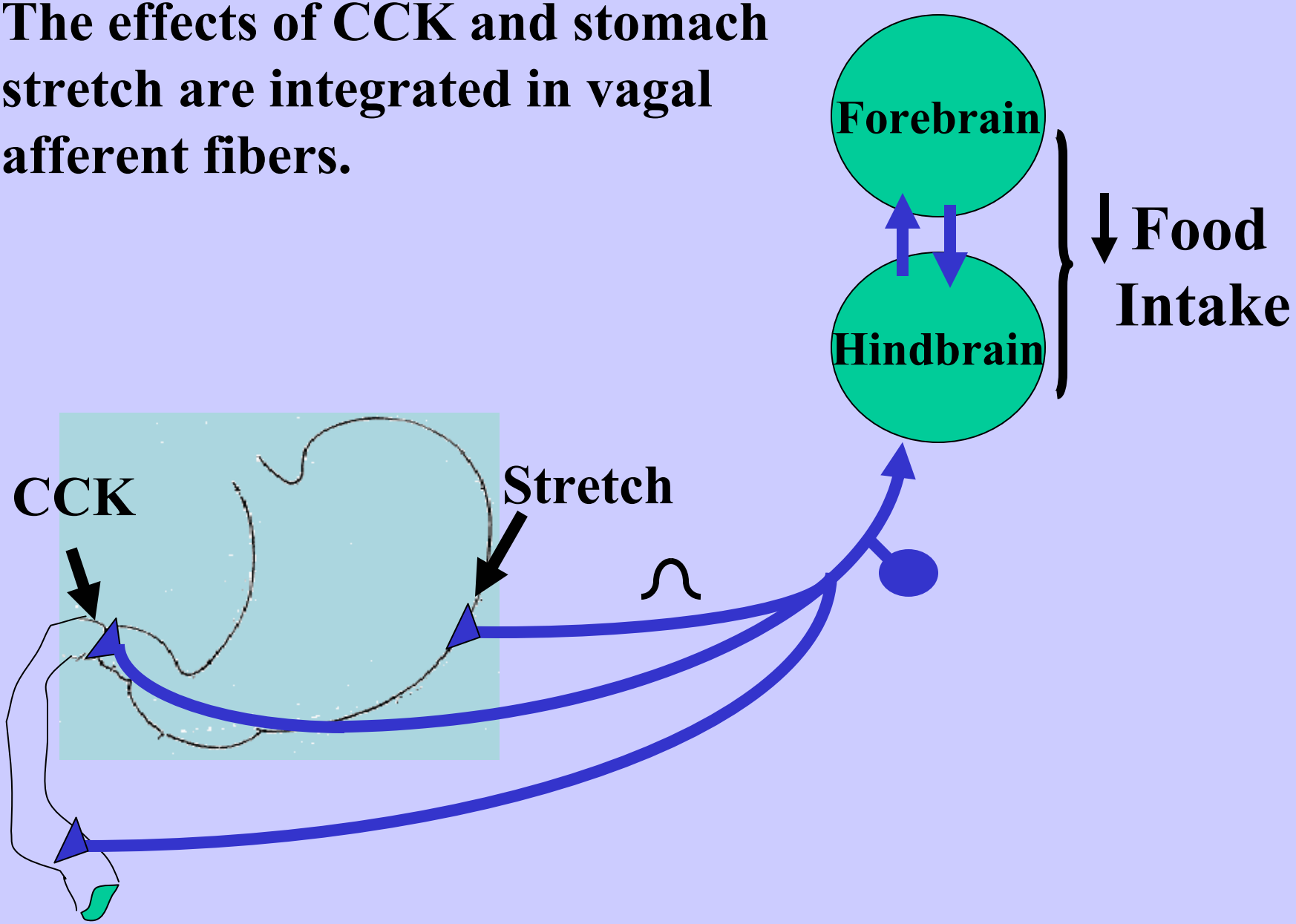
Chemical and physical information is integrated in vagal sensory nerves as well as in the brain to control meal size.



CCK released from cells in the duodenum acts locally on CCK-A receptors on vagal afferent nerves that project to the hindbrain.



The effects of CCK and stomach stretch are integrated in vagal afferent fibers.



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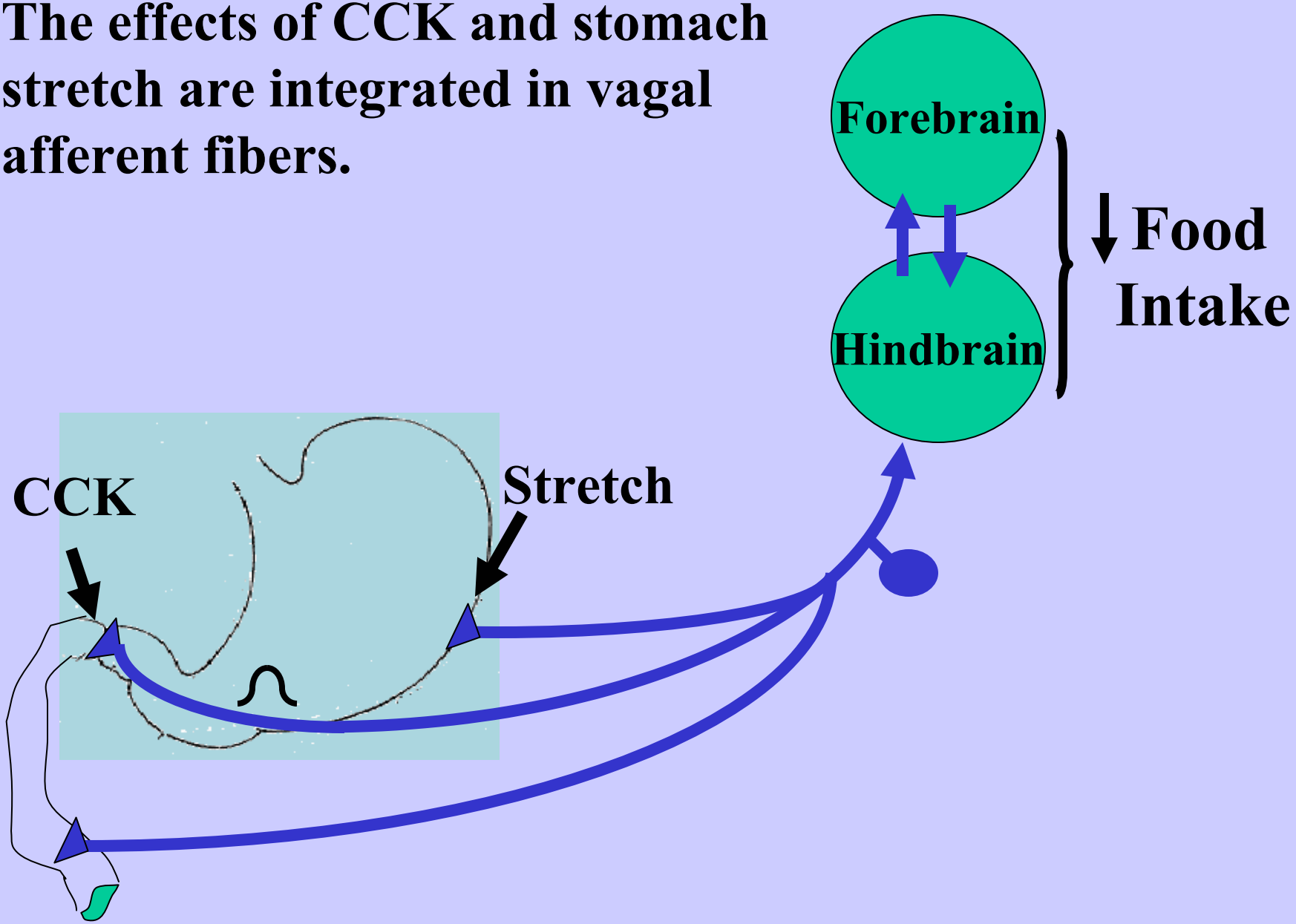

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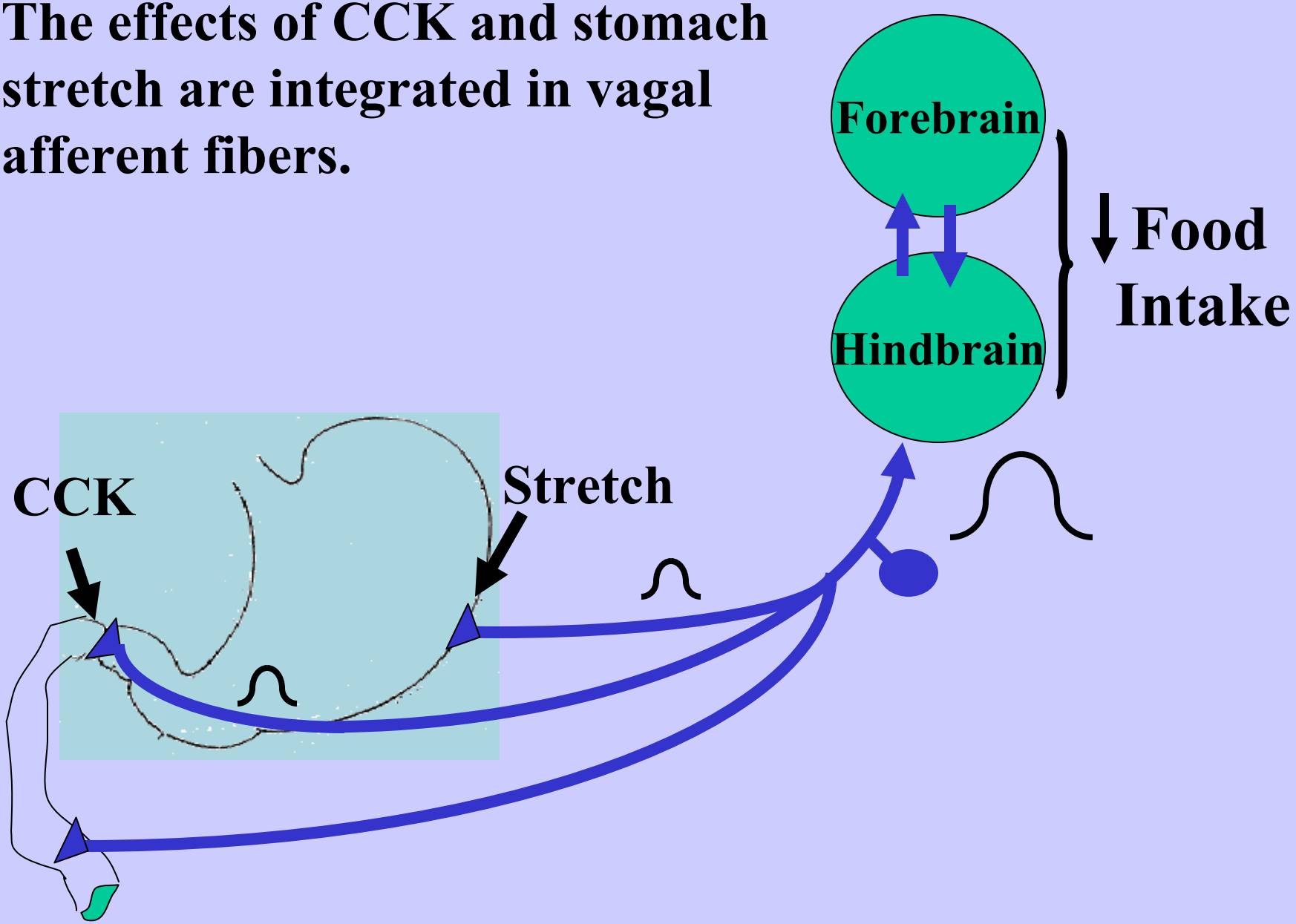
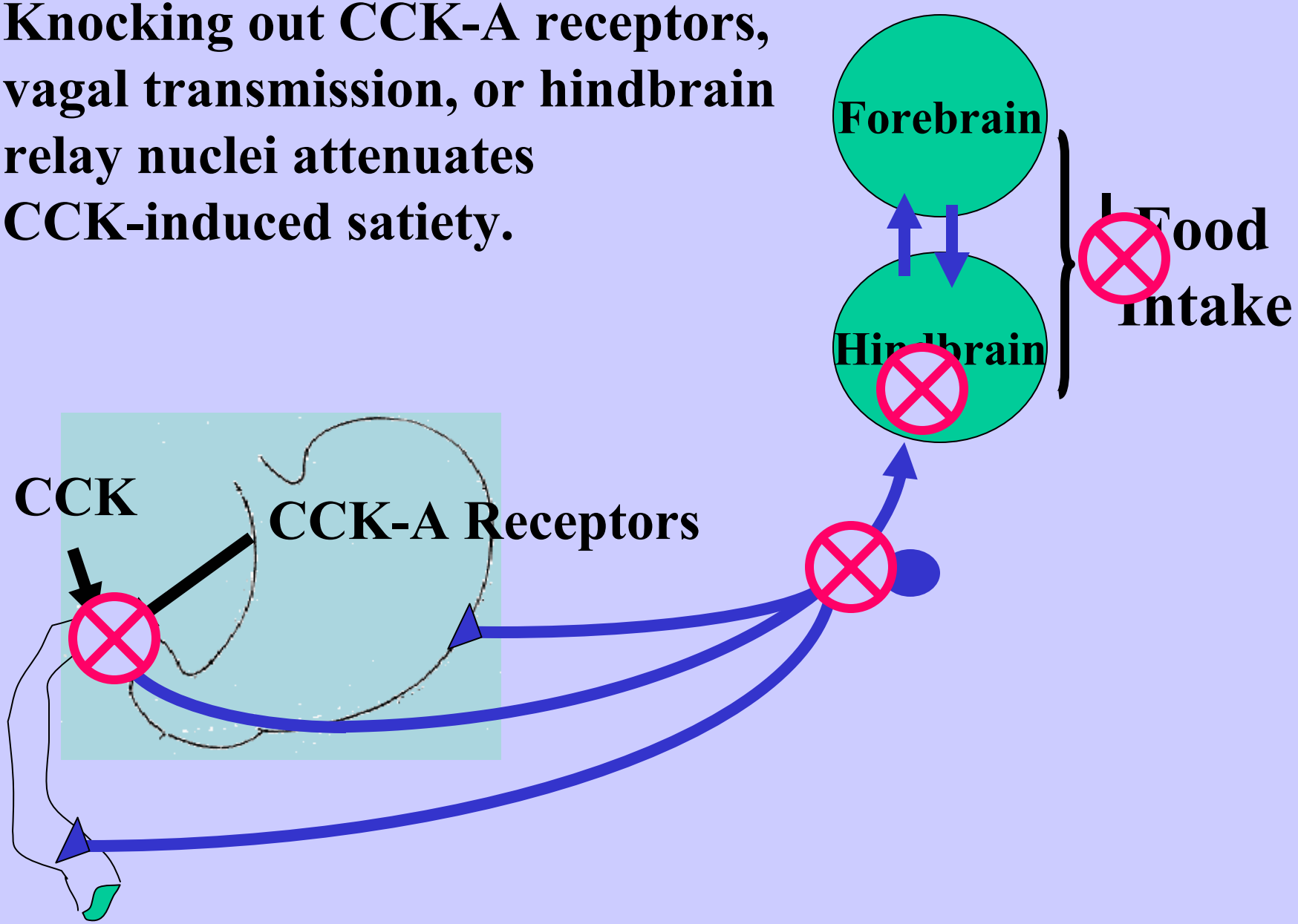
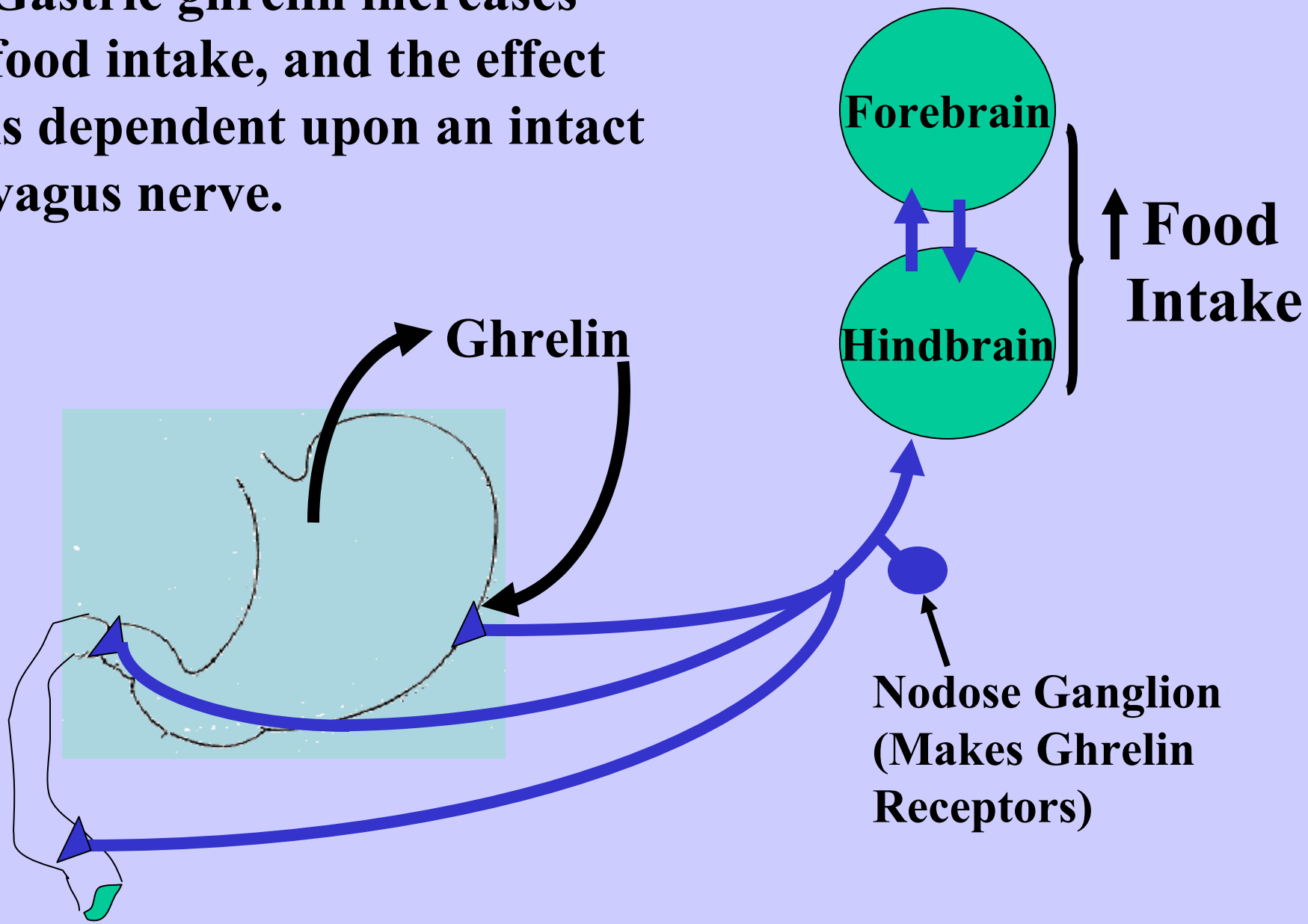
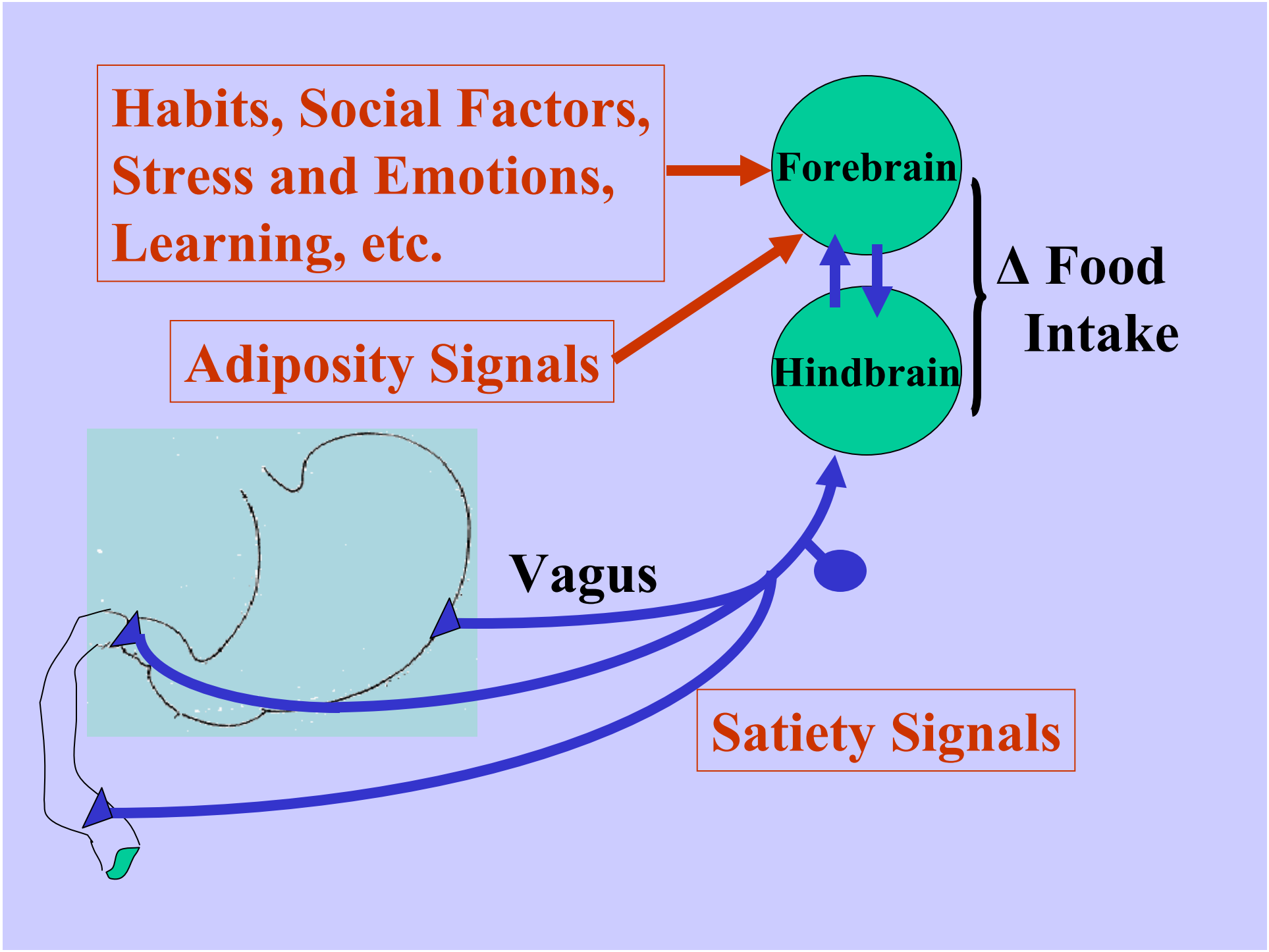


Knocking out CCK-A receptors, vagal transmission, or hindbrain relay nuclei attenuates CCK-induced satiety.



Gastric ghrelin increases food intake, and the effect is dependent upon an intact vagus nerve.




Habits, Social Factors,
Stress and Emotions,
Learning, etc.
Adiposity Signals
Forebrain
Hindbrain
Δ Food
Intake
Vagus
Satiety Signals

Can foods be used to increment endogenous CCK (or other satiety signals), leading to reduced meal size?

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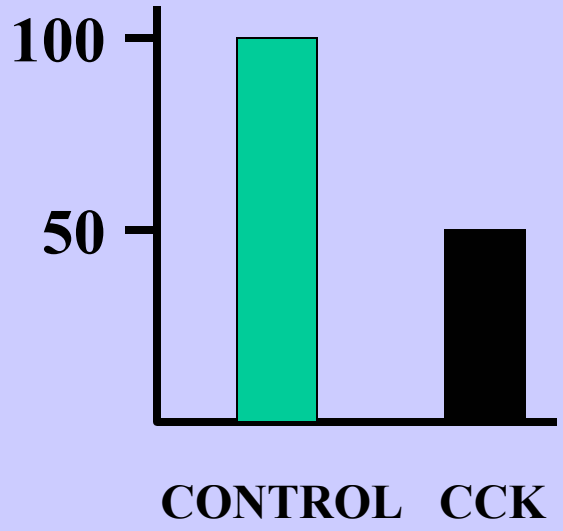
- **Soybean trypsin inhibitor (SBTI) stimulates CCK and inhibits ghrelin secretion.**
- **Potato proteinase inhibitor (POT II) stimulates CCK secretion.**
- **Phenylalanine (stimulates CCK secretion).**
- **Other (green tea, calcium [milk], water, etc.)**

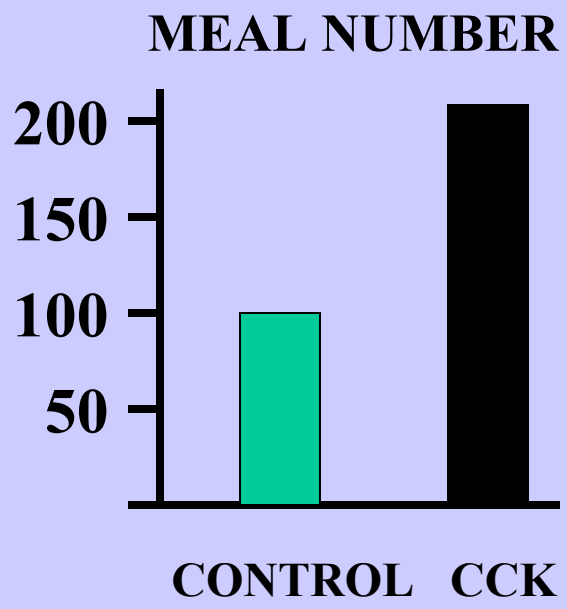
Is mimicking or triggering CCK or other satiety signals a worthwhile strategy for the food industry?

CCK REDUCES THE SIZE OF EVERY MEAL



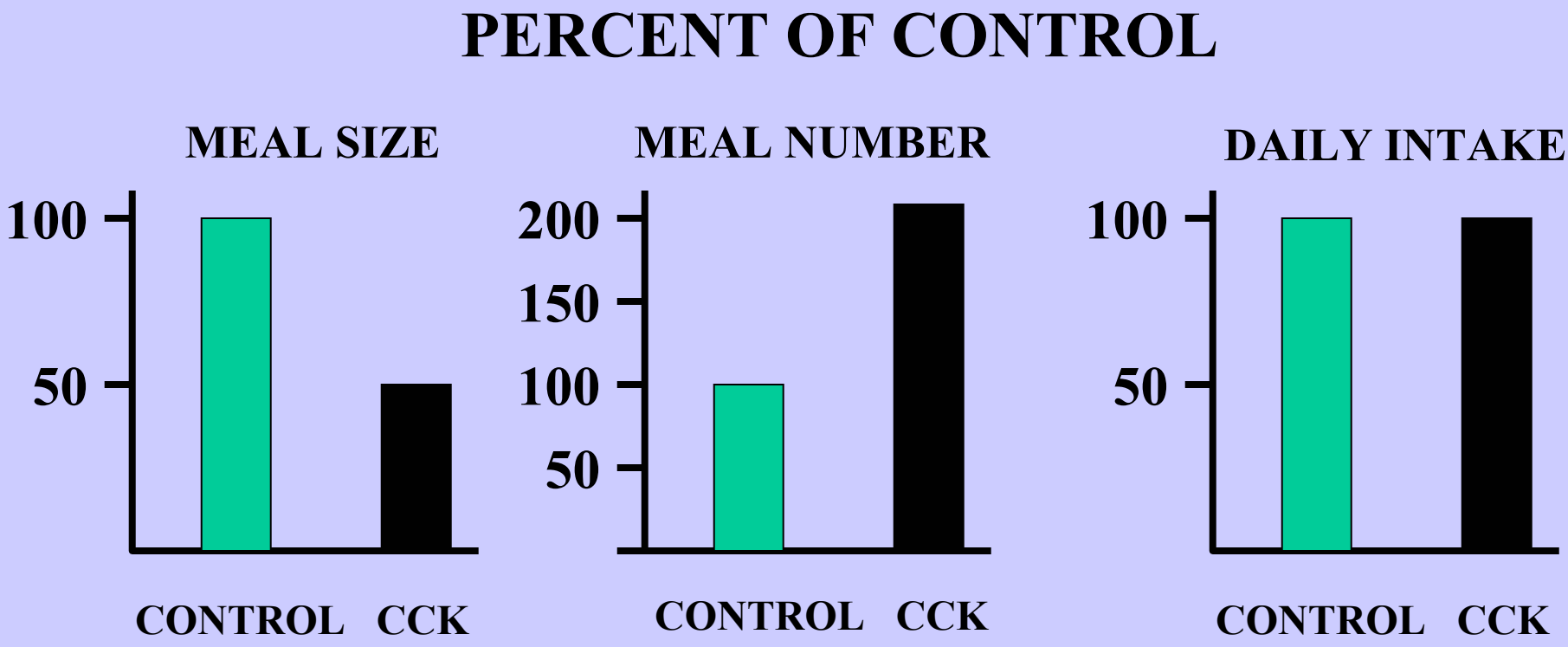
West et al., AJP 246:R776 1984

CCK INCREASES THE NUMBER OF MEALS



West et al., AJP 246:R776 1984

CCK, GIVEN ALONE, HAS NO NET EFFECT ON FOOD INTAKE OR BODY WEIGHT IN FREELY FEEDING RATS



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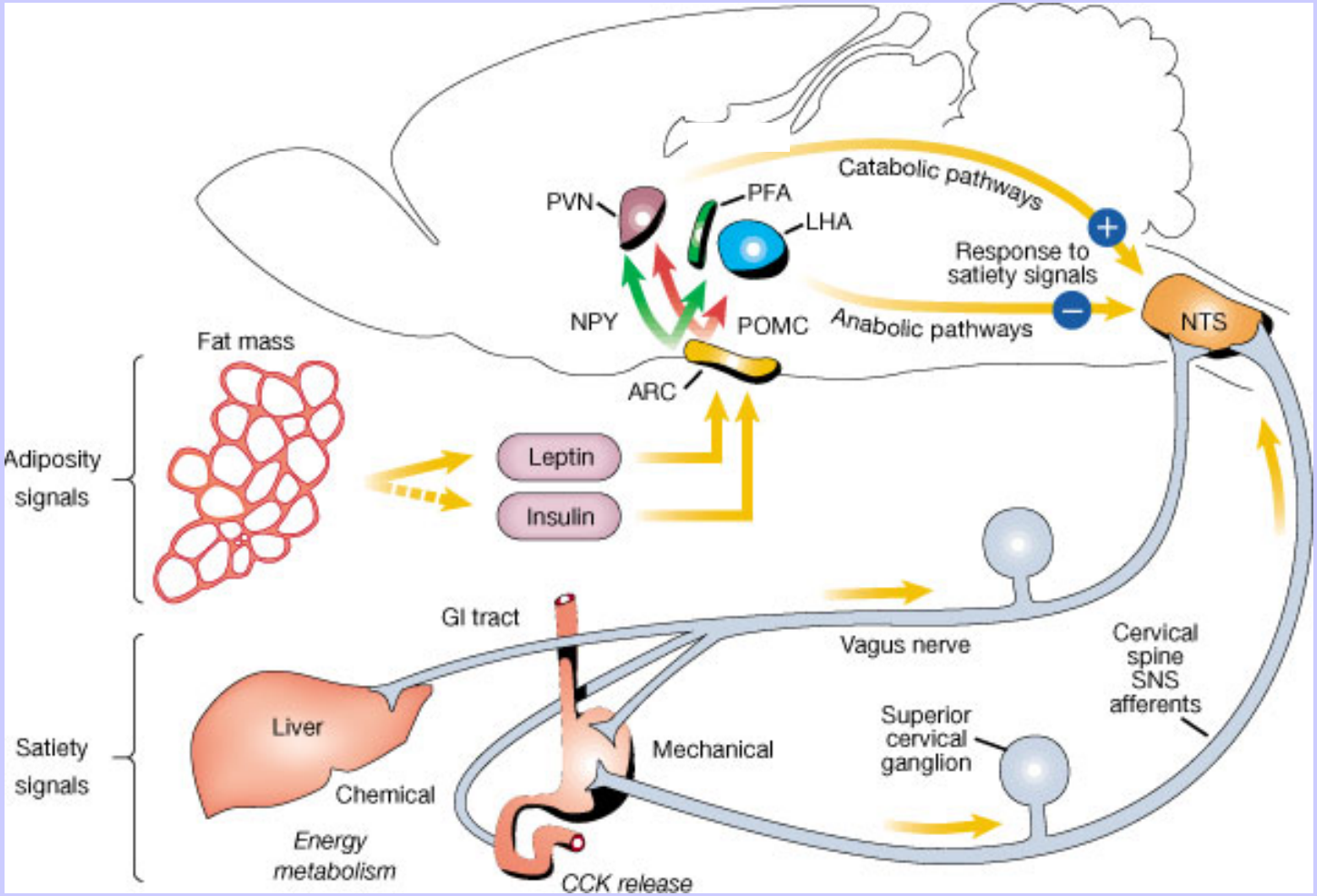
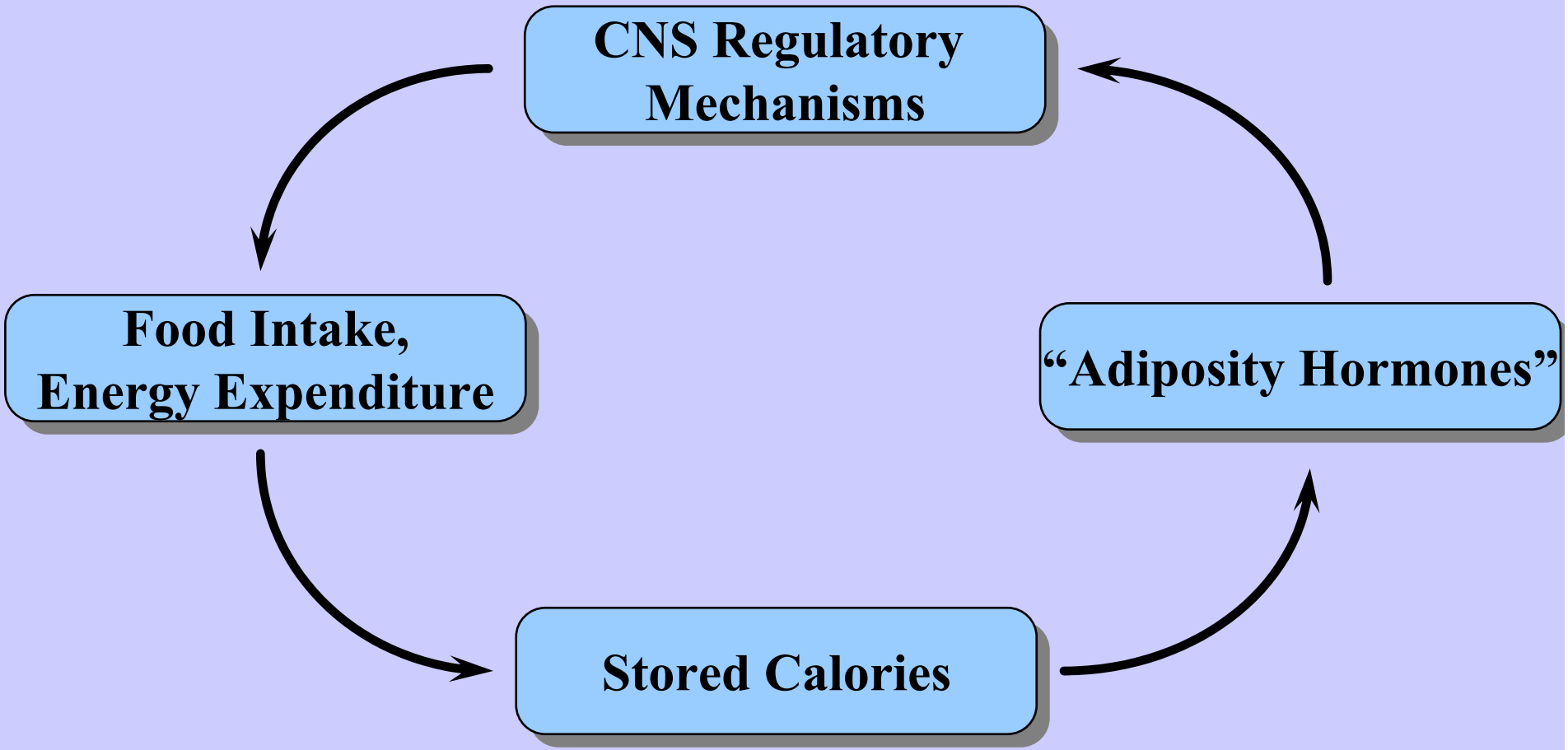
The control system over energy homeostasis is complex, relying upon several types of signals.



MW Schwartz, SC Woods et al., *Nature*, 2000

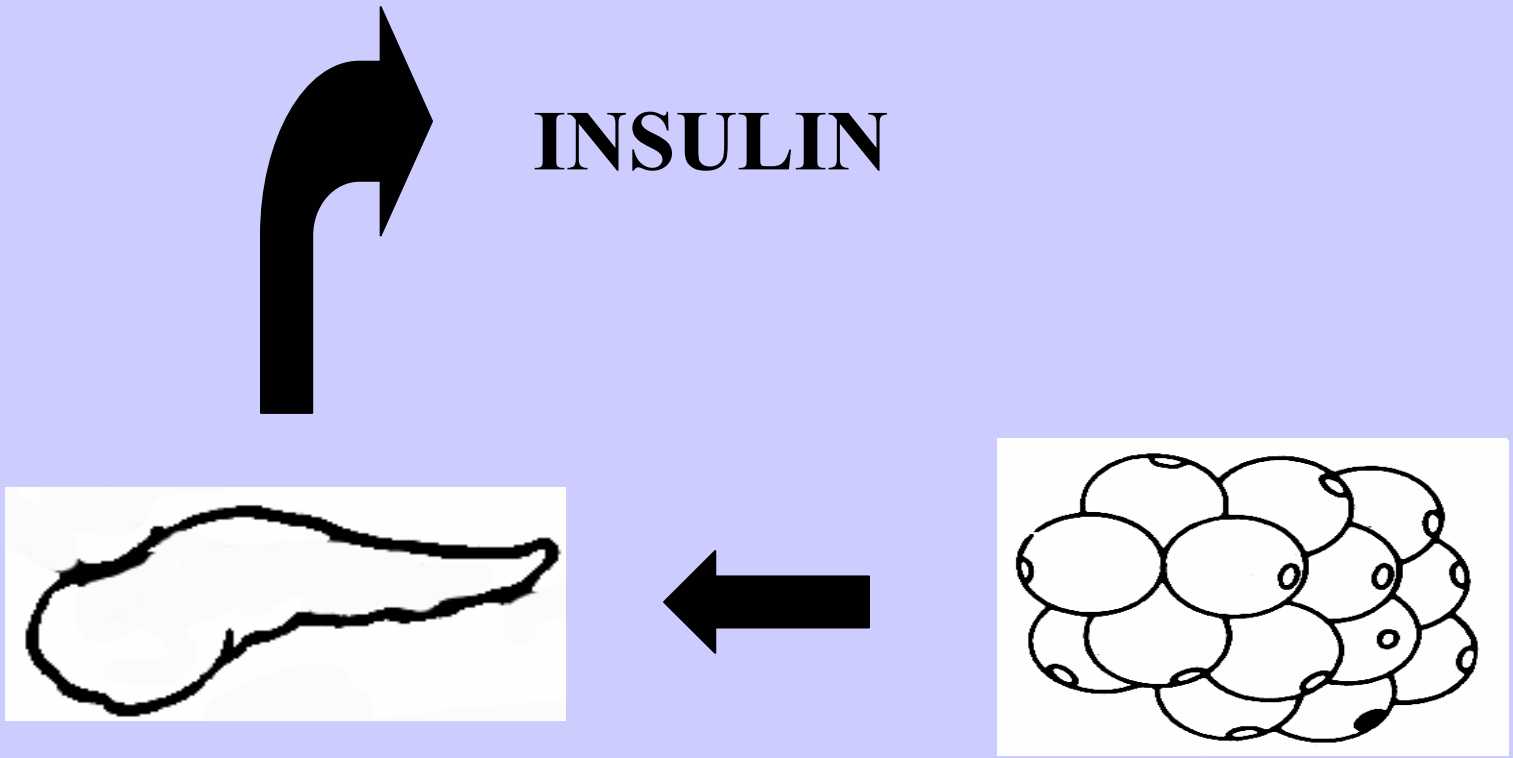
Humoral Regulation of Adiposity



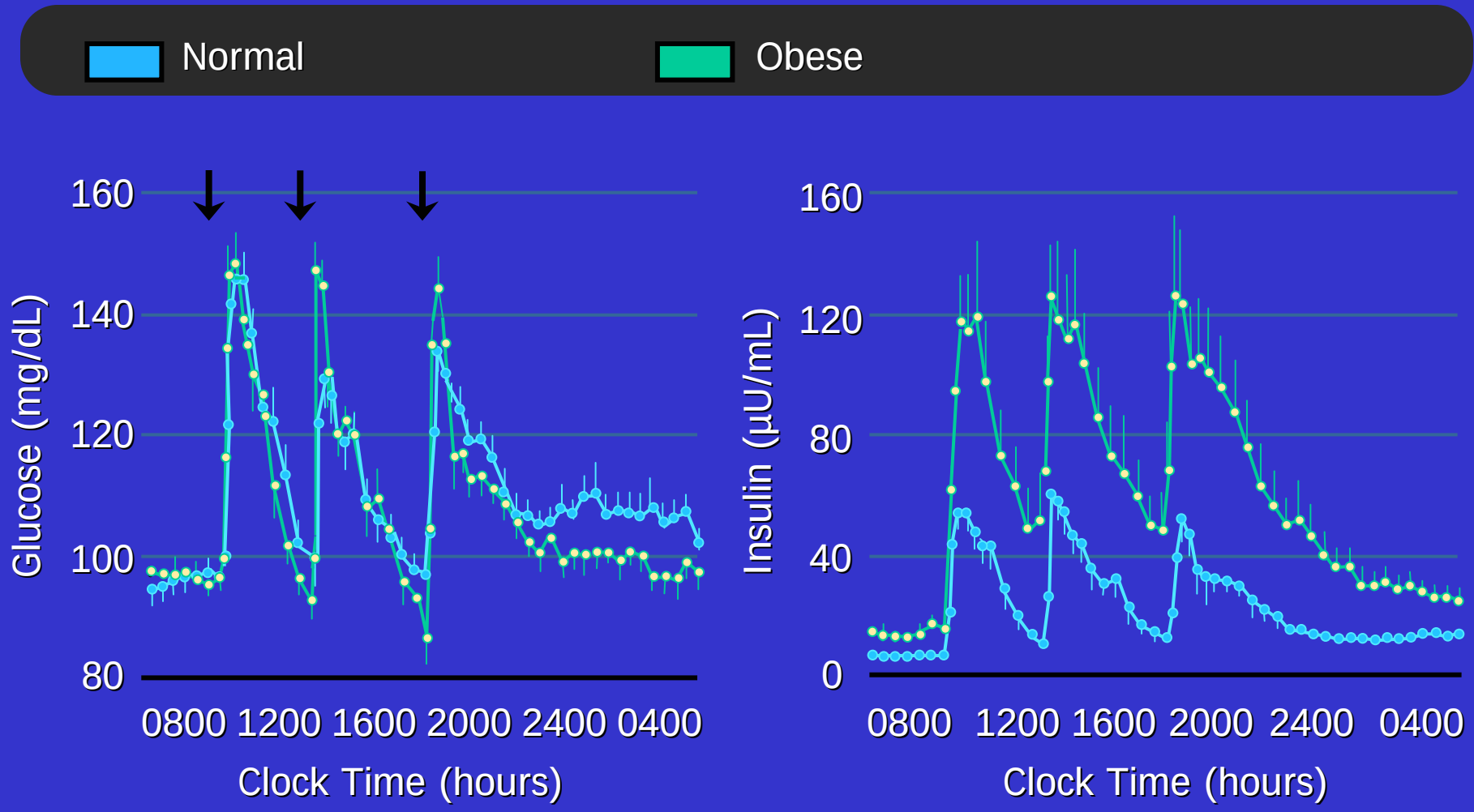
CONTROL OF BODY FAT

- **Strong evidence that key signals reach the brain via the blood**
- **Adiposity Hormones**
    - * **Insulin**

Pancreatic insulin secretion is directly proportional to the size of the fat mass.



Obese Humans Secrete More Insulin in Proportion to Adiposity



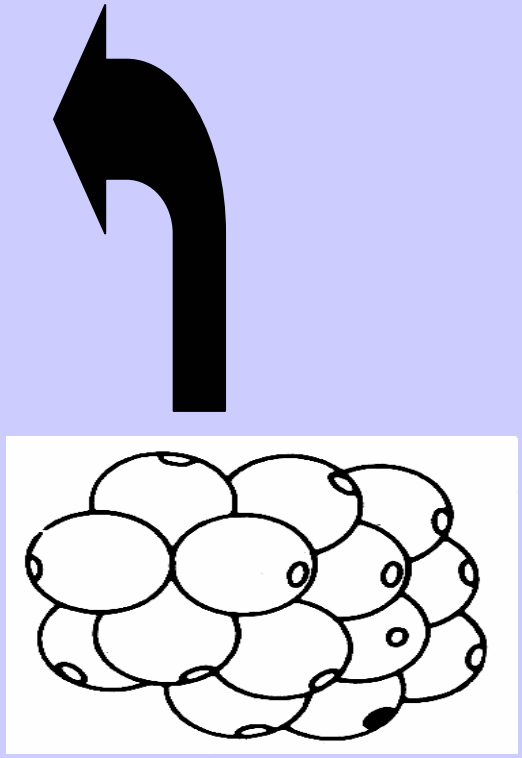
Polonsky KS, J Clin Invest 1988;81:442-8

CONTROL OF BODY FAT

- **Strong evidence that key signals reach the brain via the blood**
- **Adiposity Hormones**
    - * **Insulin**
    - * **Leptin**

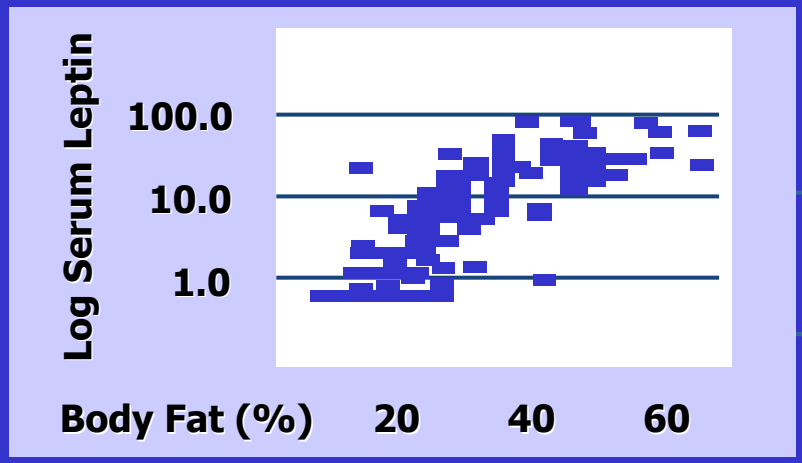
Leptin secretion is directly proportional to the size of the fat mass.

LEPTIN



WHITE FAT

Serum Leptin is Increased in Obesity



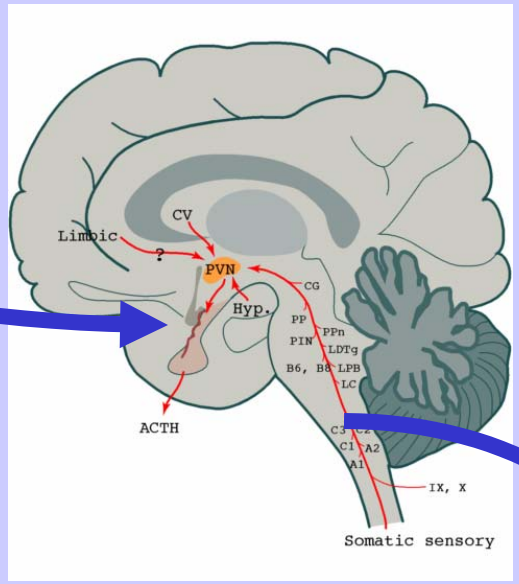
Serum Leptin (ng/mL)

100
80
60
40
20
0

Body Fat (%) 10 20 30 40 50 60 70

Considine RV, N Engl J Med 1996;334:292-5

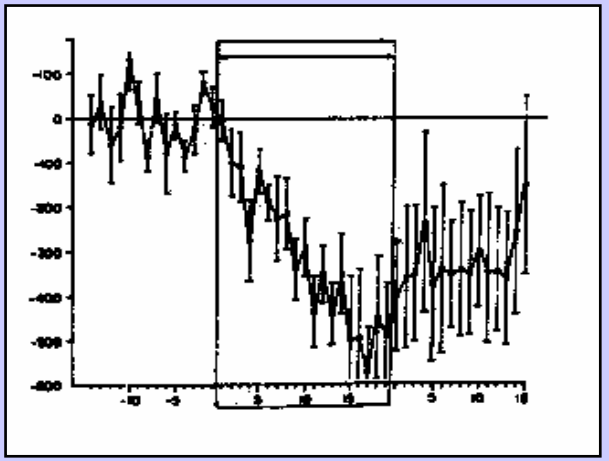
Increased Insulin or Leptin



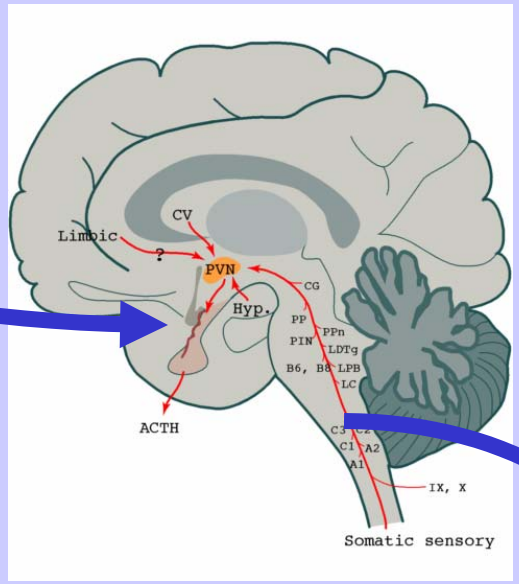
Decreased Food Intake and Increased Energy Expenditure

Increased Insulin or Leptin

INSULIN



Woods, *Nature*,1979



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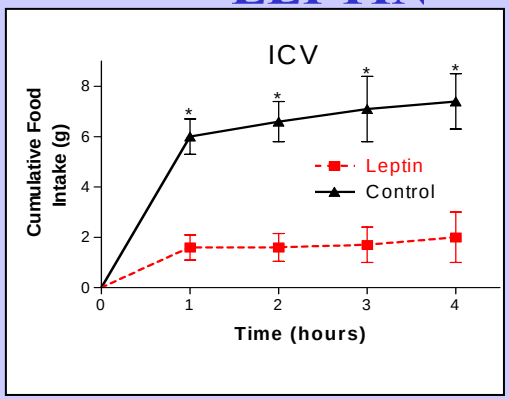
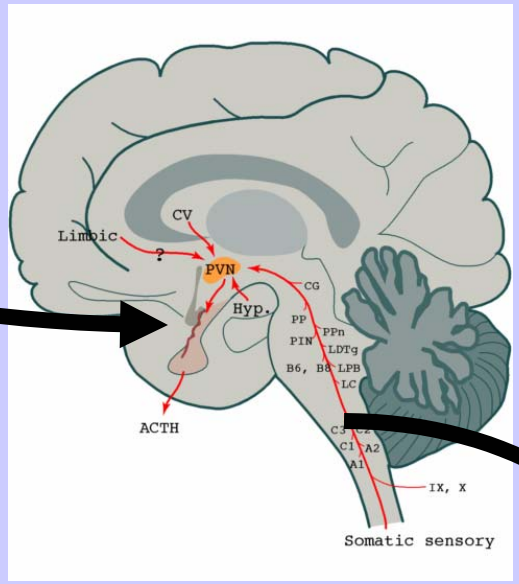


Seeley, *Horm Metab Res*,1995

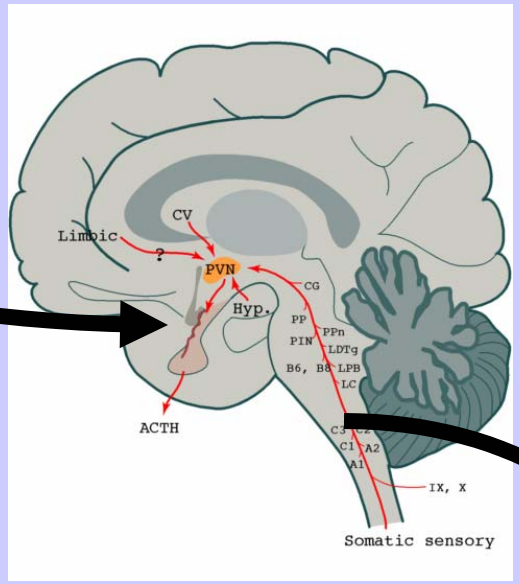
Decreased Food Intake and Increased Energy Expenditure

Decreased Insulin or Leptin Action

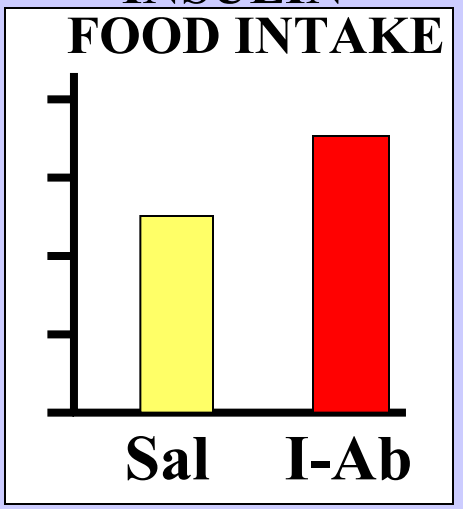


Increased Food Intake and Decreased Energy Expenditure

Decreased Insulin or Leptin Action

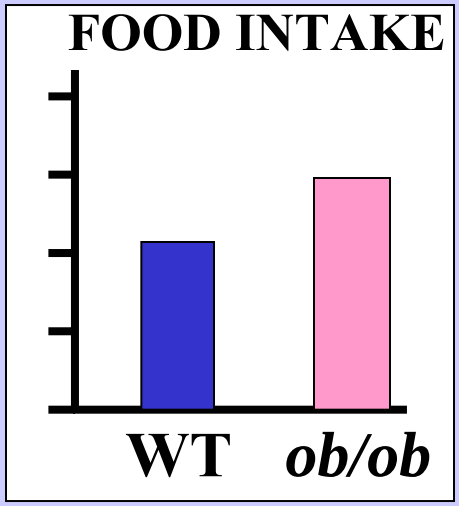


INSULIN



McGowan, *Behav NSci*,1985

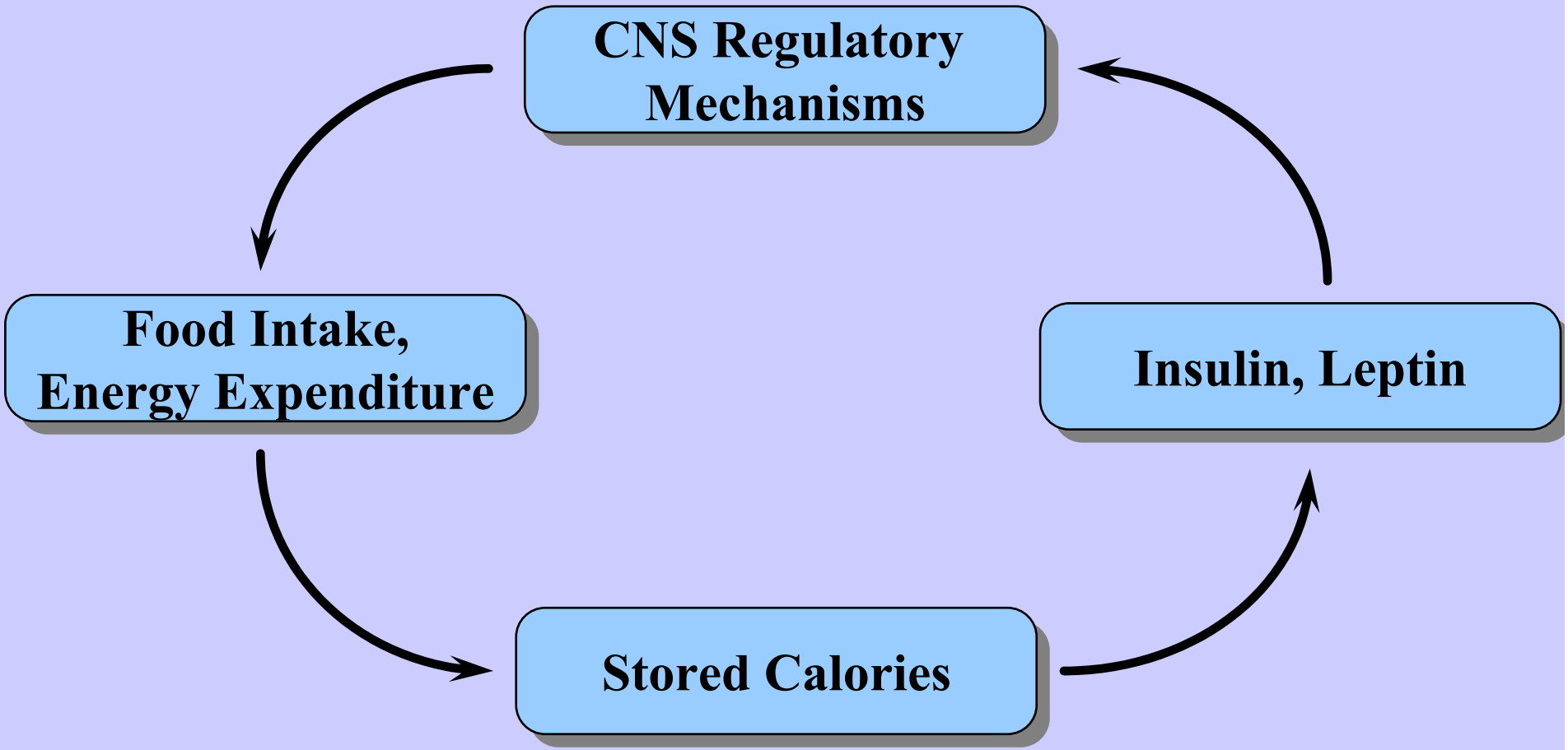
LEPTIN



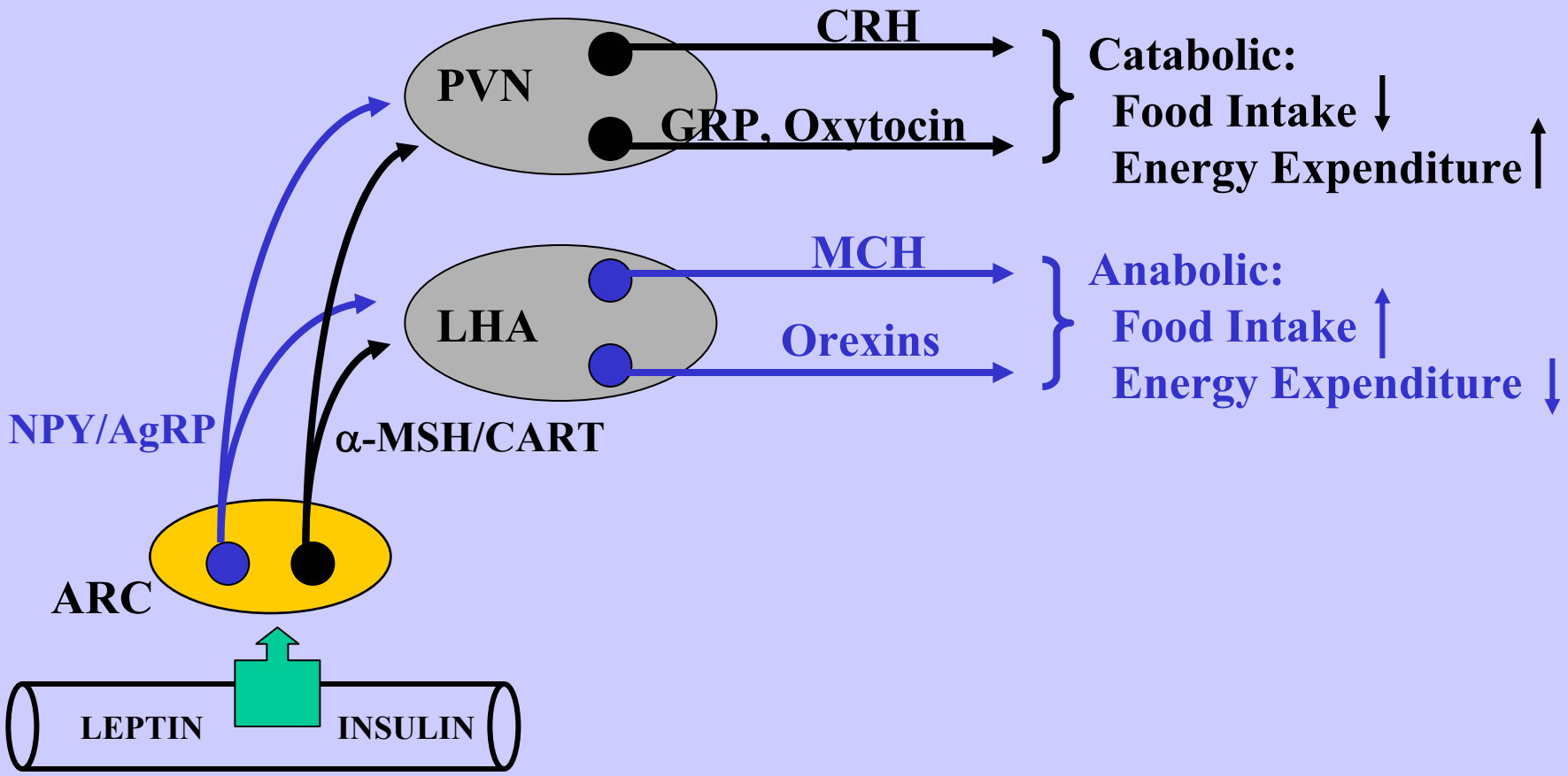
Coleman, *Diabetologia*, 1972

Increased Food Intake and Decreased Energy Expenditure

Humoral Regulation of Adiposity



The adiposity hormones, leptin and insulin, enter the hypothalamic arcuate nucleus and stimulate α-MSH/ CART neurons while inhibiting NPY/AgRP neurons, thus activating catabolic pathways while inhibiting anabolic pathways.



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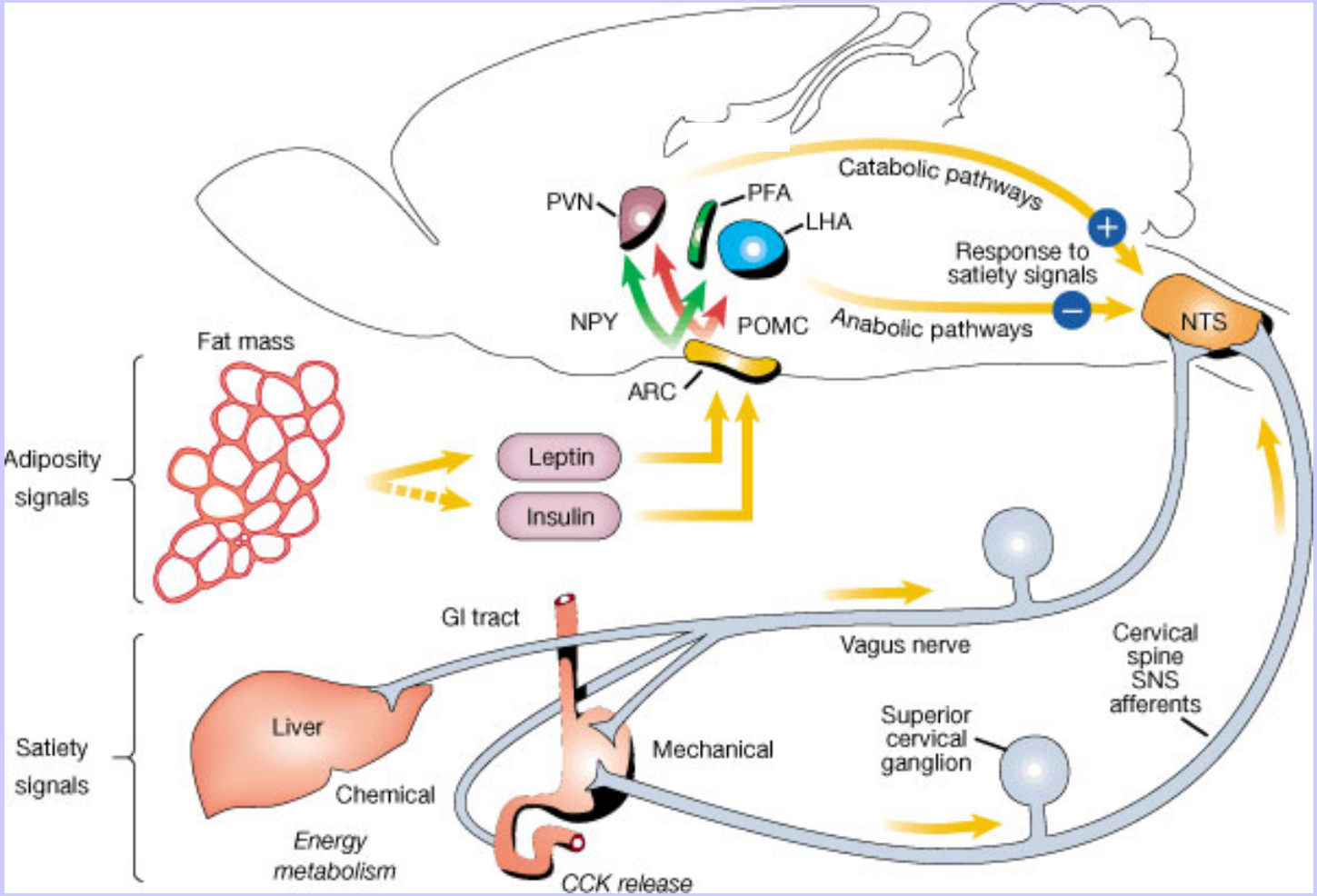
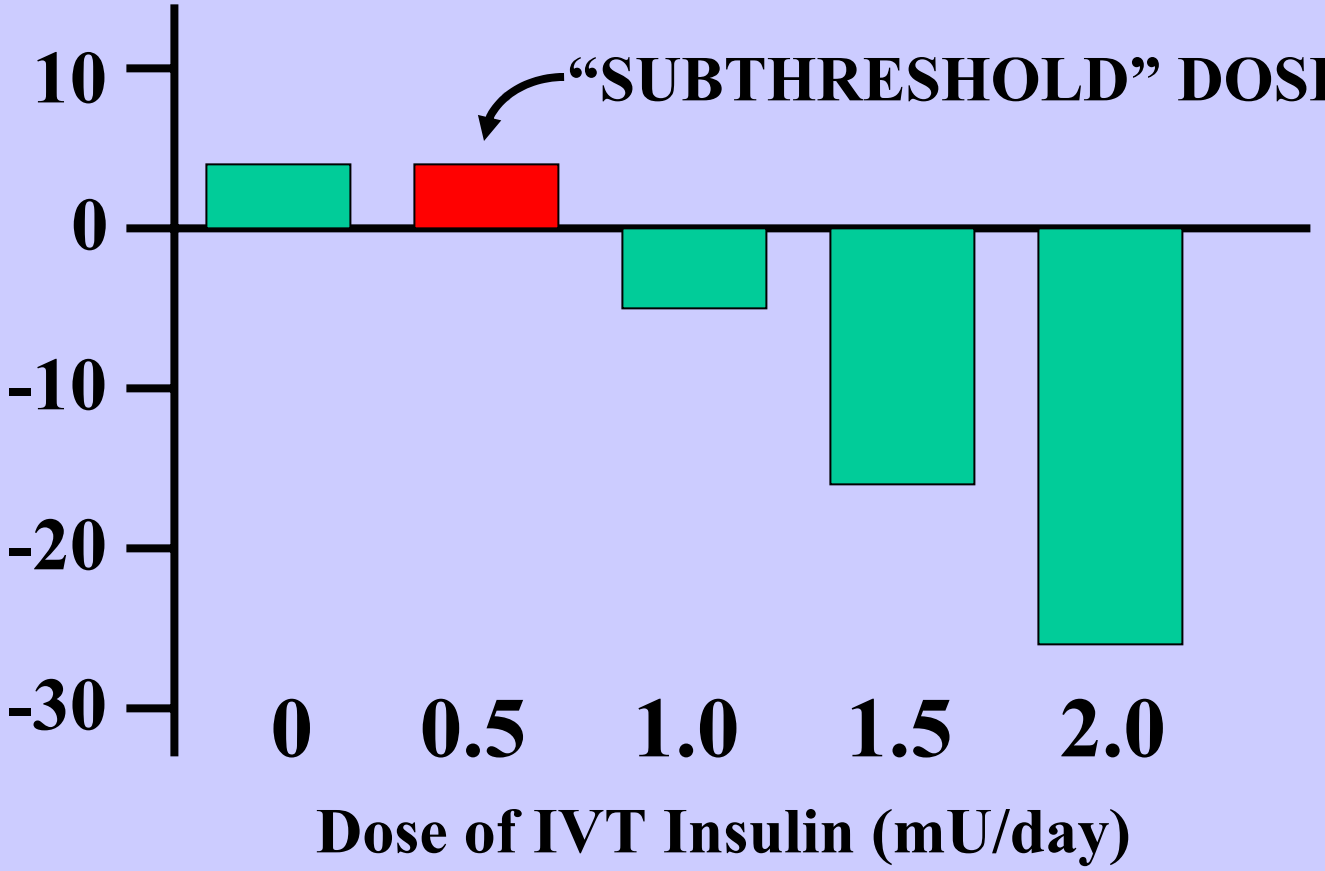


MW Schwartz, SC Woods et al., *Nature*, 2000

Features of satiety signals:

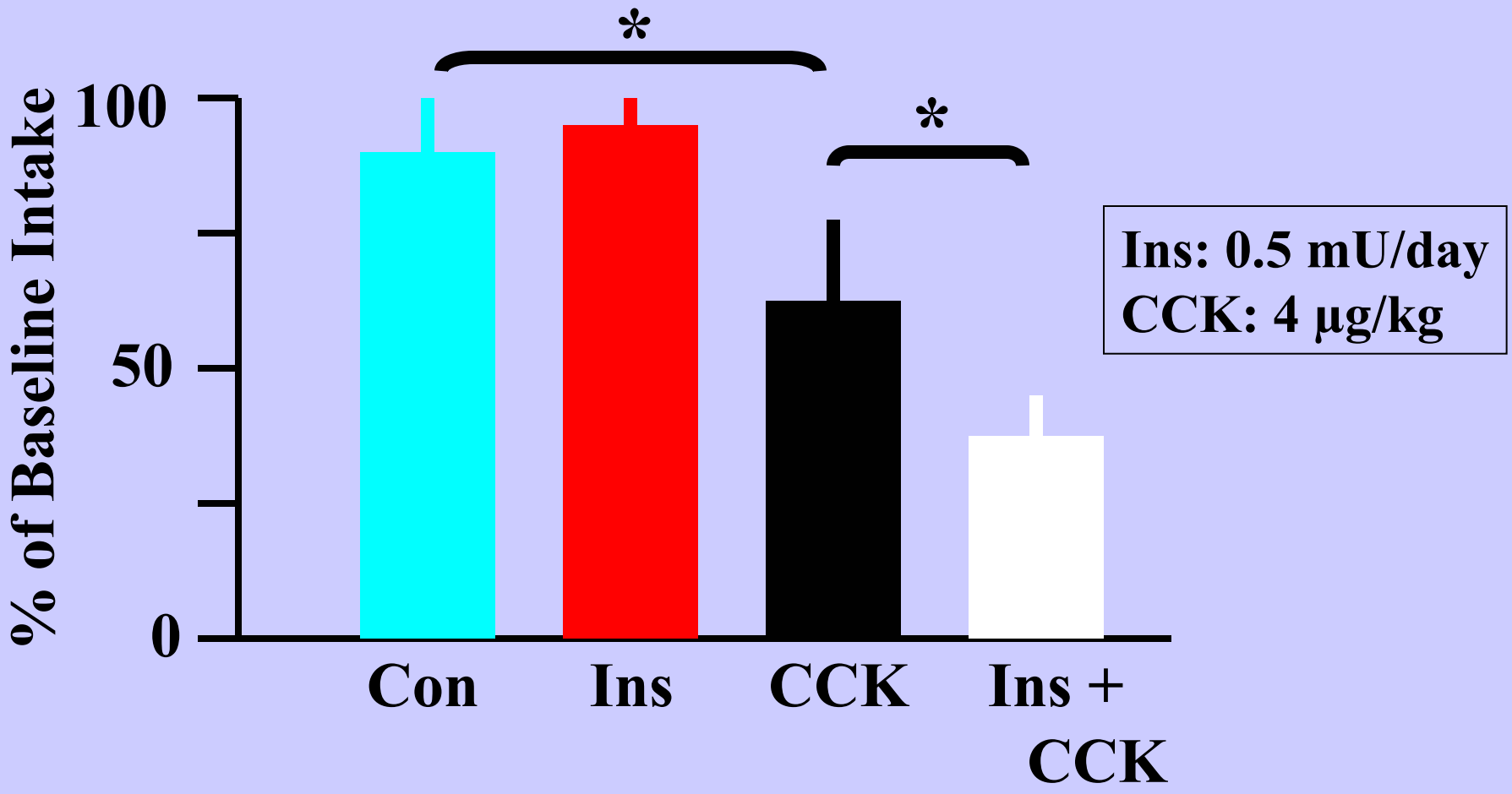
- Most are made in both the GI tract and the brain.
- They are efficacious in humans.
- Blocking their action leads to increased meal size.
- Their efficacy is enhanced when adiposity signals are elevated.

IVT insulin dose-dependently reduces body weight over 6 days (g) in rats



Riedy et al., P&B, 58: 755,1995

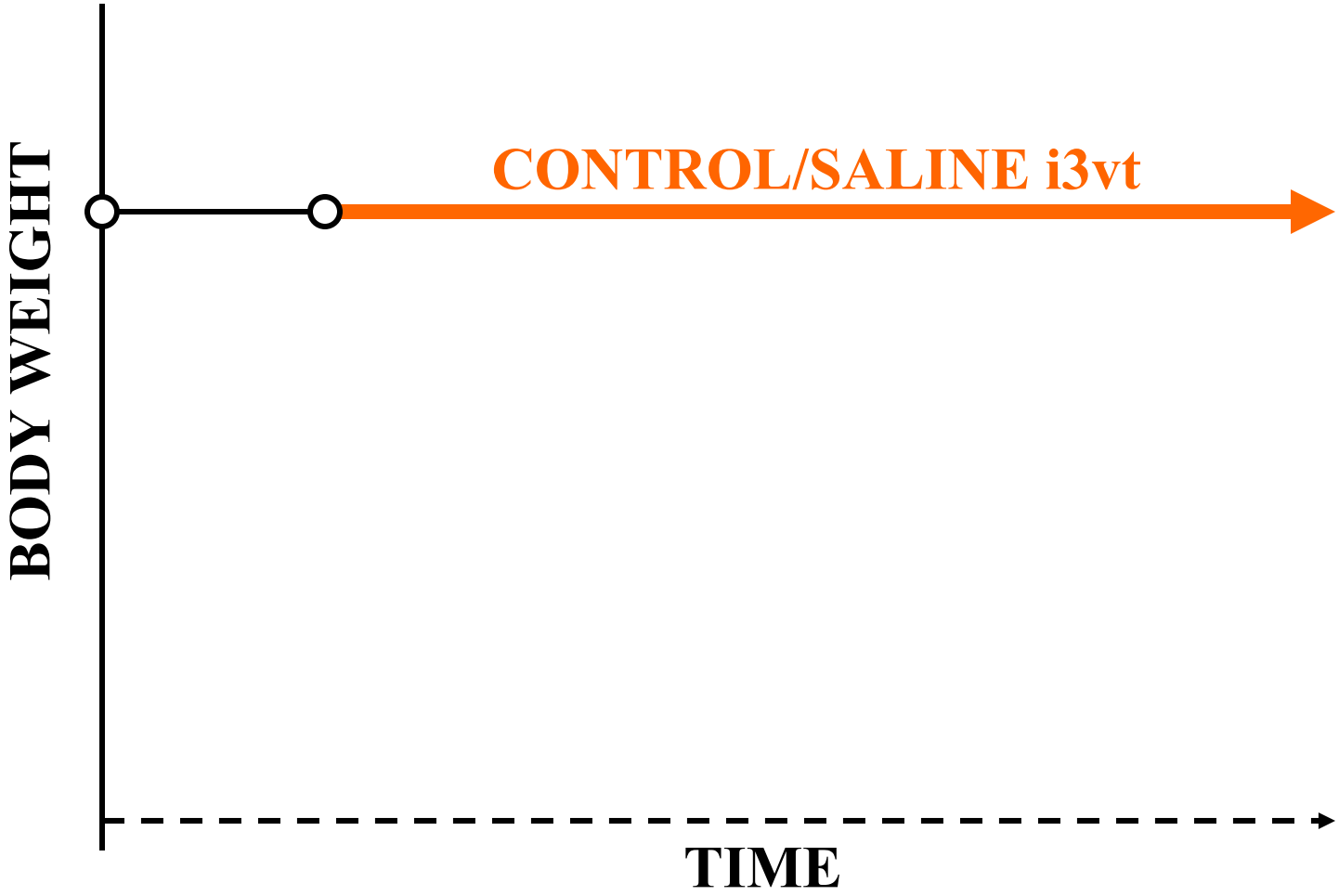
Subthreshold insulin increases the satiating effect of IP CCK



Riedy et al., P&B, 58: 755,1995

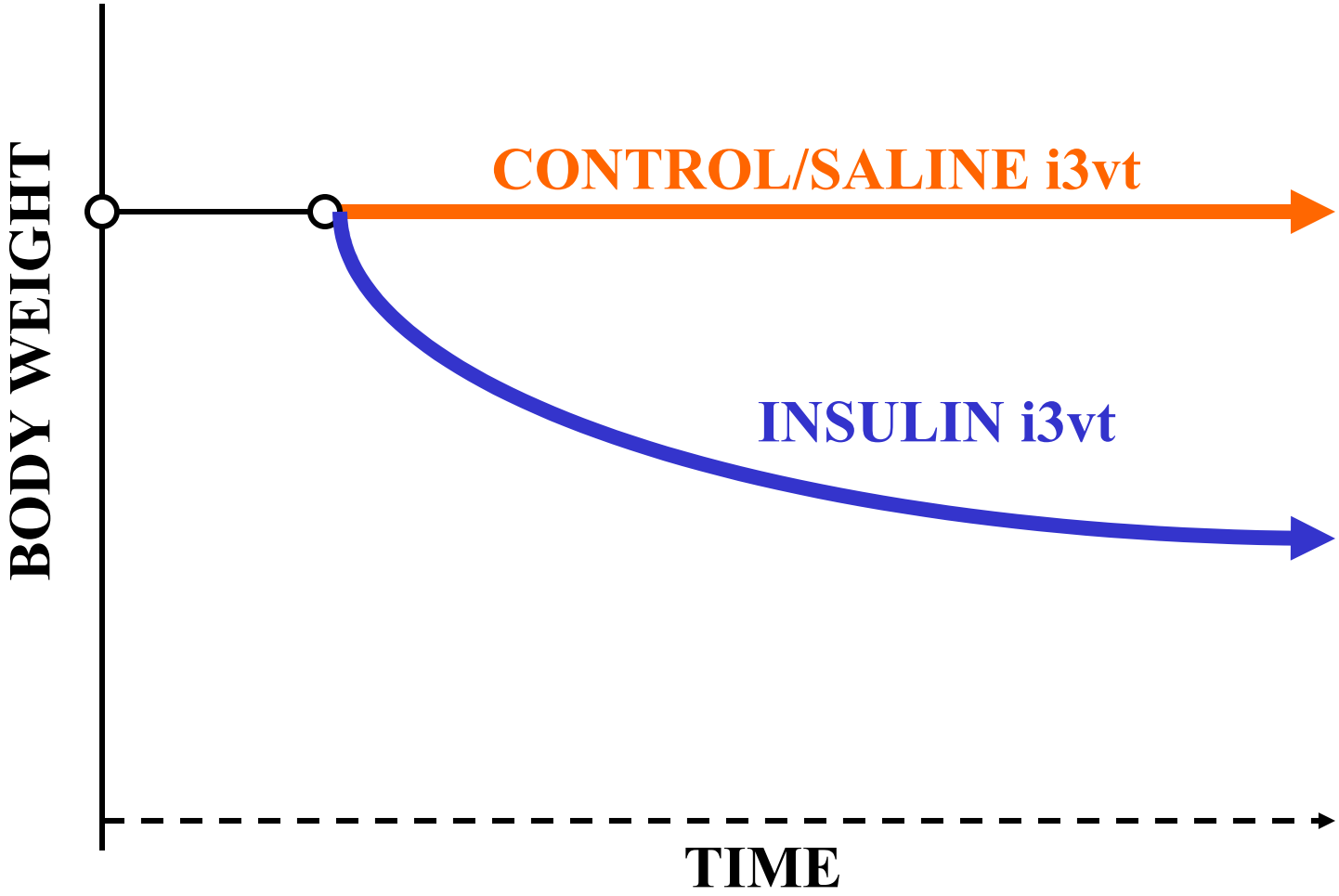
Why are insulin and leptin called "adiposity signals," and CCK and other GI peptides called "satiety signals?"

ADIPOSITY SIGNALS



M Chavez et al., *Behav Neurosci*, 1995

ADIPOSITY SIGNALS



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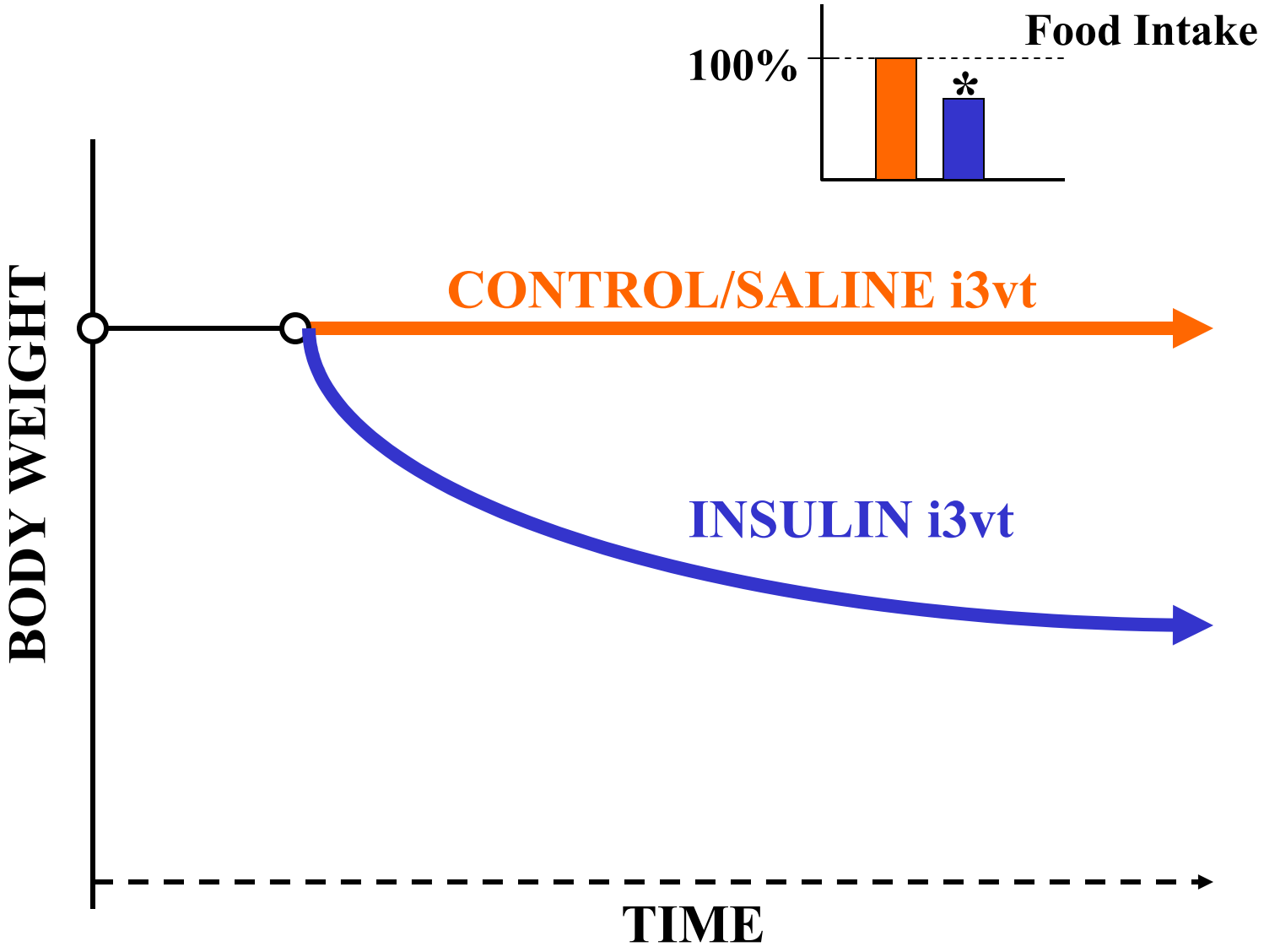

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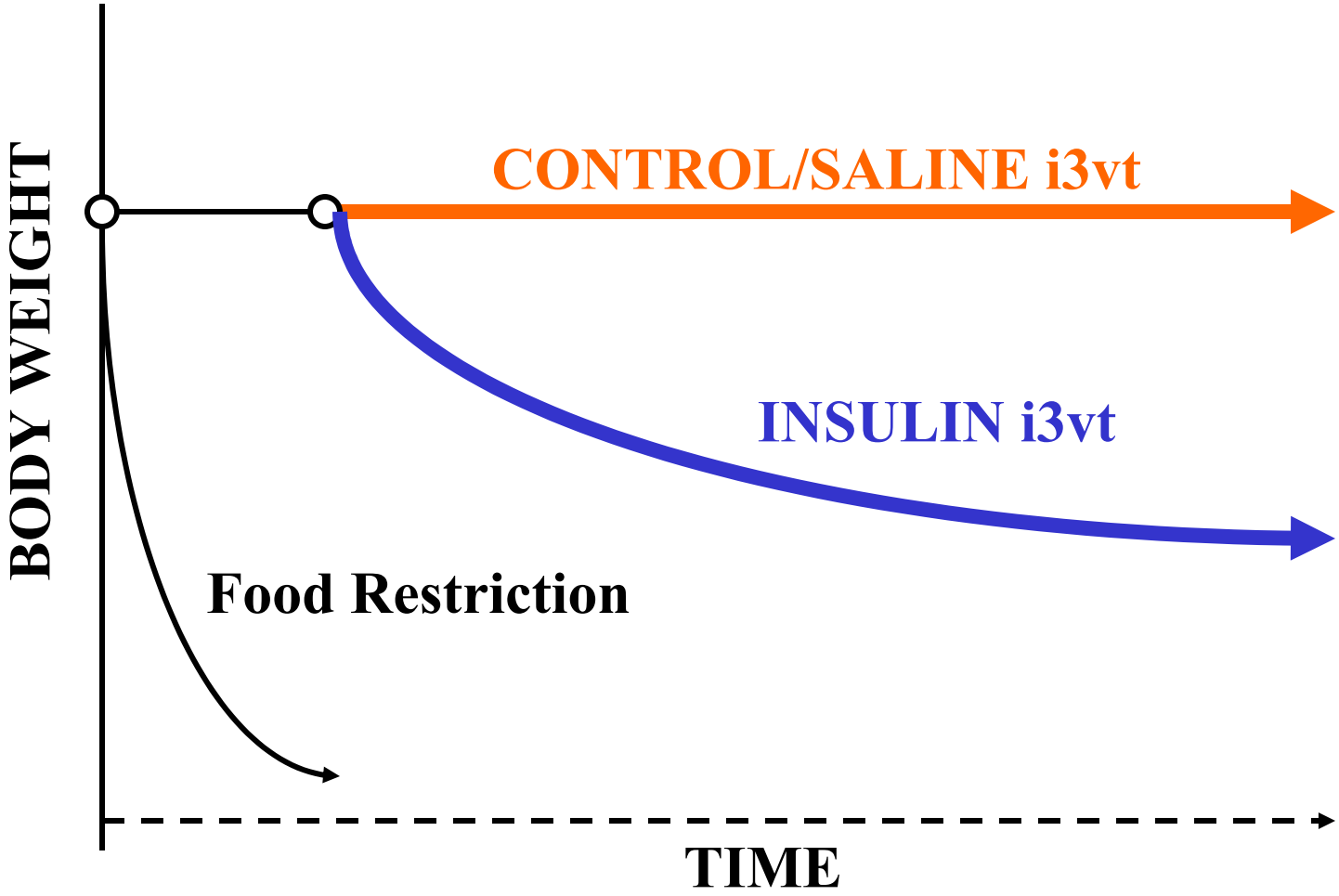

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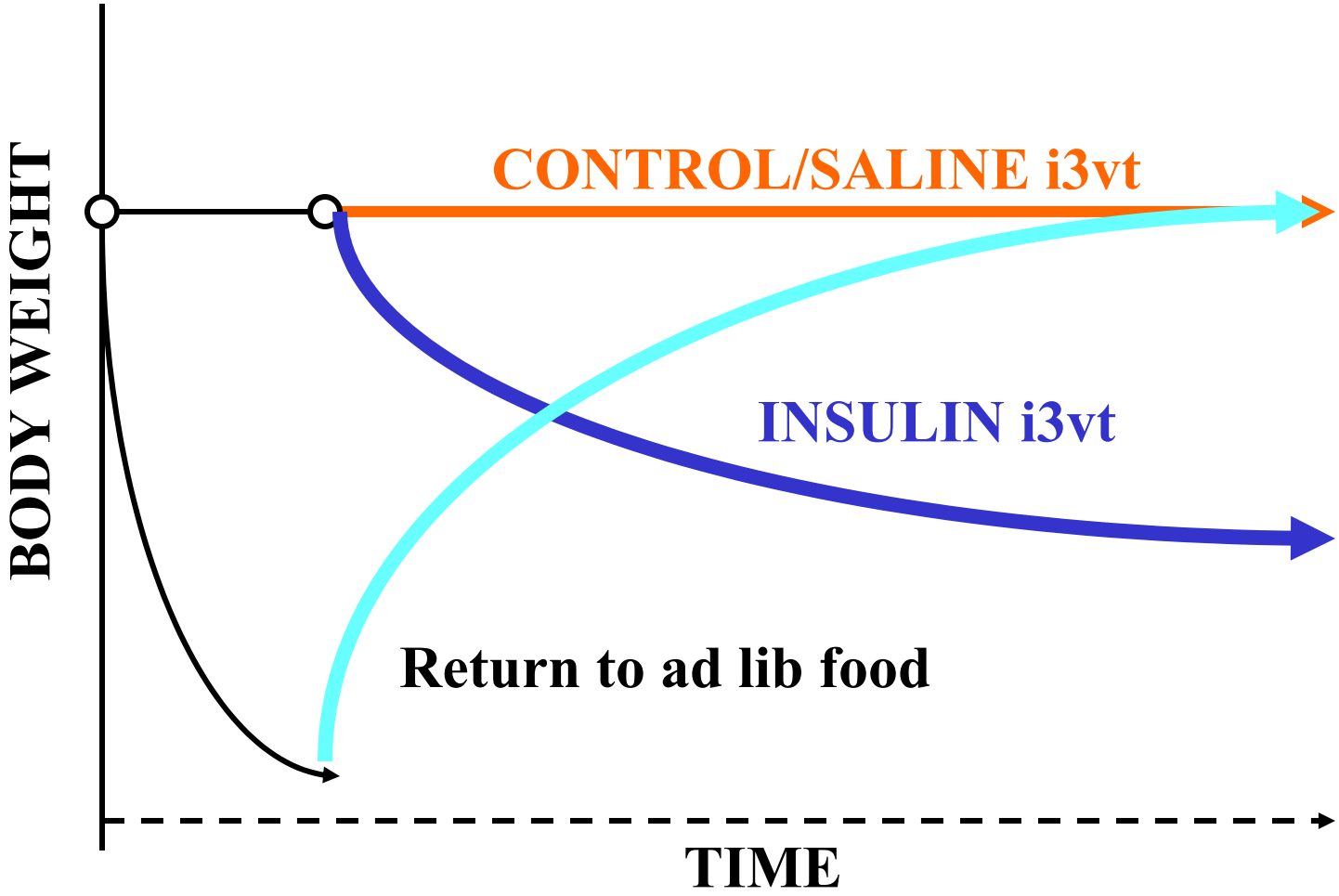

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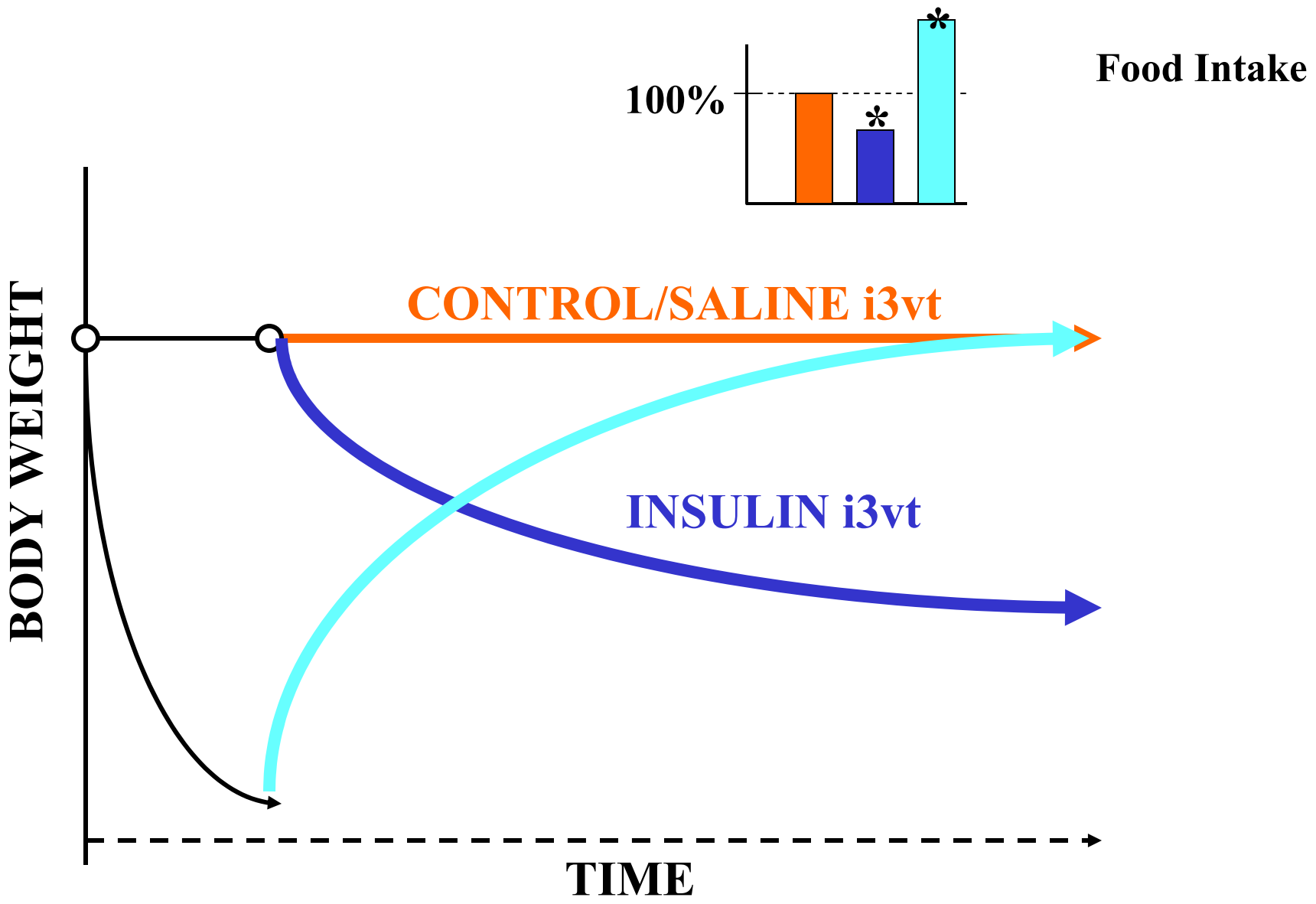
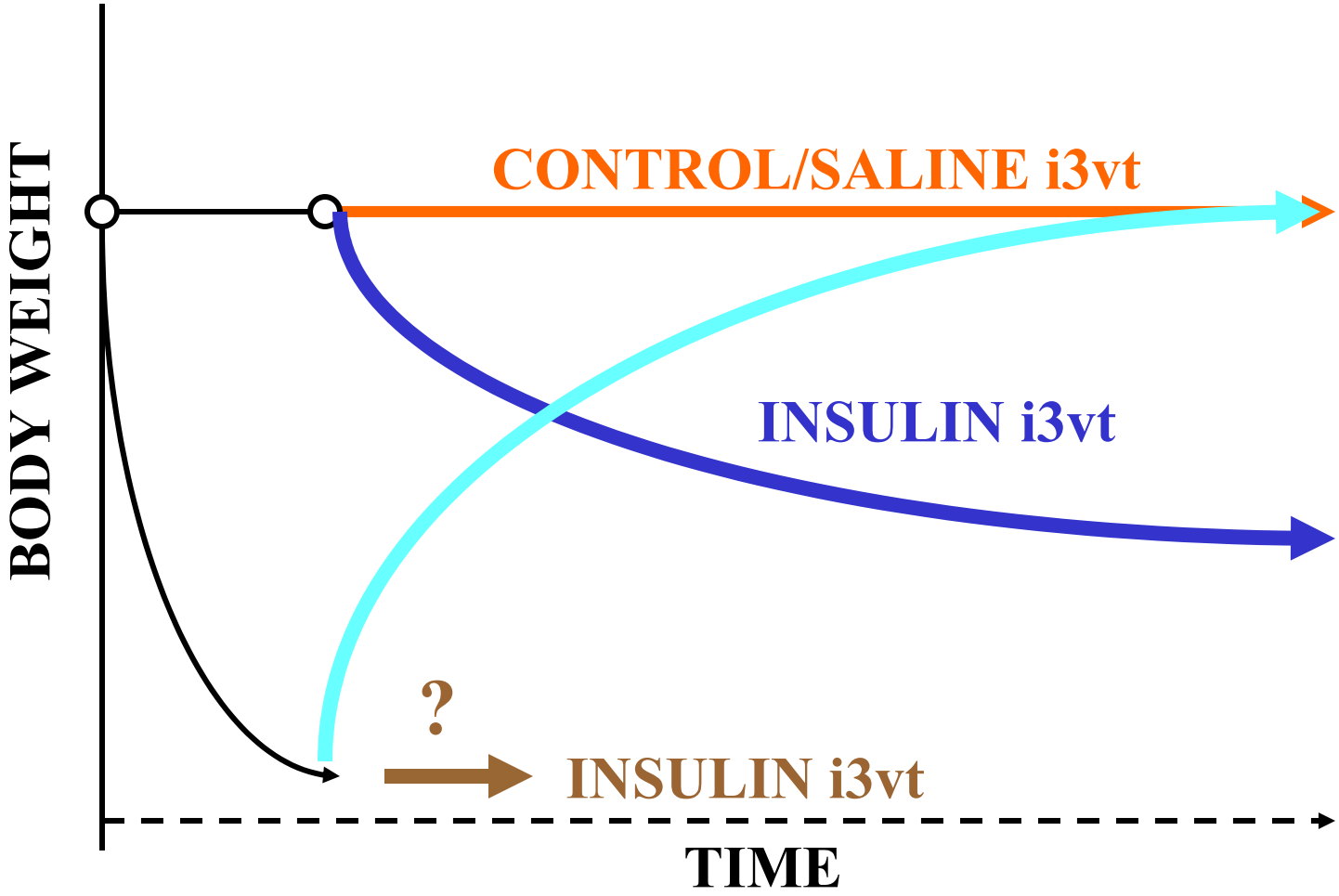


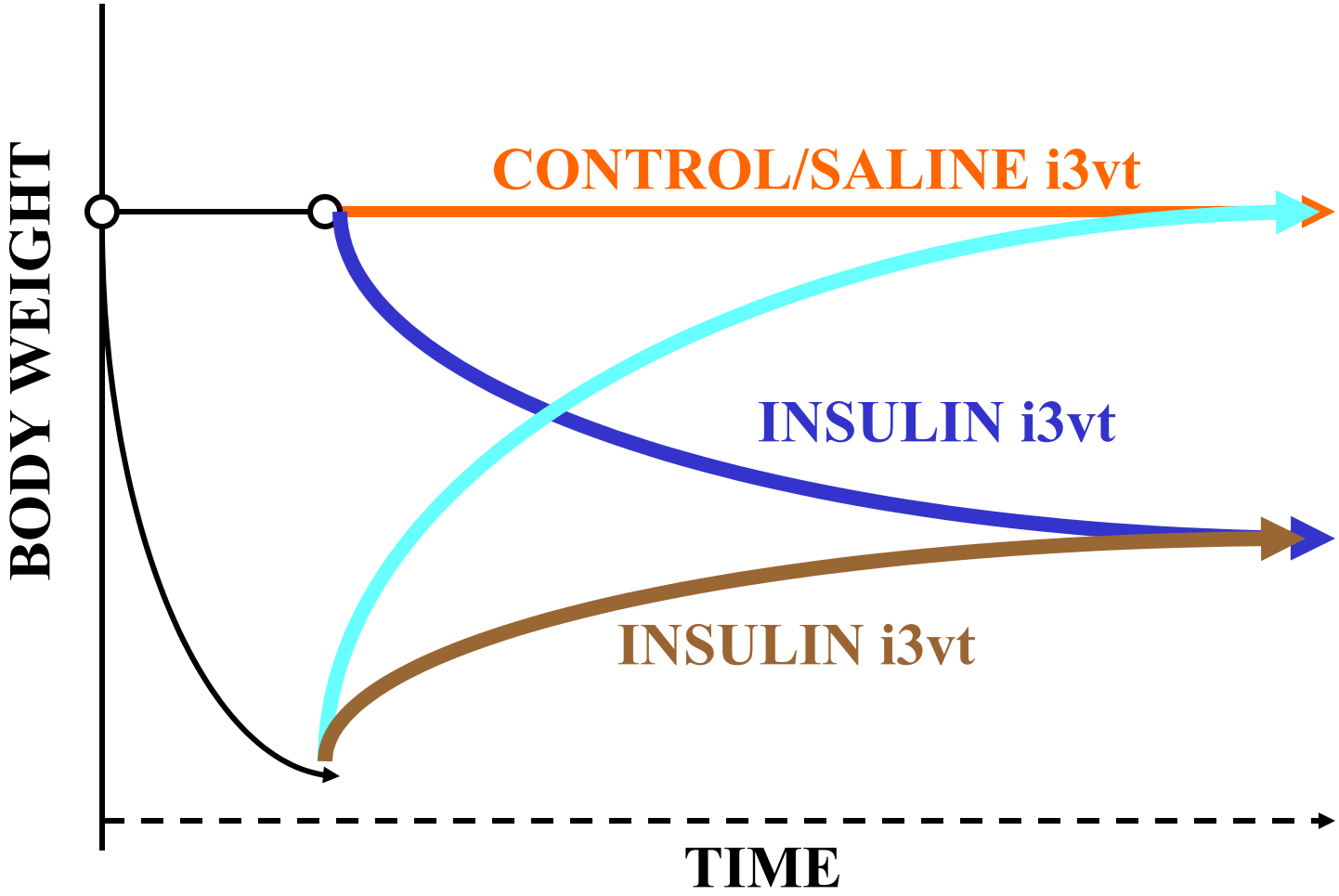
M Chavez et al., *Behav Neurosci*, 1995

ADIPOSITY SIGNALS

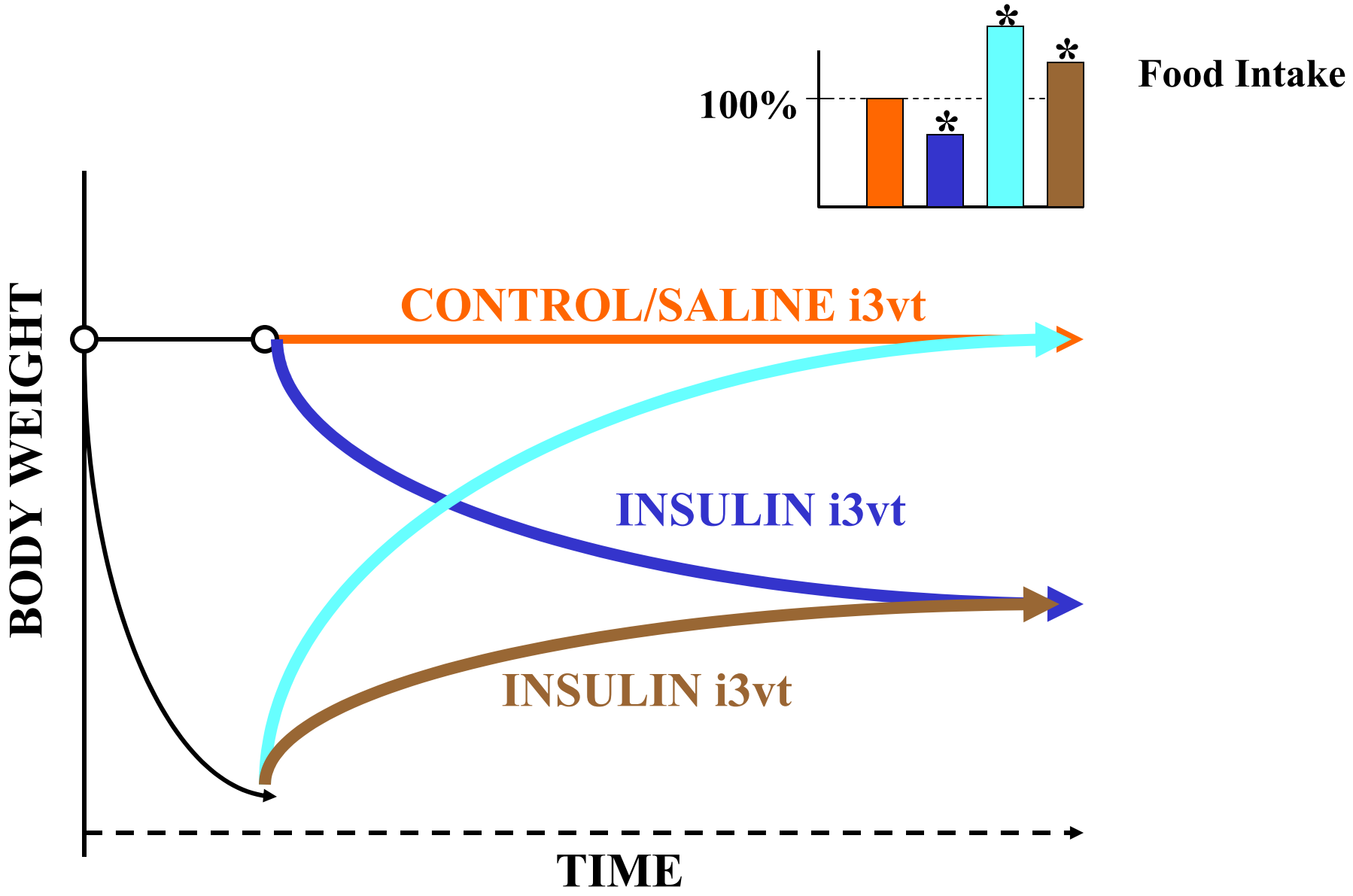


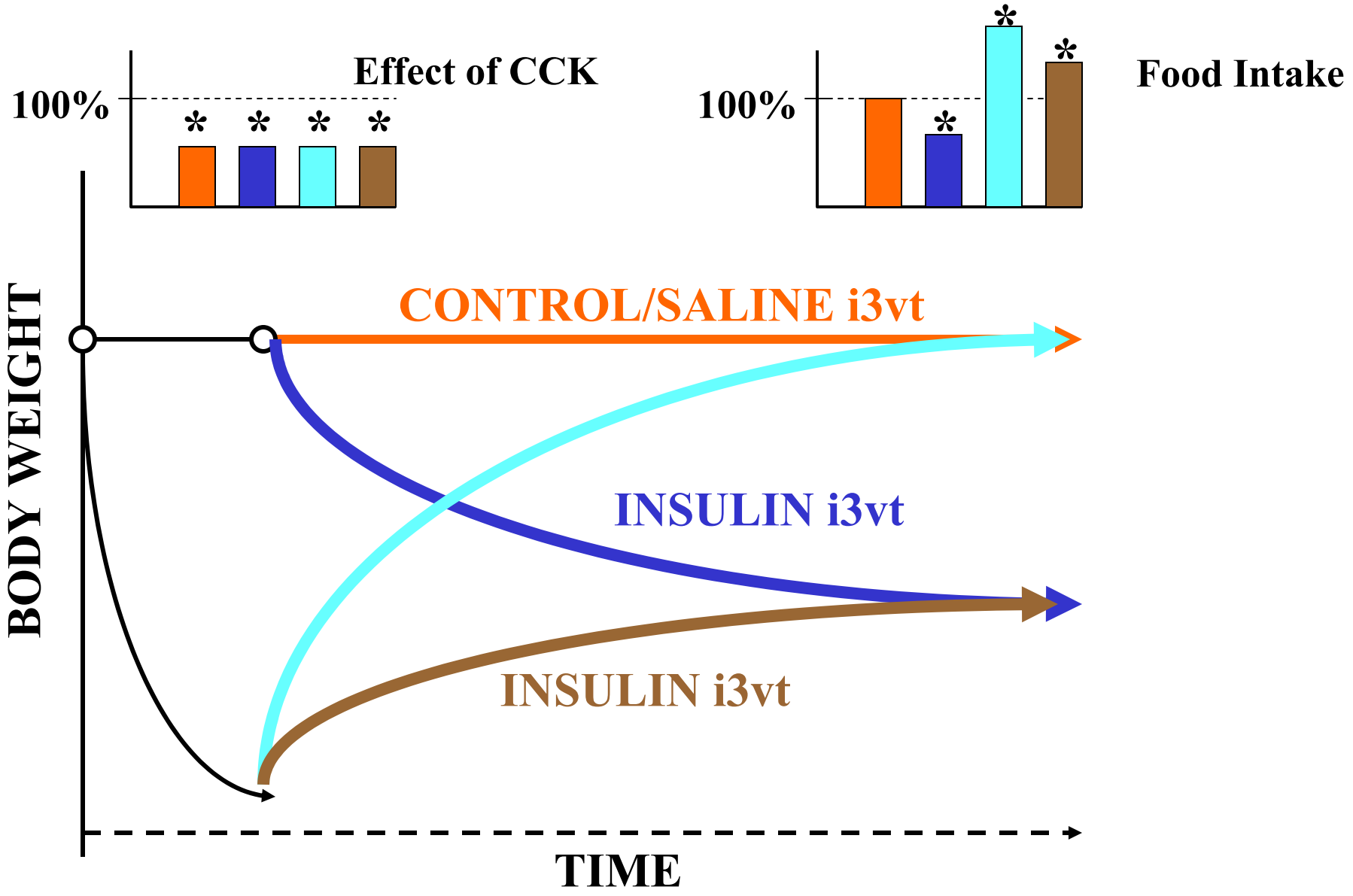
M Chavez et al., *Behav Neurosci*, 1995

ADIPOSITY SIGNALS



M Chavez et al., *Behav Neurosci*, 1995


100%
*
*
*
Food Intake
CONTROL/SALINE i3vt
INSULIN i3vt
INSULIN i3vt
BODY WEIGHT
TIME


Effect of CCK
100%
*
*
*
*
100%
*
*
*
Food Intake
BODY WEIGHT
CONTROL/SALINE i3vt
INSULIN i3vt
INSULIN i3vt
TIME

Satiety signals:

Reduce meal size comparably

- **In lean animals**
- **In genetically obese animals**
- **In diet-induced obese animals**

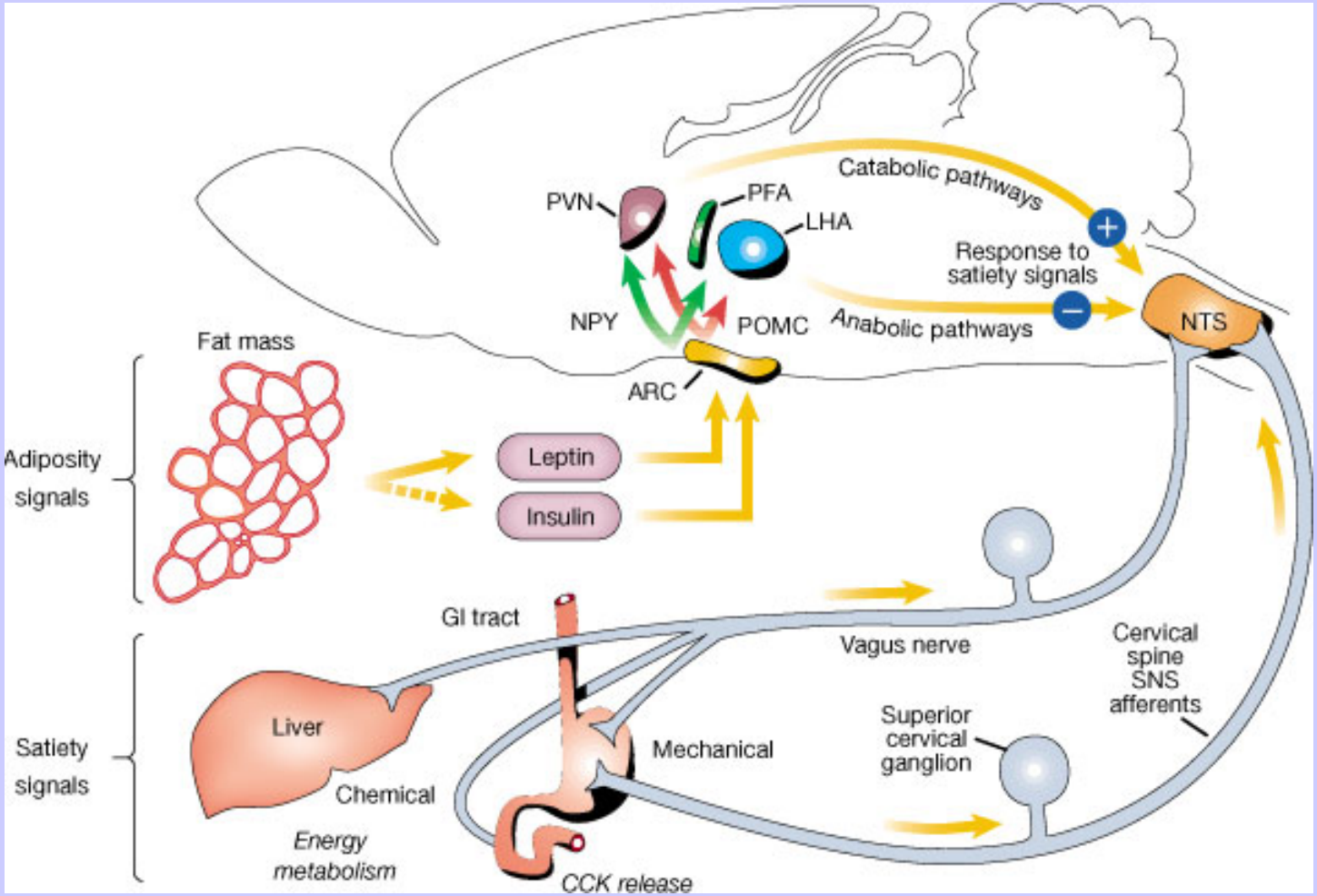
Have minimal effects on body weight

Adiposity signals:

Reduce body weight by enhancing the effect of satiety signals on each meal.

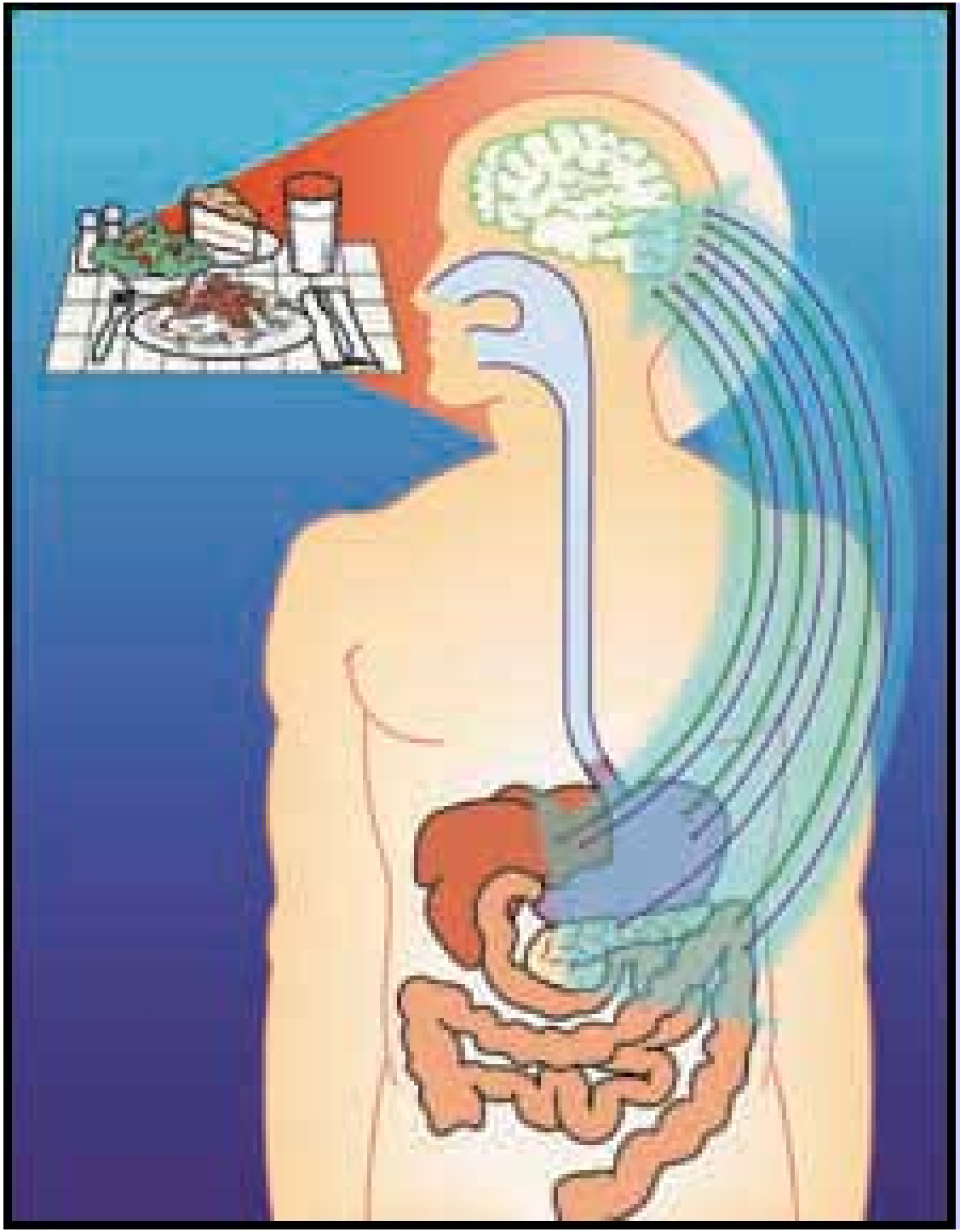
Have to be increased locally in the brain or else decreased systemically, and on a chronic basis, to be efficacious.

Leptin (Prevention of weight regain)
Insulin (Mimetics)

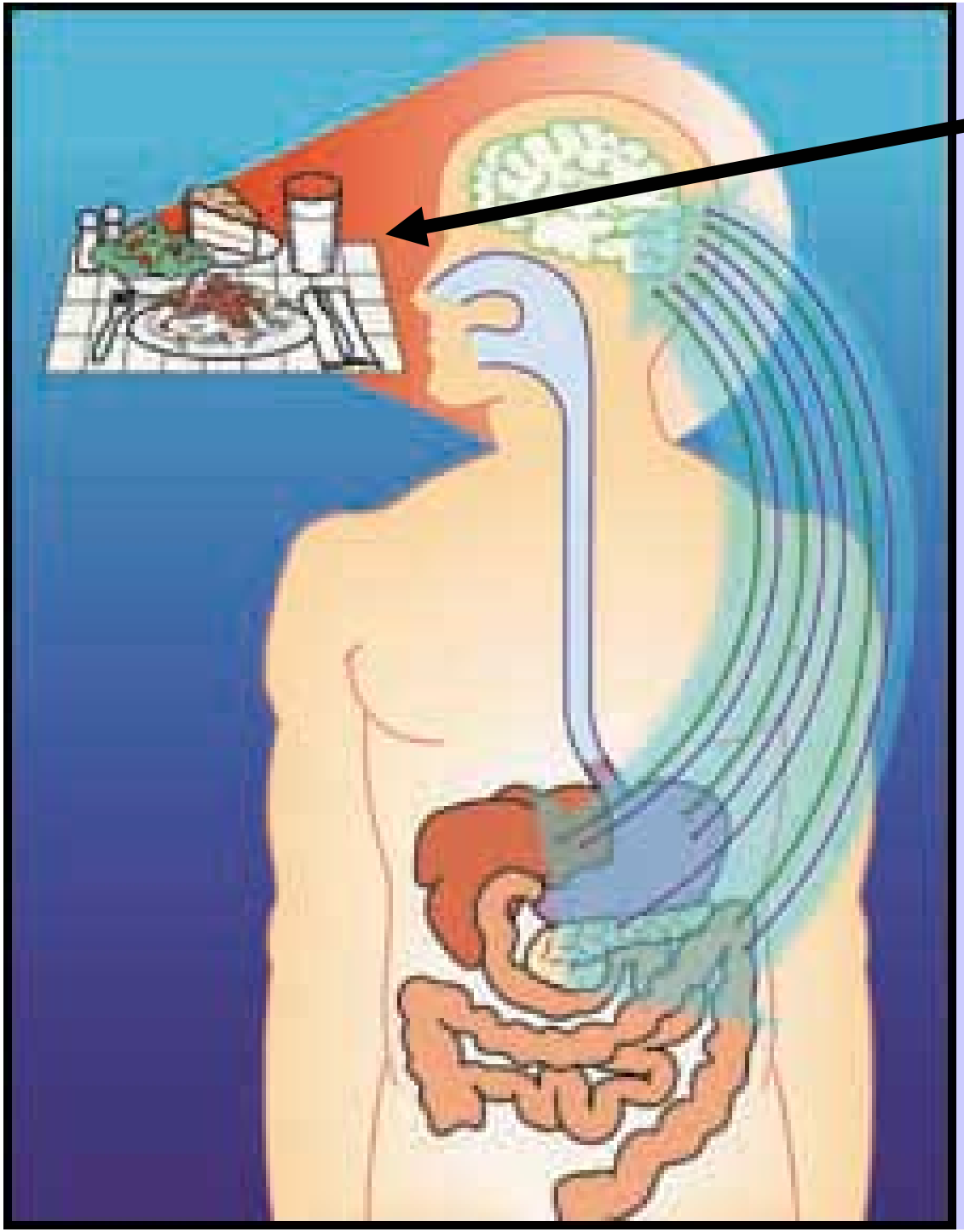


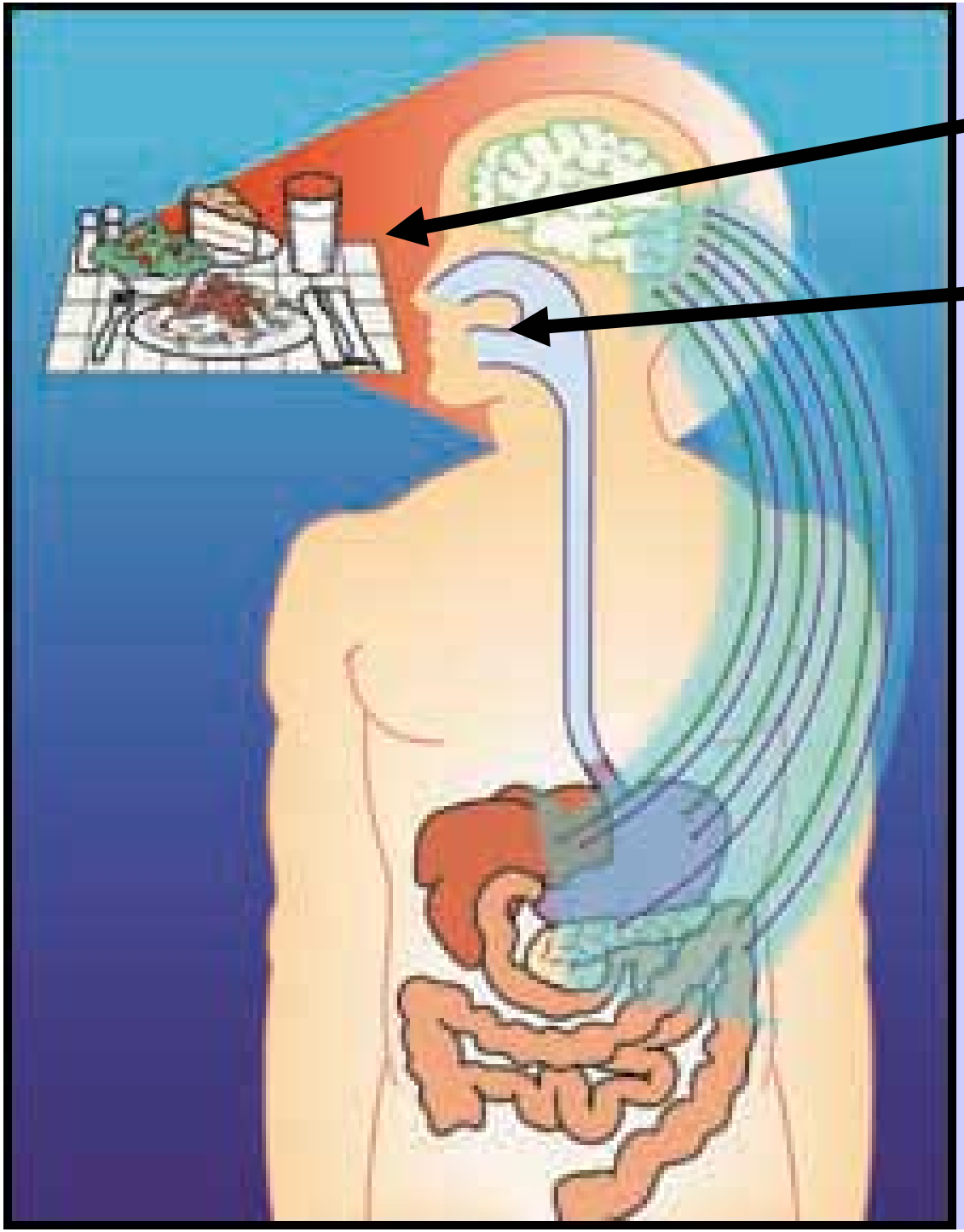
MW Schwartz, SC Woods et al., *Nature*, 2000

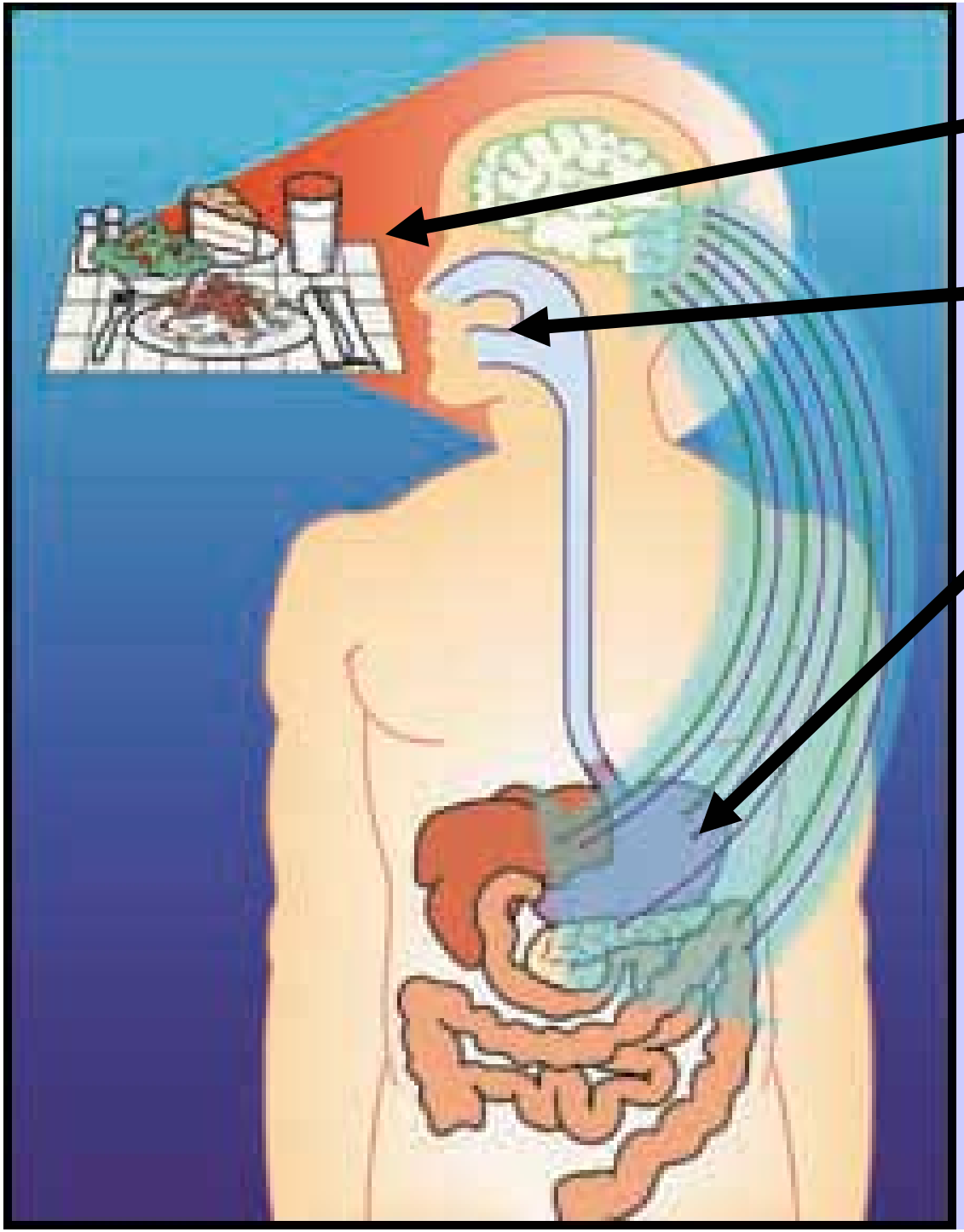
What are the best targets for intervention by the food industry?



Meal-Related Signals


Sight and Smell

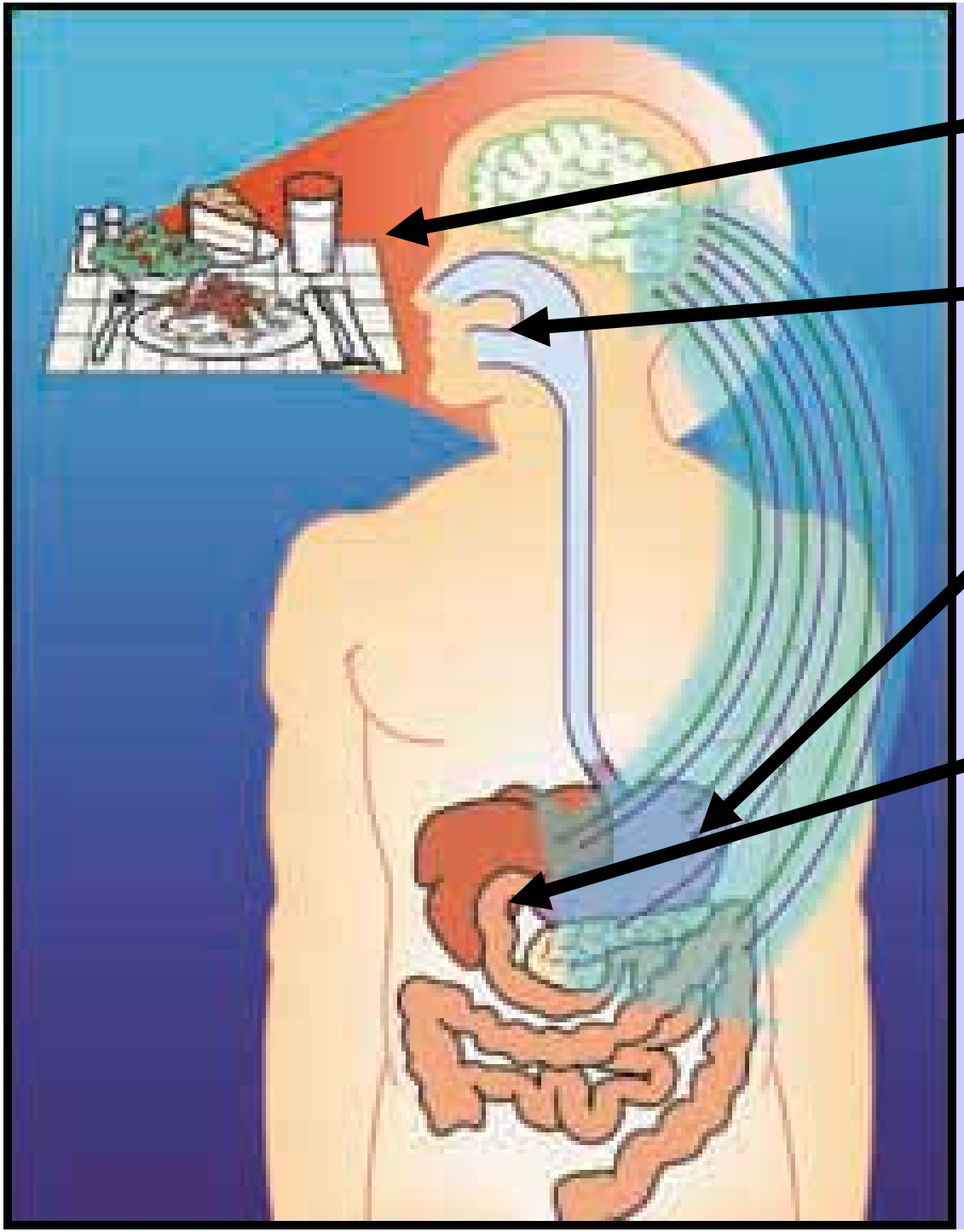

Sight and Smell
Taste



Sight and Smell

Taste

Stomach Signals (Ghrelin, GRP, Stretch)

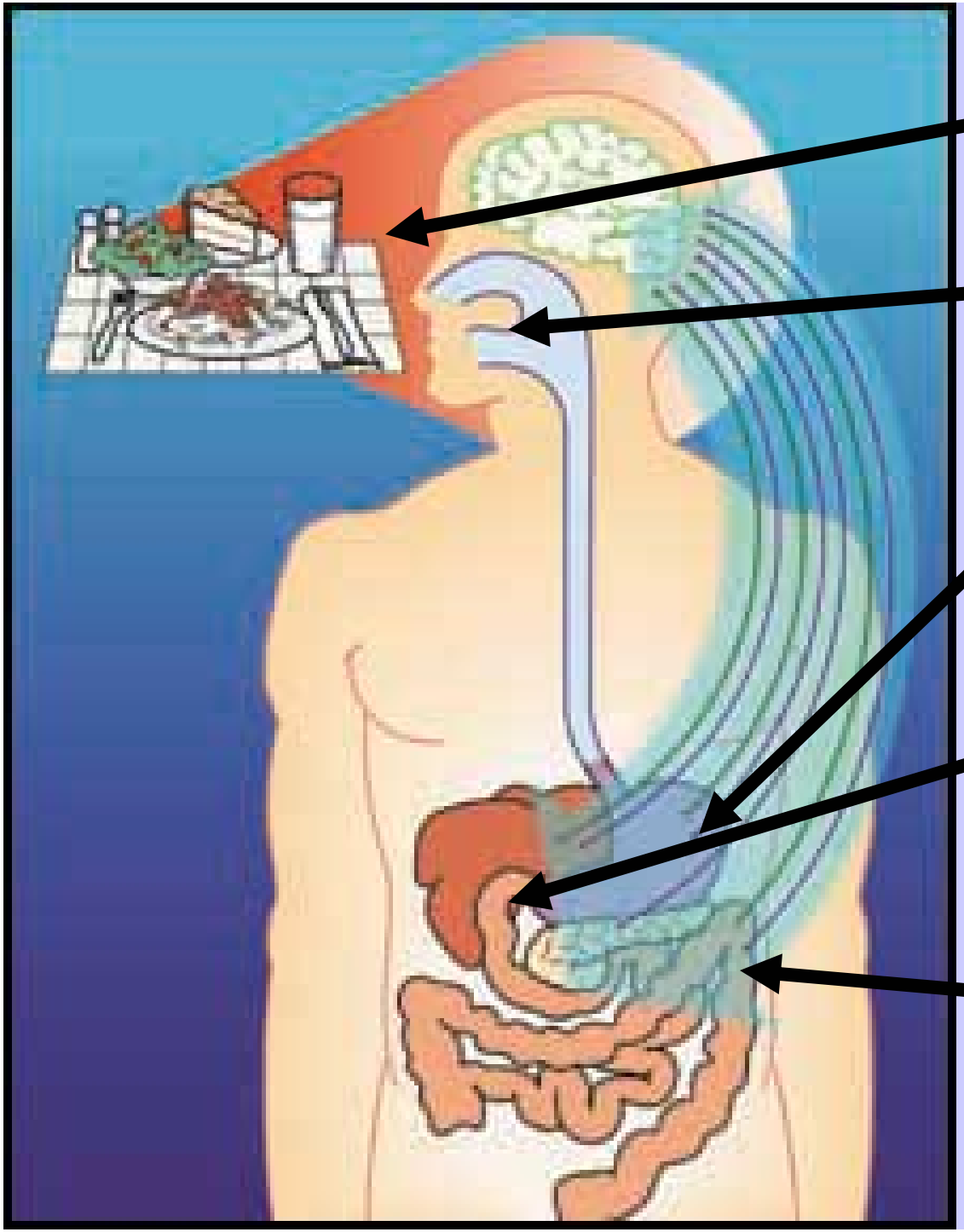


Sight and Smell

Taste

Stomach Signals
(Ghrelin, GRP)

Duodenal Signals
(CCK)



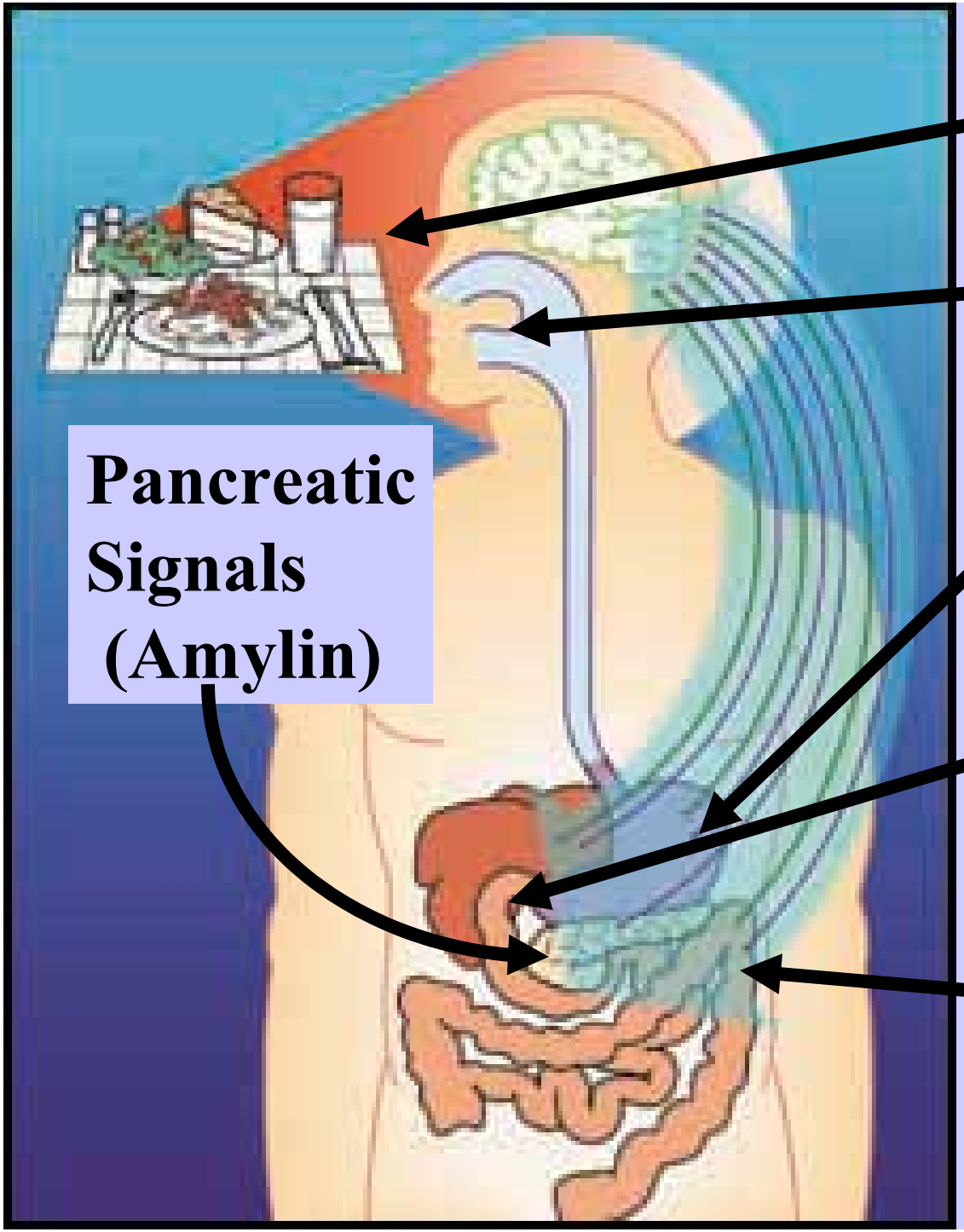
Sight and Smell

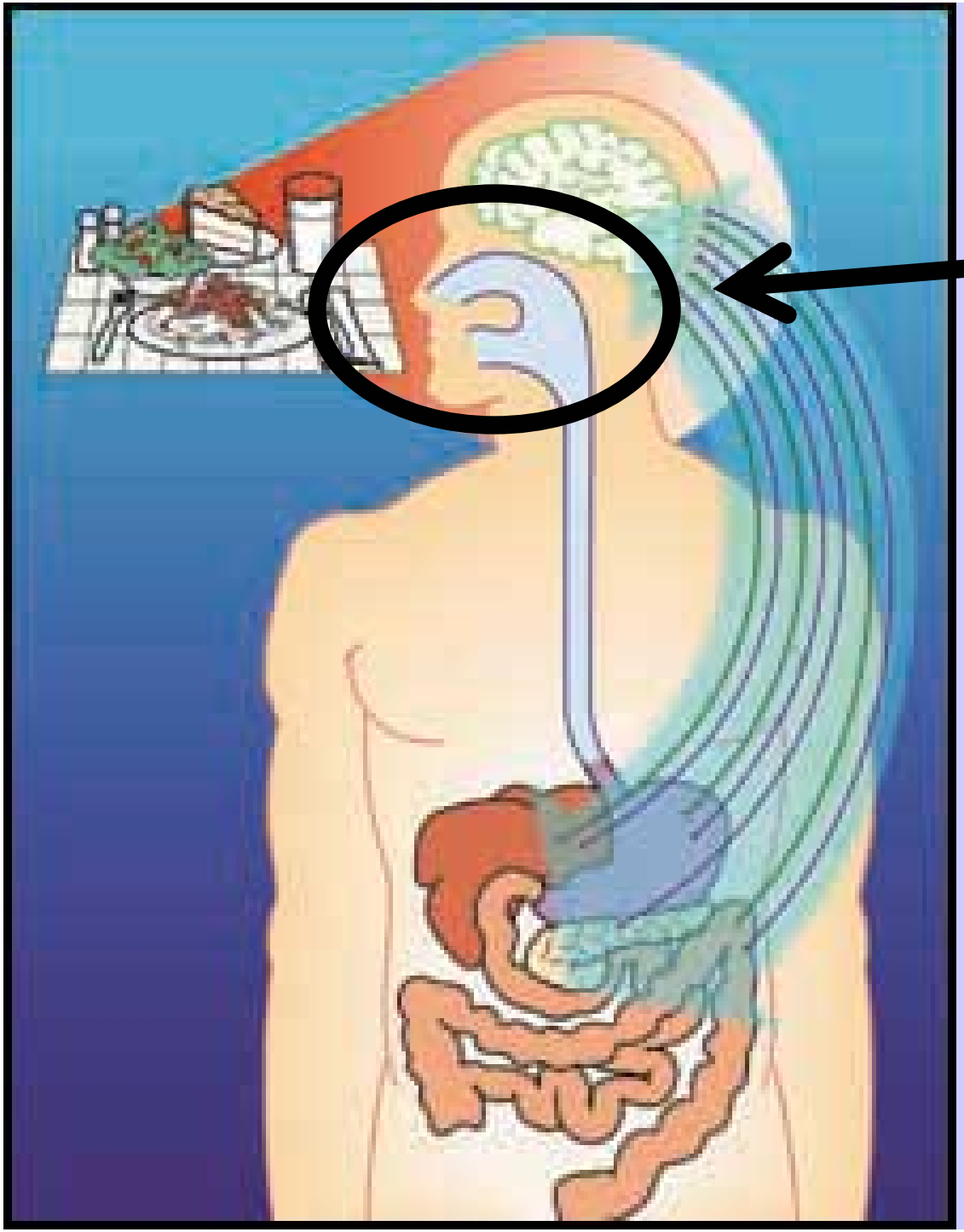
Taste

Stomach Signals
(Ghrelin, GRP)

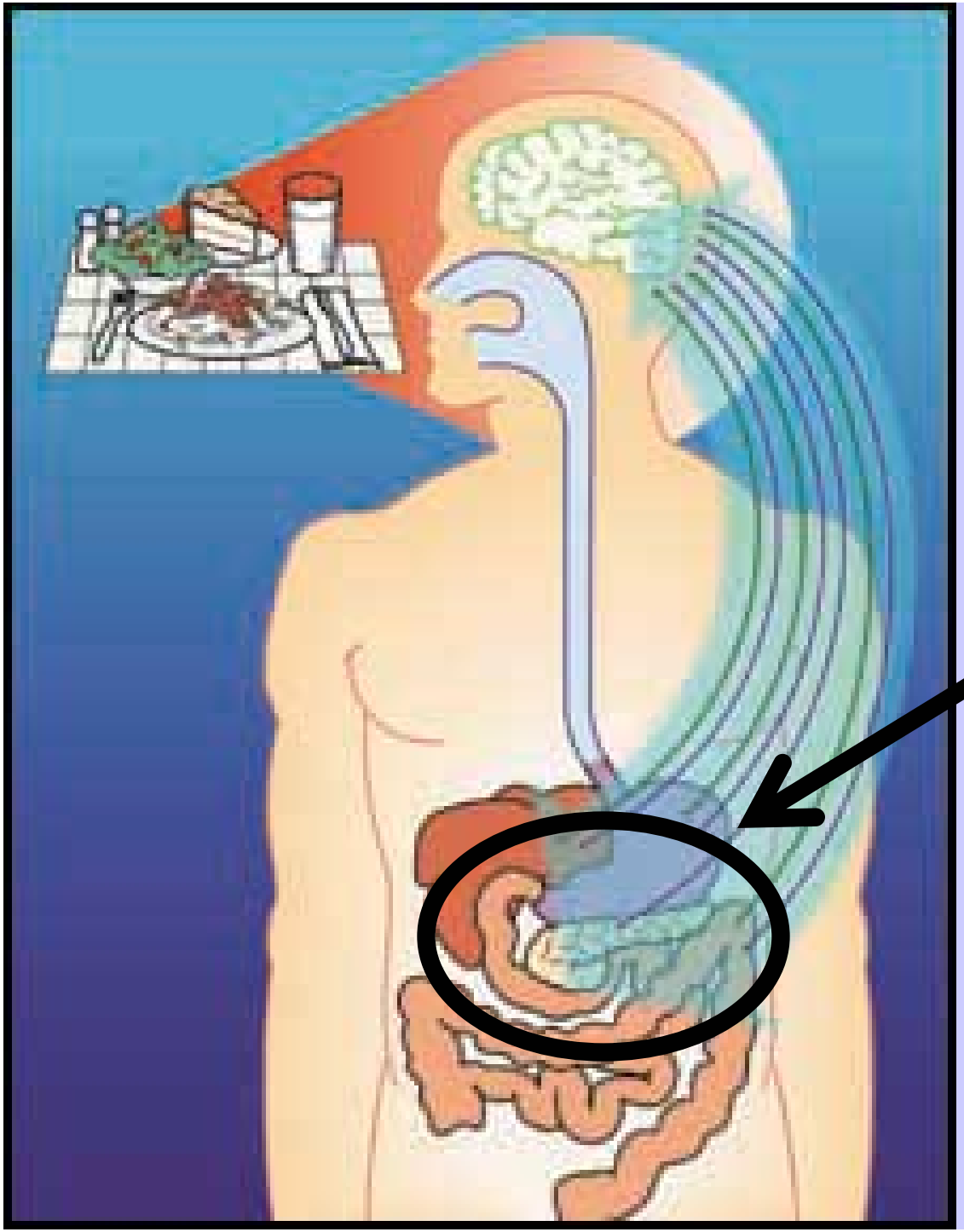
Duodenal Signals
(CCK)

Lower Intestinal
(PYY, Apo A-IV
GLP-1)

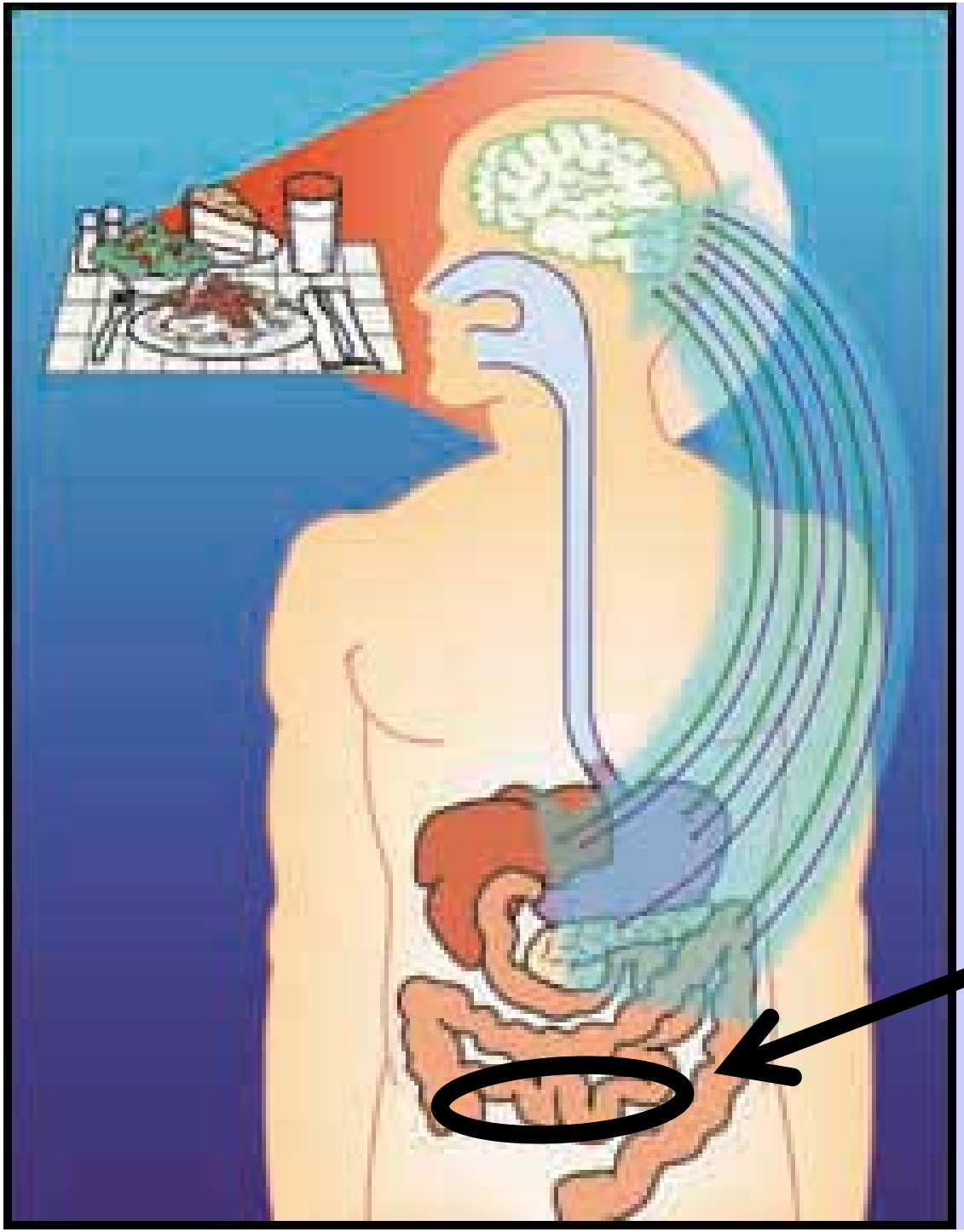

Sight and Smell
Taste
Stomach Signals
(Ghrelin, GRP)
Duodenal Signals
(CCK)
Lower Intestinal
(PYY, Apo A-IV
GLP-1)
Pancreatic
Signals
(Amylin)



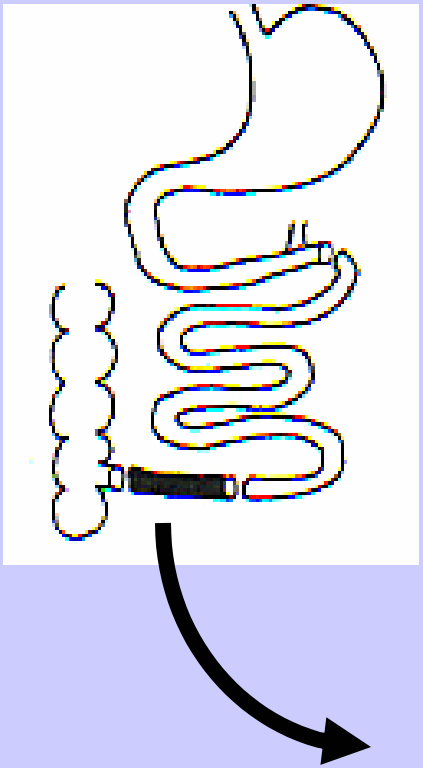
Sight, smell, palatability, mouth feel



Gastric and duodenal signals

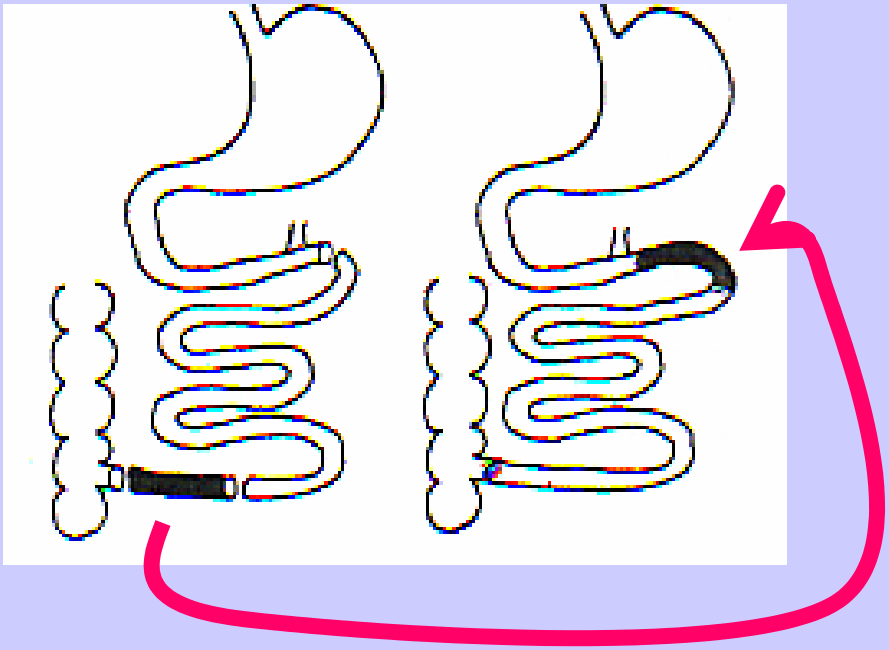

Ileal
signals

Ileal Transposition



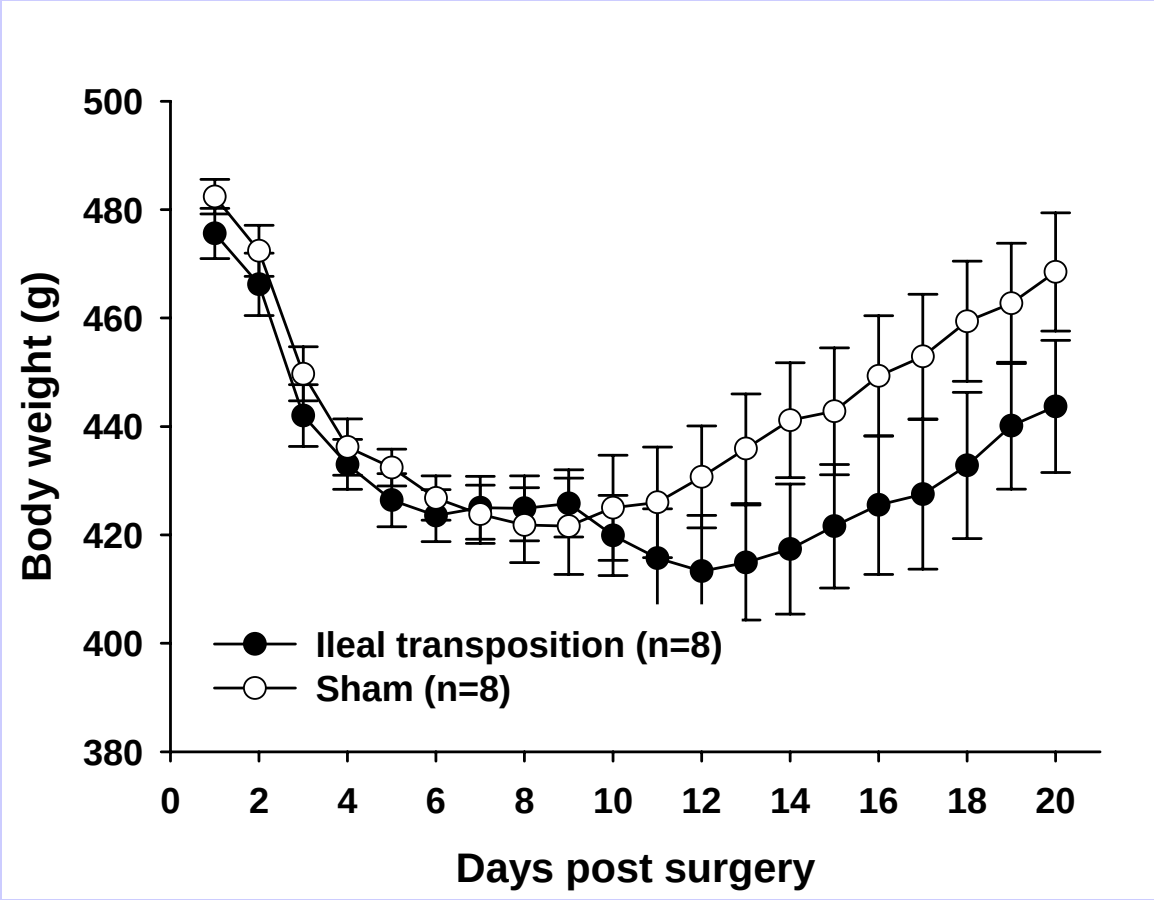
GLP-1, PYY, Apo A-IV

Ileal Transposition



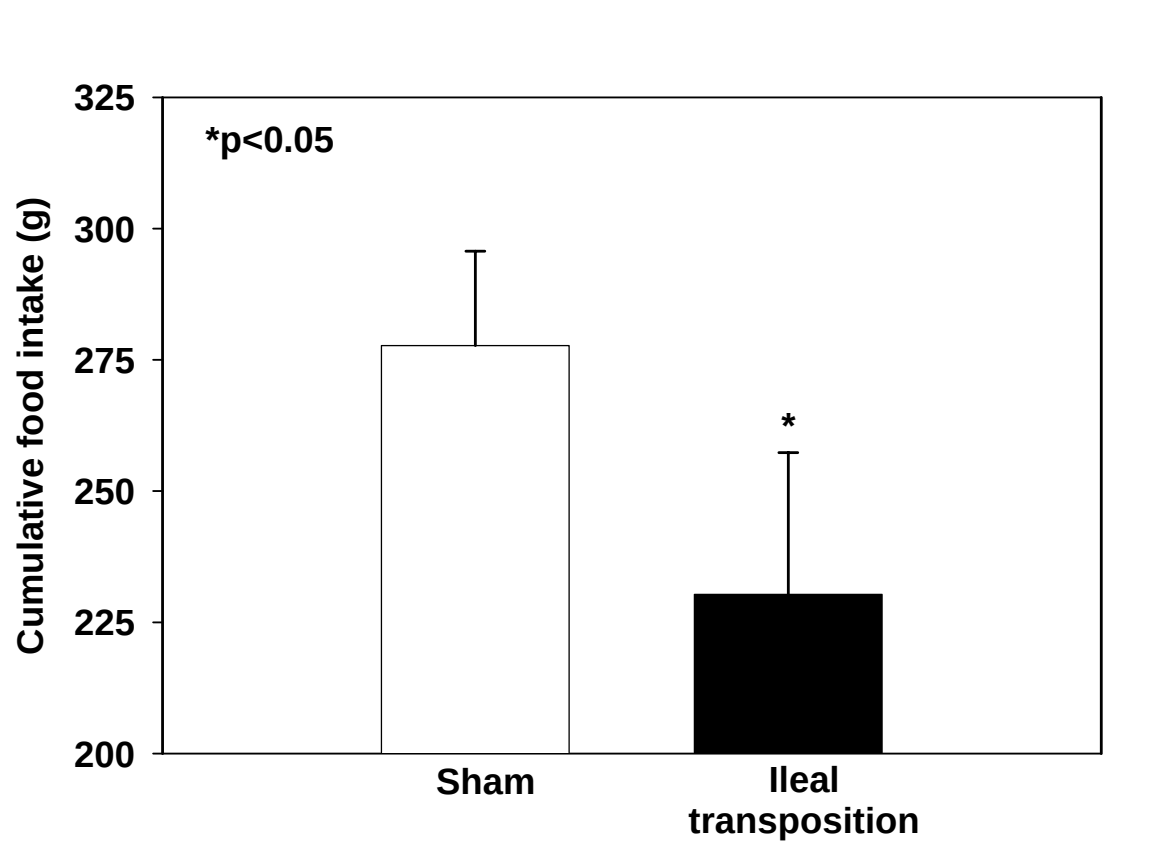
A short segment of ileum is transposed anteriorly such that chyme stimulates it earlier in the sequence of digestion.

Ileal Transposition (IT)



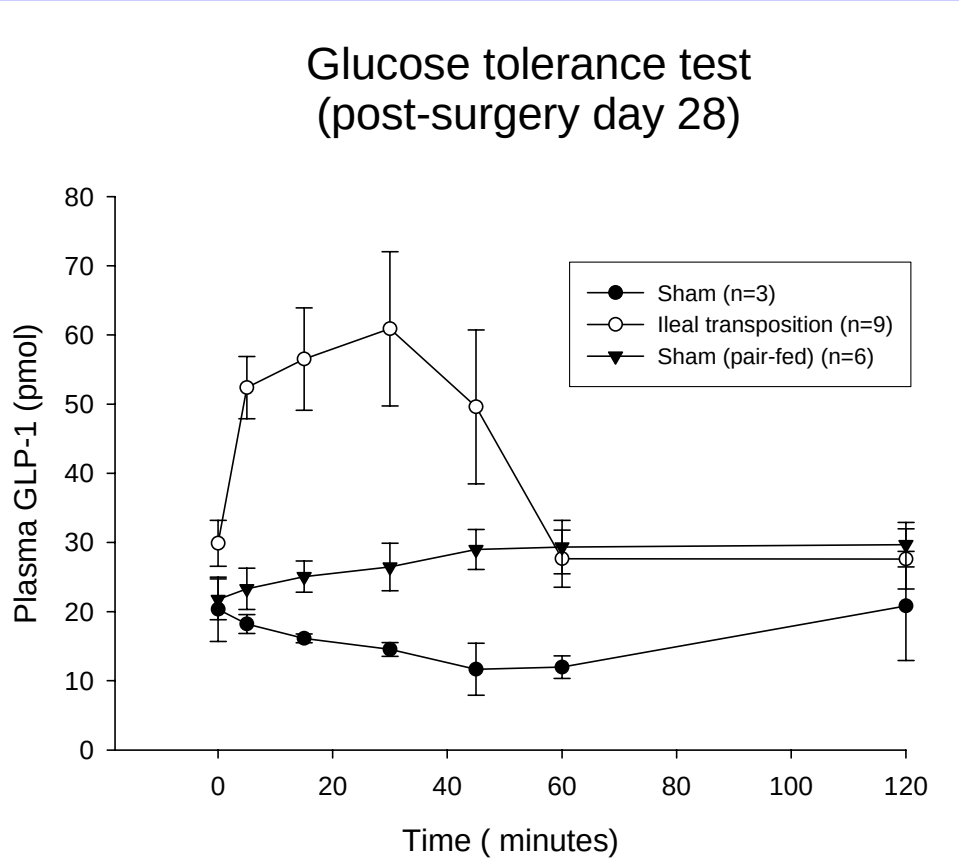
IT causes a small but reliable loss of weight.

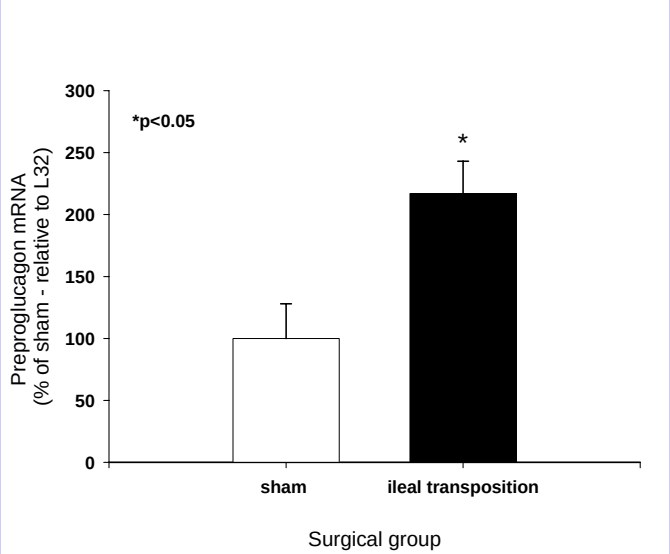
Ileal Transposition



IT rats eat less food.

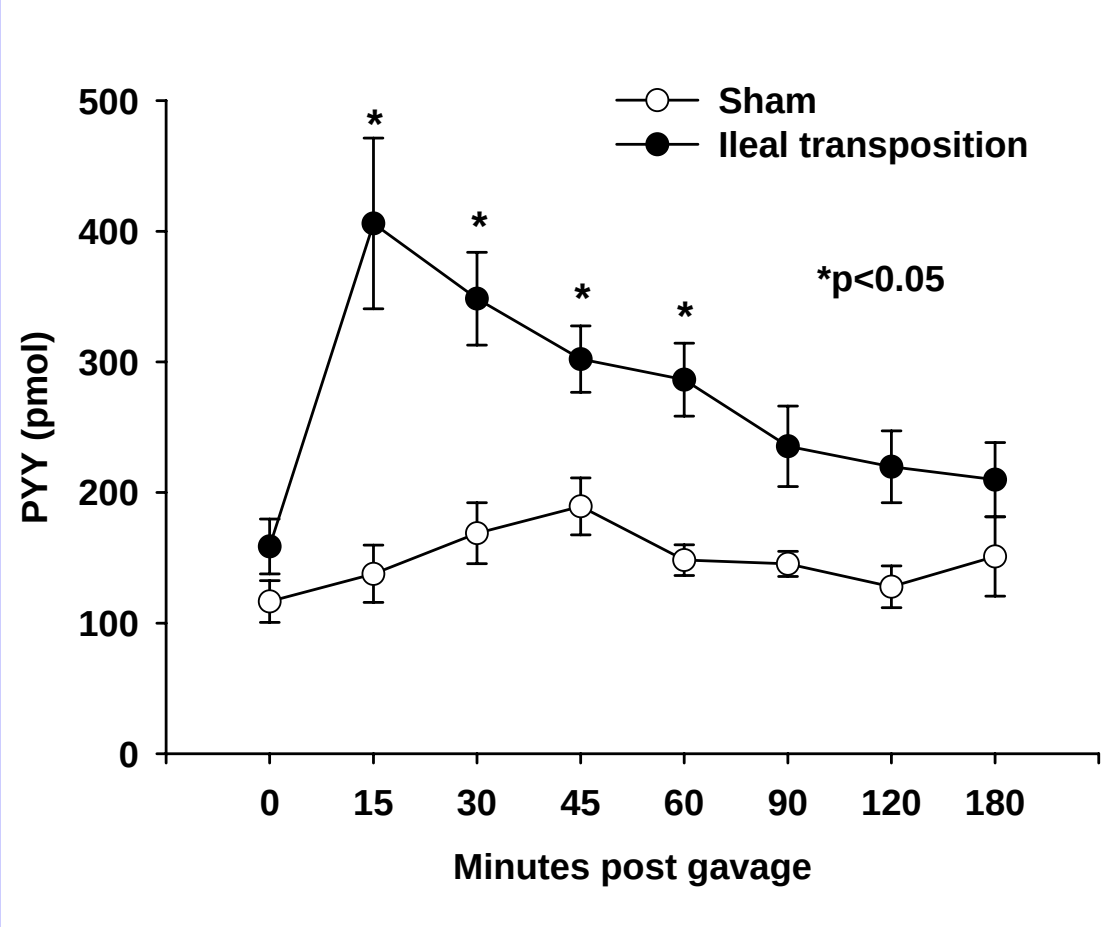
Ileal Transposition

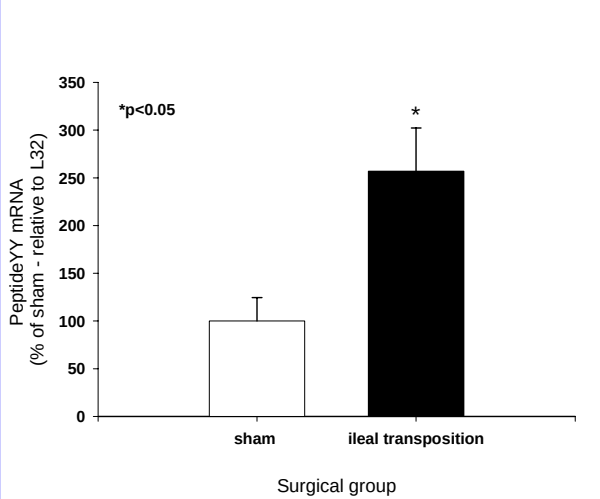




IT rats make and secrete more GLP-1.

Ileal Transposition



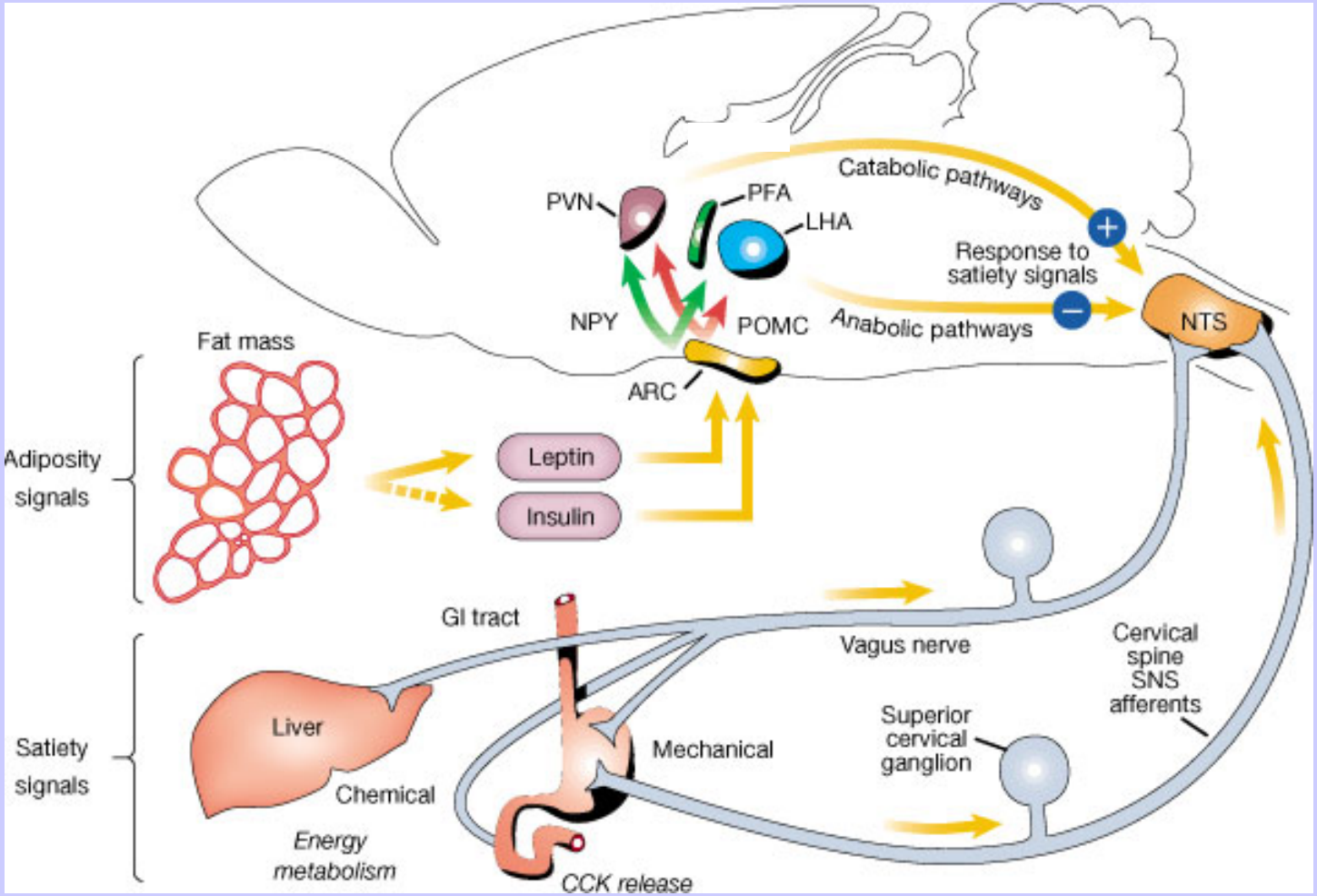


IT rats make and secrete more PYY.

What are the best targets for intervention by the food industry?

Perhaps foods or food additives could be developed that stimulate the ileum early during meals.

The control system over energy homeostasis is complex, relying upon several types of signals.



MW Schwartz, SC Woods et al., *Nature*, 2000

Possible Food Approaches

1. Foods/nutrients that uniquely influence satiety signals
    a. Soybean trypsin inhibitors
        West
        CCK-1 KO; half-lives
    b. Density a la Rolls

2. Foods/nutrients that uniquely influence adiposity signals
    a. GLP-1/Apo A-IV

3. Foods/nutrients that mimic the effects of bypass

4. Foods/nutrients that reduce cephalic responses

Why the mouth isn’t the place

DeCastro People don’t eat food that they Perceive as unpalatable

Sham eating: Internal signals must arise distal To the stomach