Main points:

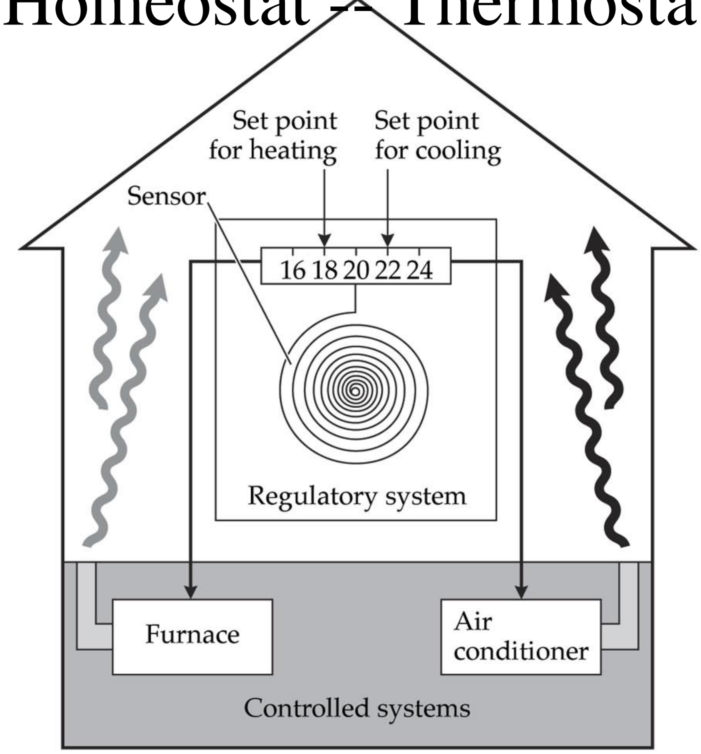
1. Motivations impel us to seek things we need
2. We use multiple cues to regulate these needs
3. Changes to any part of system can disrupt regulation

Study Questions:

1. Give plausible arguments for and against the idea that leptin treatments would aid in weight loss.

2. How does the brain integrate multiple signals in the control of feeding?

Homeostat -- Thermostat



AN INTRODUCTION TO BEHAVIORAL ENDOCRINOLOGY, Third Edition, Figure 9.2

Obesity Trends Among U.S. Adults between 1985 and 2009

Definitions:

- Obesity: Body Mass Index (BMI) of 30 or higher.

- Body Mass Index (BMI): A measure of an adult's weight in relation to his or her height, specifically the adult's weight in kilograms divided by the square of his or her height in meters.

Obesity Trends Among U.S. Adults between 1985 and 2009

Source of the data:

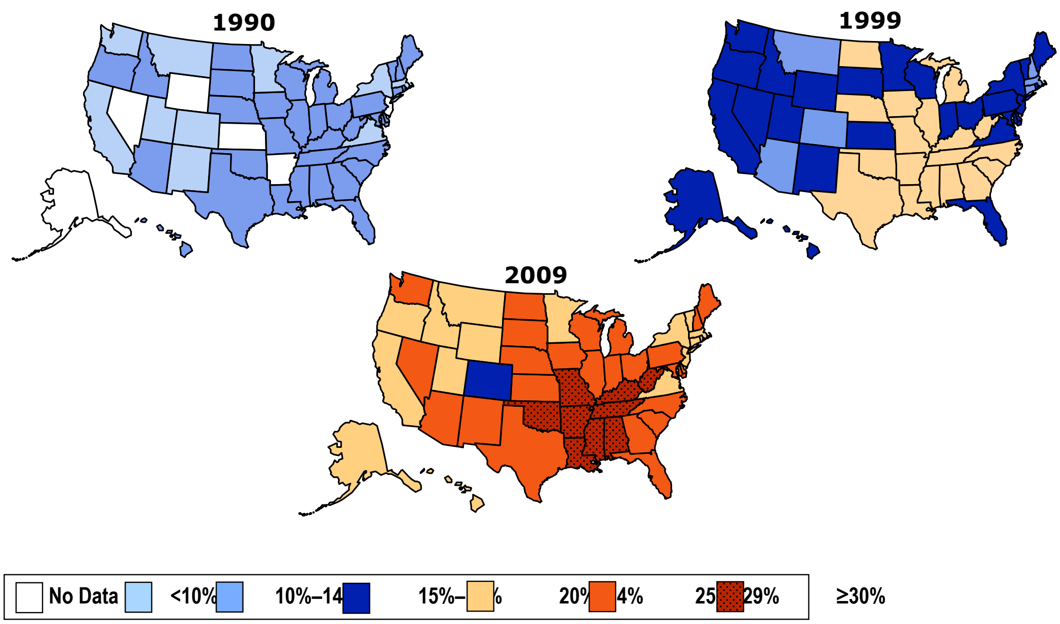
- The data shown in these maps were collected through CDC's Behavioral Risk Factor Surveillance System (BRFSS). Each year, state health departments use standard procedures to collect data through a series of telephone interviews with U.S. adults.

- Prevalence estimates generated for the maps may vary slightly from those generated for the states by BRFSS (http://aps.nccd.cdc.gov/brfss) as slightly different analytic methods are used.

Obesity Trends* Among U.S. Adults

BRFSS, 1990, 1999, 2009

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



- In 1990, among states participating in the Behavioral Risk Factor Surveillance System, ten states had a prevalence of obesity less than 10% and no states had prevalence equal to or greater than 15%.
- By 1999, no state had prevalence less than 10%, eighteen states had a prevalence of obesity between 20-24%, and no state had prevalence equal to or greater than 25%.
- In 2009, only one state (Colorado) and the District of Columbia had a prevalence of obesity less than 20%. Thirty-three states had a prevalence equal to or greater than 25%; nine of these states (Alabama, Arkansas, Kentucky, Louisiana, Mississippi, Missouri, Oklahoma, Tennessee, and West Virginia) had a prevalence of obesity equal to or greater than 30%.

What is causing this?

Altered diet & lifestyle?

Changes to environment??

Obesogens, endocrine disruptors

Transgenerational effects???

Proc Biol Sci. 2011 Jun 7;278(1712):1626-32. Canaries in the coal mine: a cross-species analysis of the plurality of obesity epidemics.

Klimentidis YC, Beasley TM, Lin HY, Murati G, Glass GE, Guyton M, Newton W, Jorgensen M, Heymsfield SB, Kemnitz J, Fairbanks L, Allison DB.

PARAPHRASED FROM ABSTRACT

A dramatic rise in obesity has occurred among humans within the last several decades.

What about animals? - 20 000 animals from 24 populations

All getting heavier -- primates and rodents living in research colonies, as well as among feral rodents and domestic dogs and cats.

Could there be as-of-yet unidentified and/or poorly understood factors (e.g. viral pathogens, epigenetic factors).

No details, but look how many factors!!!

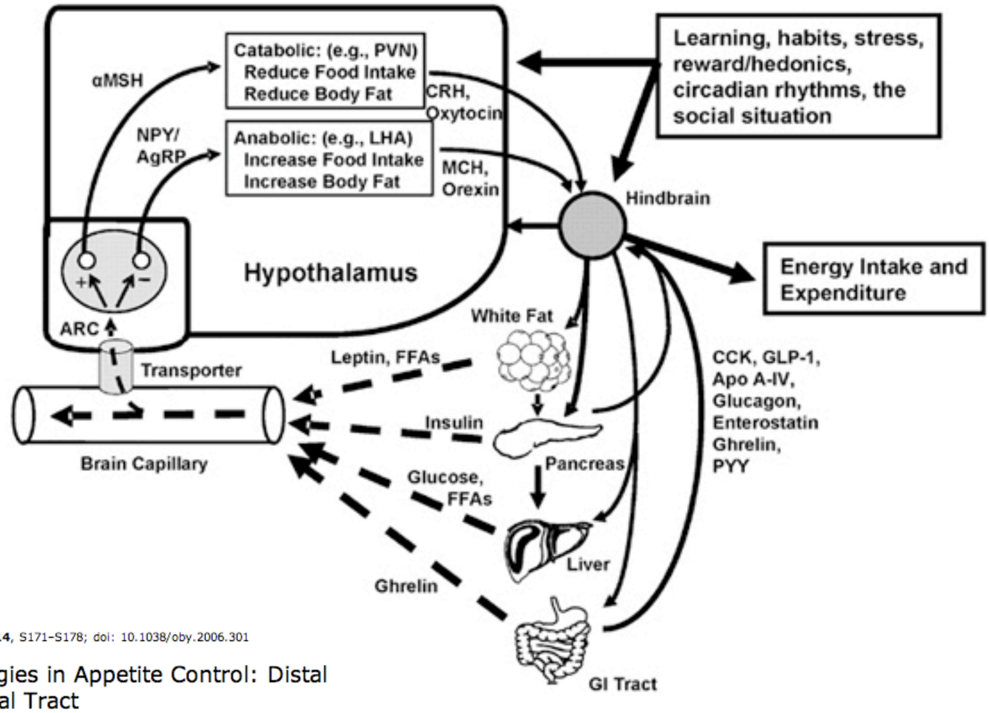
We will talk about a few specific ones

1874 J Clin Endocrinol Metab, March 2005, 90(3):1871–1887 Speiser *et al.* • Childhood Obesity

TABLE 2. Factors critical in the regulation of appetite and energy balance

Central nervous system-appetite regulation command: Ventro-medial-hypothalamus, paraventricular nucleus, lateral hypothalamus area	
Appetite stimulation pathway	Appetite suppressing pathway
Agouti-related protein	Cocaine and amphetamine reg. transcript (CART)
GABA	Corticotropin-releasing hormone (CRH)
Galanin	Dopamine
Glutamate	Melanocortin receptors (MC3R, MC4R)
MCH	α-Melanocyte-stim.-hormone (MSH)
Neuropeptide Y	POMC
Norepinephrine	Neurotensin
Opioids (β-endorphin, dynorphin, met-enkephalin)	Serotonin (5-hydroxy-tryptamine)
Orexins, hypocretins	

Peripheral incoming signals		Central nervous system outgoing signals
Suppressing	Stimulating	
Amylin	Cortisol	Parasympathetic nervous system: vagus nerve
Bombesin	Ghrelin	Energy storage by glucose-stimulated insulin secretion
GLP1	Glucose (low)	Sympathetic nervous system: α-adrenergic activation
Glucagon		Stress, cold (lipolysis, heat production, thyroid activation)
Leptin		
Protein		
Insulin		

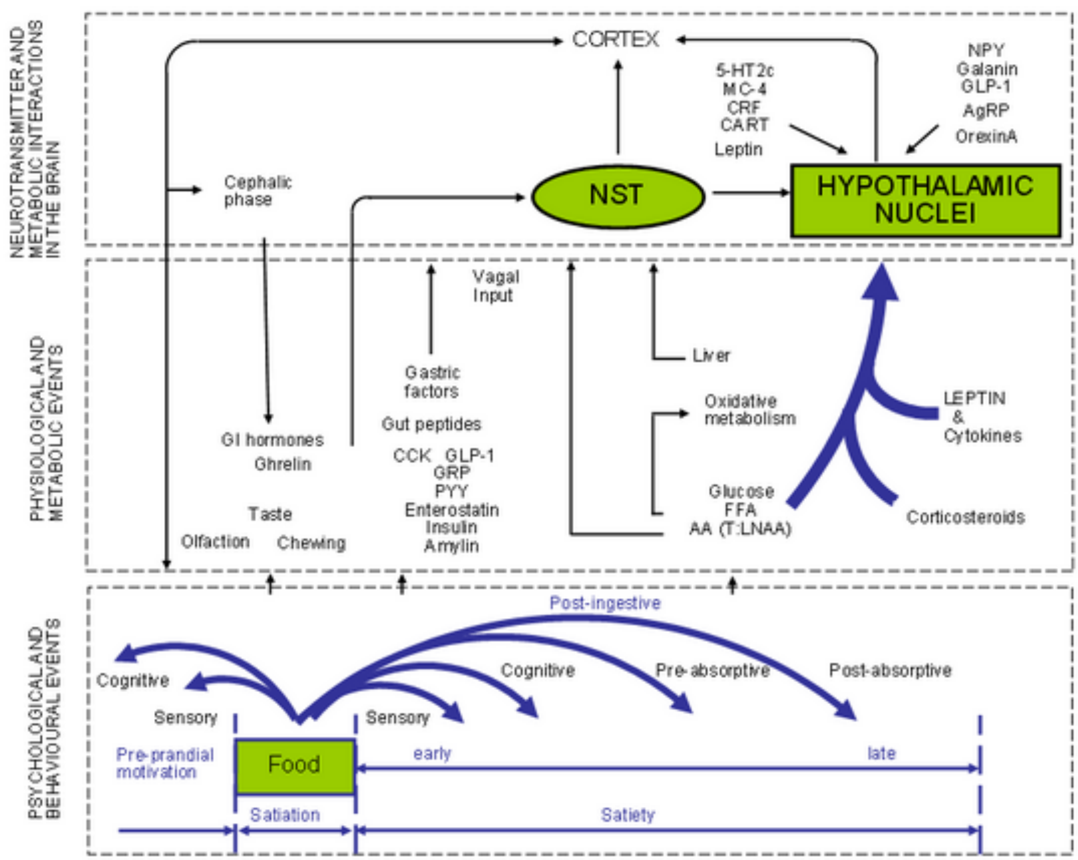


Obesity Research (2006) **14**, S171–S178; doi: 10.1038/oby.2006.301

Dietary Synergies in Appetite Control: Distal Gastrointestinal Tract

Stephen C. Woods[*]

[*]Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio.



Genetic Screening

Leptin –

few obese humans have mutation

24 week clinical trial

no drug - lost 3 lbs

low dose - same amount

high dose - lost 16 lbs

some people gained weight

MC4R –

most common genetic mutation in obese individuals

about 4% of early childhood obesity

Polygenic – not screening for specific genes

30+ genes associated; together ~30% of variance

Genes and Environment – Pima Indians

US

50% have diabetes

198 lbs

Fat increased from 15% to 40% of diet

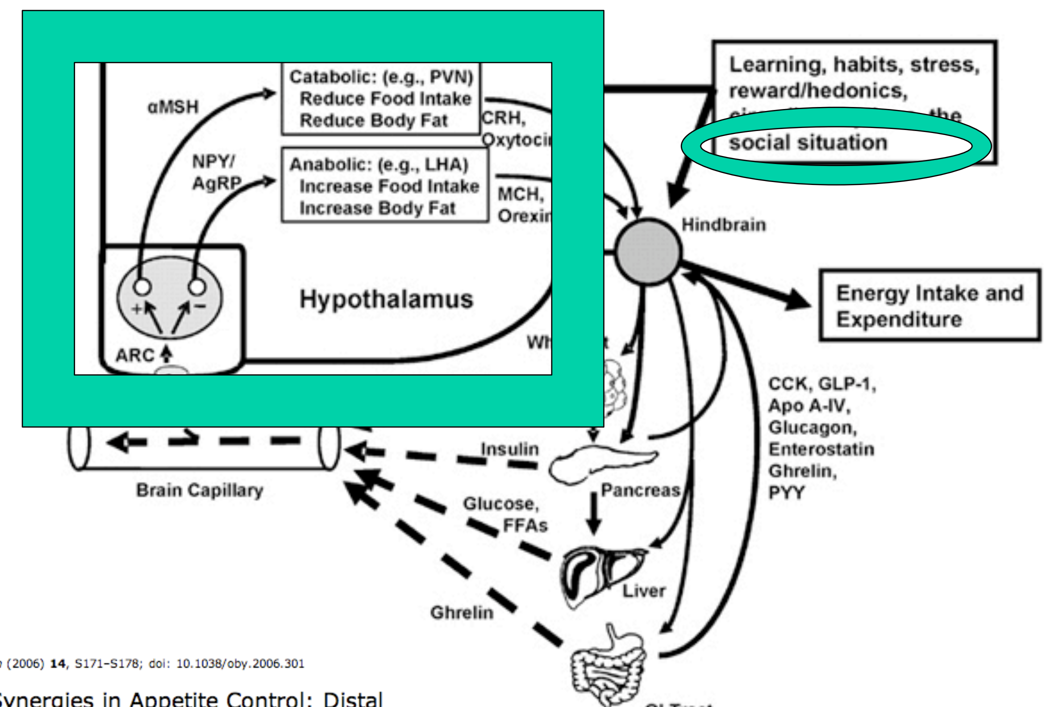
Mexico

Little diabetes

141 lbs

Thrifty Gene Hypothesis

http://diabetes.niddk.nih.gov/dm/pubs/pima/obesity/obesity.htm



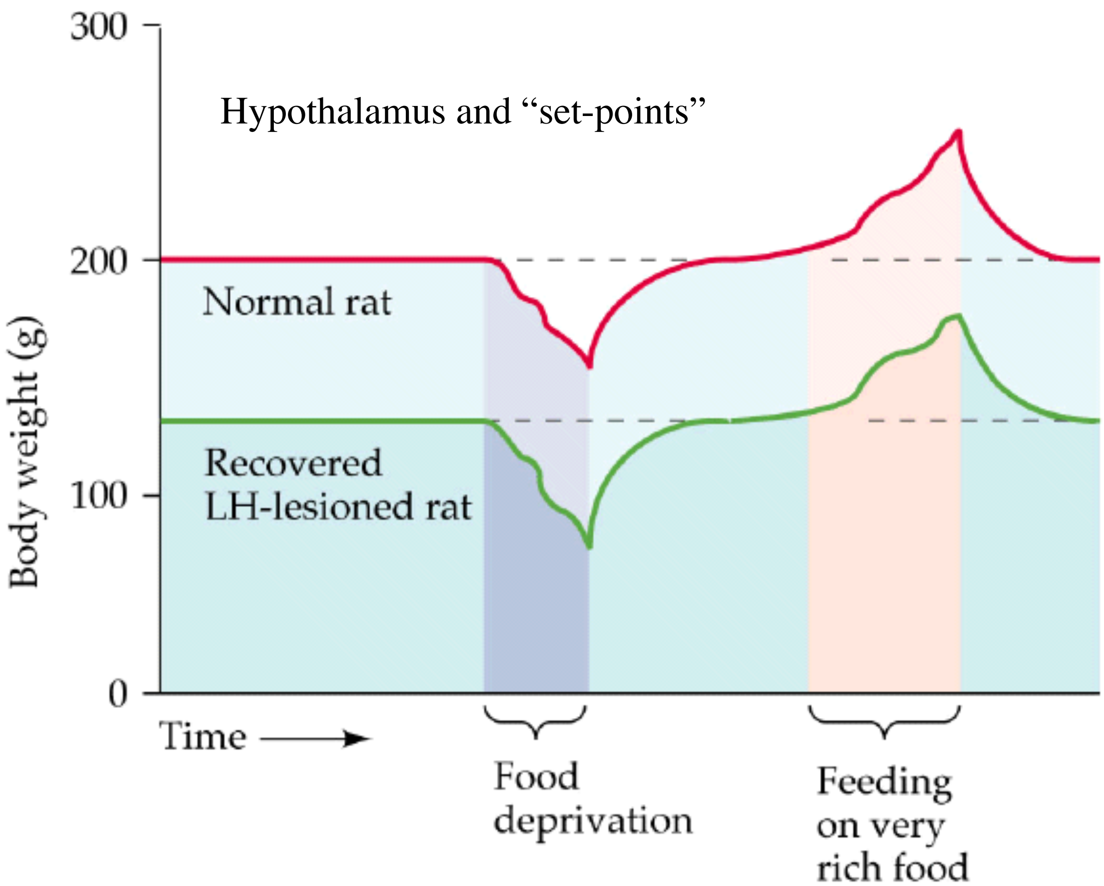
Obesity Research (2006) **14**, S171–S178; doi: 10.1038/oby.2006.301

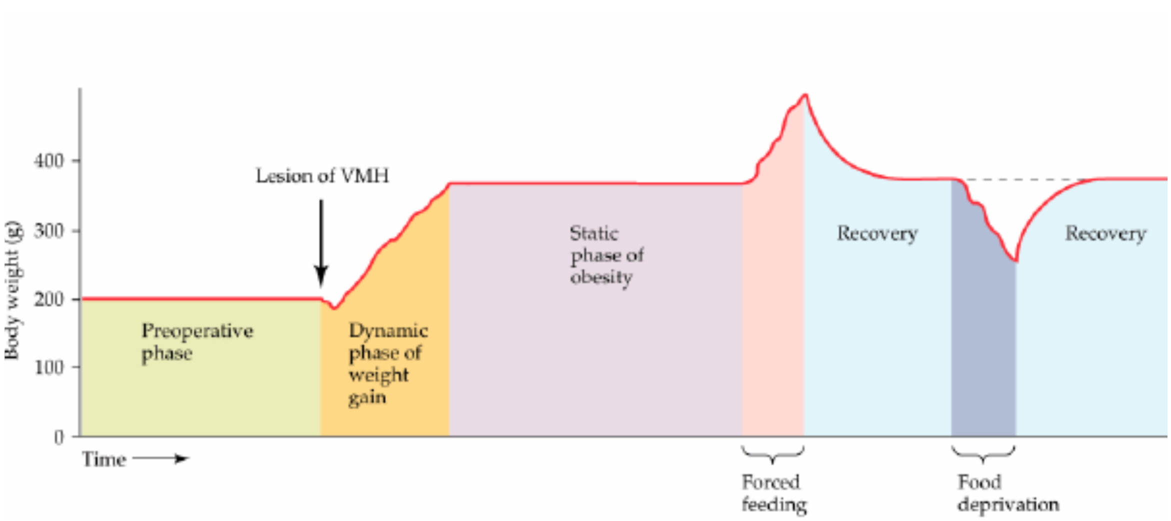
Dietary Synergies in Appetite Control: Distal Gastrointestinal Tract

Stephen C. Woods*

*Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio.

Hypothalamus and "set-points"





British Journal of Nutrition (1997), 77, Suppl. 1, S39–S55 S39

Socio-cultural determinants of meal size and frequency

BY JOHN M. DE CASTRO

Department of Psychology, Behavior and Neurobiology Program, Georgia State University, Atlanta, GA 30303, USA

Total energy intake and the frequency and size of meals are profoundly influenced by the socio-cultural context in which it occurs. Simply eating with one other person increases the average amount ingested in meals by 44% and with more people present the average meal size grows even larger. The impact of social facilitation of energy intake on the individual appears to result from genetic effects both on the individuals' sensitivity to the presence of other people and also on the number of other people an individual tends to eat with. Culture markedly affects the choice of foods in the diet and the pattern of meals over the day. However, many of the social, psychological and physical variables that influence intake are similar across cultures.

Meal size: Meal frequency: Eating behaviour

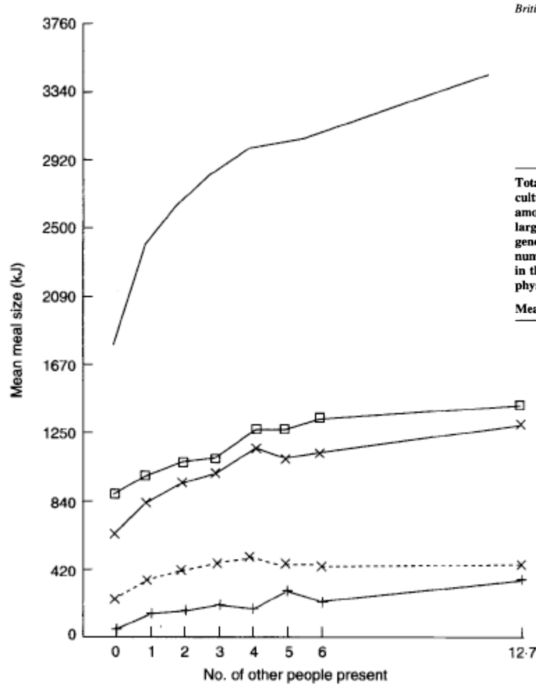
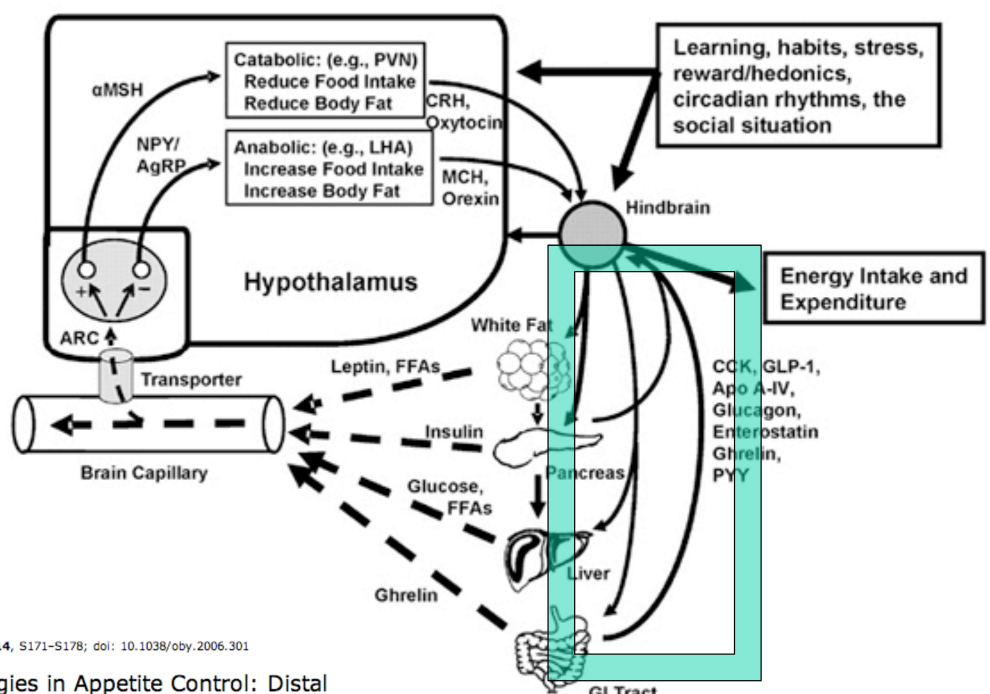


Fig. 1. Mean amount ingested in meals of total food energy (——), carbohydrate (□–□), fat (×–×), protein (×---×) and alcohol (+ – +) as a function of the number of other people eating with the subject.



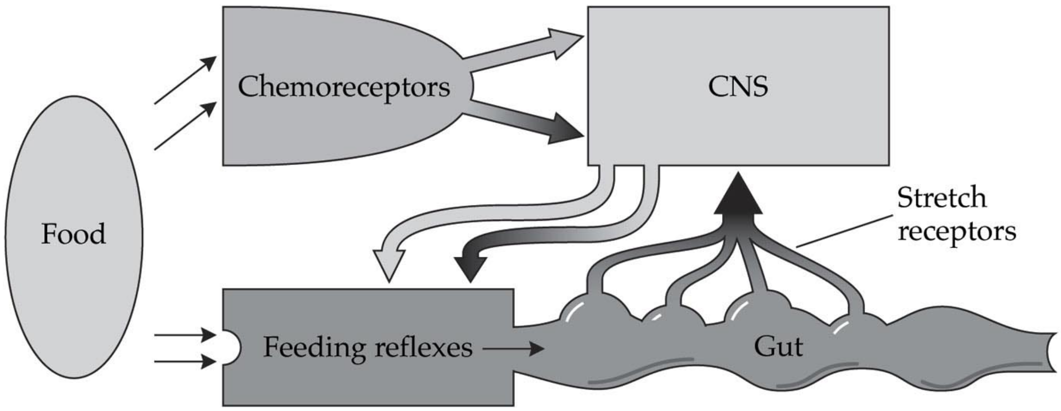
Obesity Research (2006) **14**, S171–S178; doi: 10.1038/oby.2006.301

Dietary Synergies in Appetite Control: Distal Gastrointestinal Tract

Stephen C. Woods*

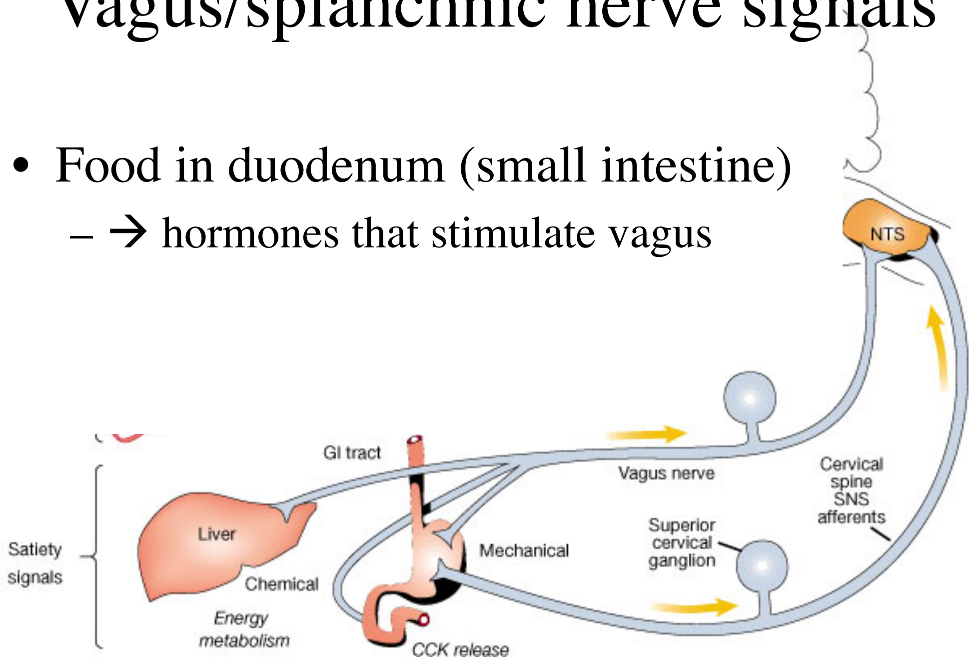
*Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio.

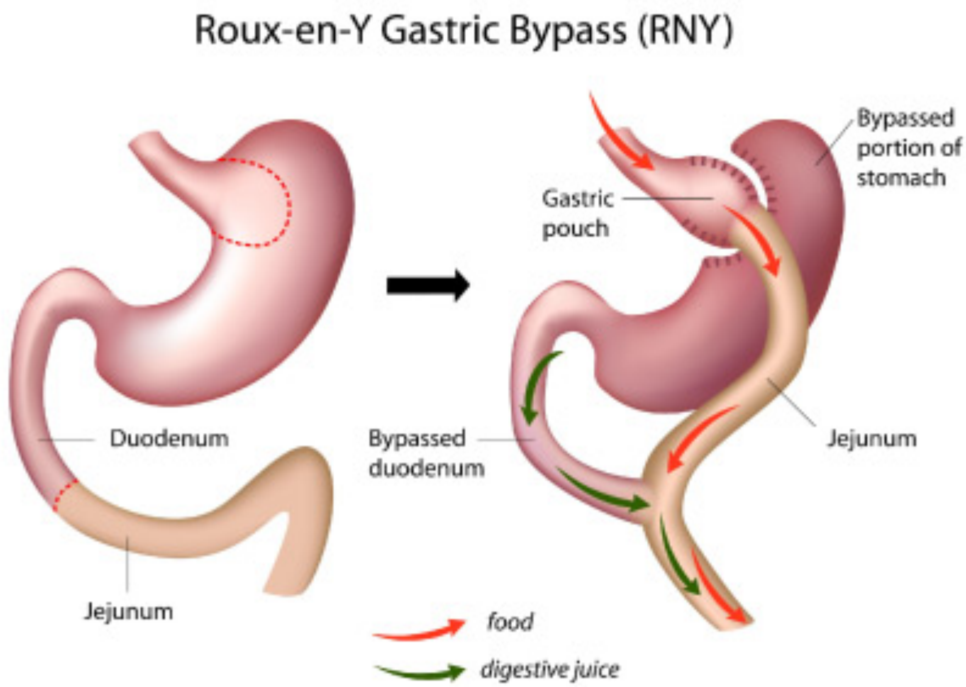
Size-o-stat



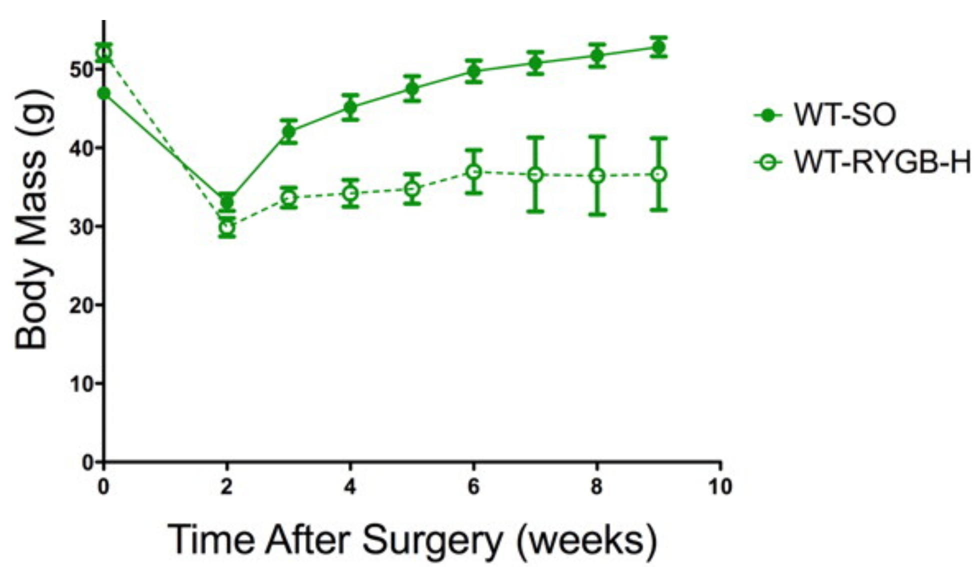
Vagus/splanchnic nerve signals

- Food in duodenum (small intestine)
  - → hormones that stimulate vagus

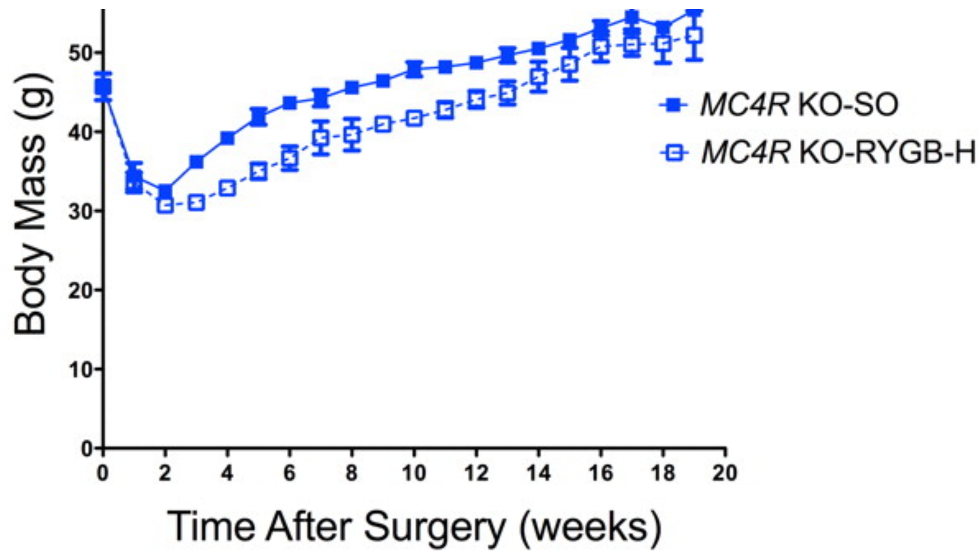




Gastric Bypass (Roux-en-Y)



Need MC4R to work well
"Knockout" mice lack MC4R gene



Melanocortin Receptor Obesity Program

PALATIN
TECHNOLOGIES, INC.

INTRODUCTION

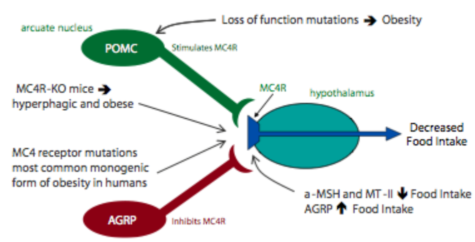
Palatin Technologies has an exclusive global licensing and research collaboration agreement with AstraZeneca AB, a major international pharmaceutical and healthcare business, to discover, develop and commercialize compounds that target melanocortin receptors for the treatment of obesity, diabetes and related metabolic syndrome.

The collaboration, based on Palatin's melanocortin receptor program for the treatment of obesity, includes access to compound libraries, core technologies and expertise in melanocortin receptor drug discovery and development.

MELANOCORTIN SYSTEM

The melanocortin system consists of five G protein-coupled receptors known as MC1-R, MC2-R, MC3-R, MC4-R and MC5-R. The functions of the receptors are modulated by the endogenous peptides α-, β-, and γ-melanocyte stimulating hormone (α- β- and γ-MSH) and the adrenocorticotropic hormone (ACTH), all of which are products of the pro-opiomelanocortin (PMOC) gene. In addition, the endogenous antagonists agouti and agouti-related protein (AGRP) also regulate the receptors functions.

The Melanocortin Receptor System and Obesity

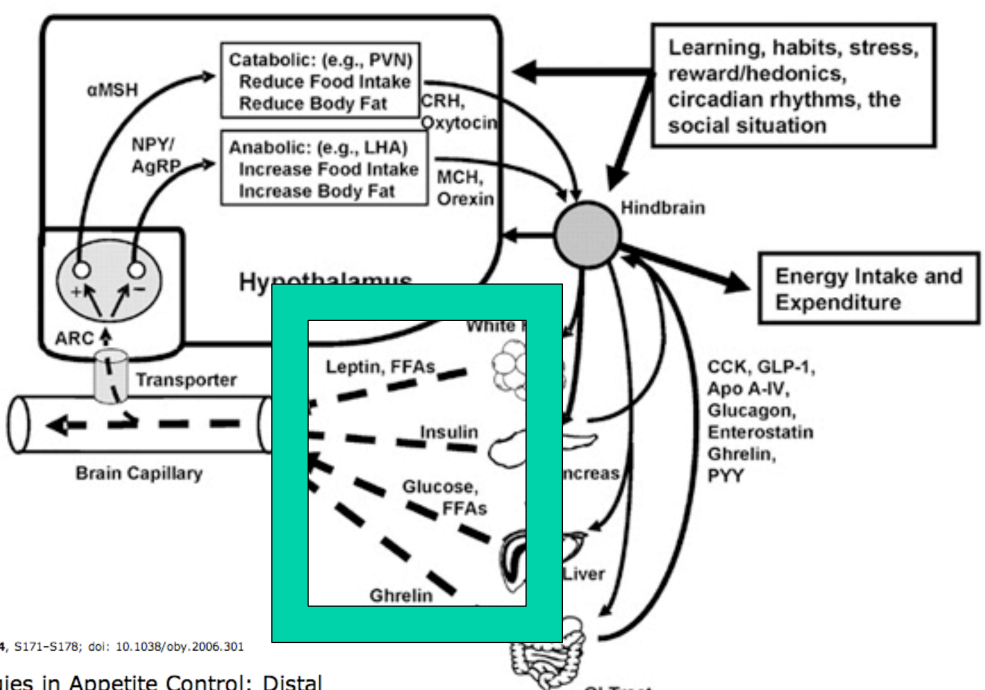


What about treating people with MC4R agonists

Not bad results on weight loss
Very bad side effects

Novel agonist compounds

fewer side effects?



Obesity Research (2006) **14**, S171–S178; doi: 10.1038/oby.2006.301

Dietary Synergies in Appetite Control: Distal Gastrointestinal Tract

Stephen C. Woods*

*Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio.

Food

1. energy -- calories
2. nutrients -- amino acids, minerals, vitamins etc.

Metabolism

Body uses:

Glucose (brain)

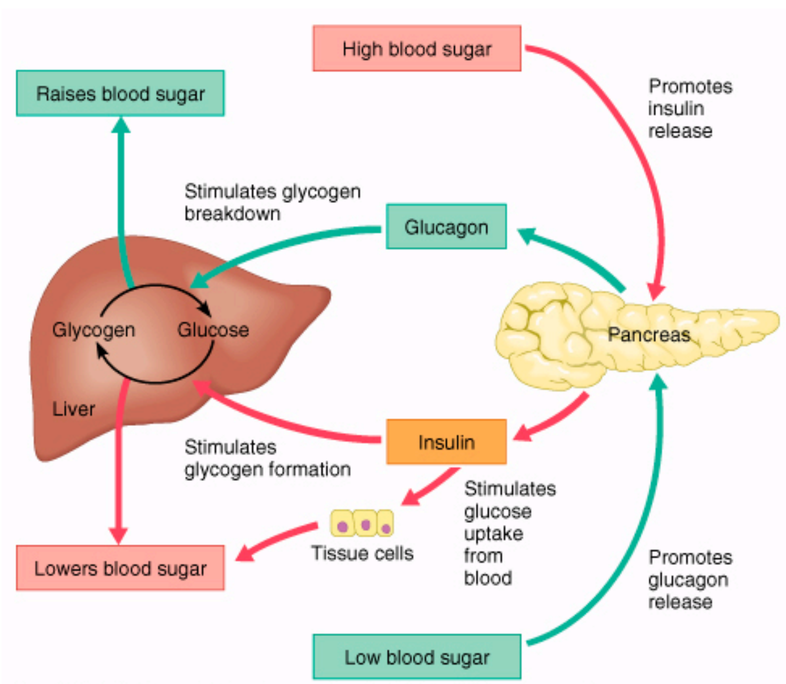
Glucose and fatty acids (body) lipids/fats

Glucose comes from

Carbohydrates broken into glucose (other sugars)

Fat into fatty acids, glucose

A little metabolism



Insulin from pancreas is key player

Glucose as glycogen in liver
Need insulin from pancreas to store this
**Insulin also necessary for cells to use glucose

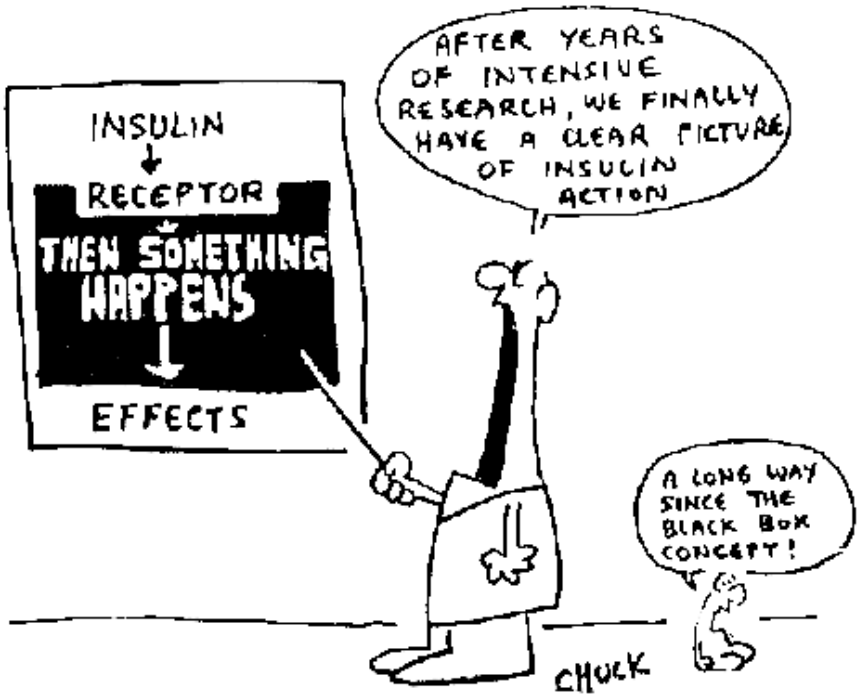
Where does insulin come from?

1. food in gut --> Hs --> pancreas --> insulin
2. glucose = further release
3. conditioned response

when you eat a meal at certain time; anticipate the meal with insulin

Insulin's effects are complex

- If insulin is chronically high
  - Glucose into cells; less in blood → hunger
- If insulin is chronically low (diabetes)
  - Glucose remains in blood, cells "starve" → hunger



Learning

Specialized learning mechanisms

E.g., Garcia effect – avoid foods that made you sick

Expectation triggers hormonal events

Prepares you for a mean

Learn association between caloric content and meal size

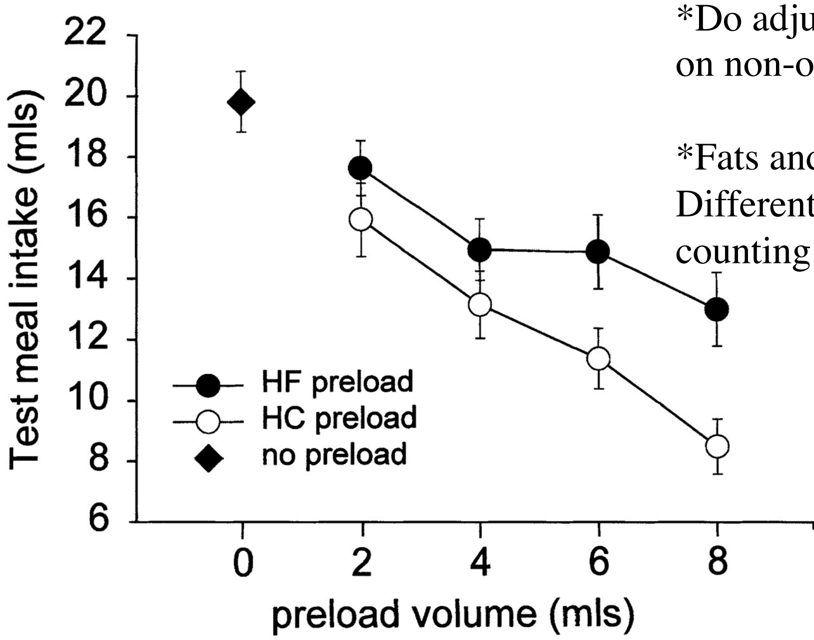
Preload Experiments

Does meal-size depend just on nutrients in our system?
What factors matter?
Do we always eat a meal of a fixed size?

Fast several groups of rats for a fixed amount of time
- e.g., 12 h
- they will be hungry
- see how much liquid diet (easy to measure) they consume

HF-high fat; HC-high carbohydrate
Can give intra-gastrically too

Experiment 2A: intake of a 10% sucrose test meal after isocaloric (2.3 kcal/ml) HF and HC preloads as a function of preload volume.



*Do adjust meal size based on non-oral factors

*Fats and carbs interpreted Differently – not just counting calories or volume

Warwick Z S et al. Am J Physiol Regul Integr Comp Physiol 2000;278:R196-R200

AMERICAN JOURNAL OF PHYSIOLOGY
Regulatory, Integrative and Comparative Physiology

Self test question

If an investigator wanted to test whether the body can calculate caloric content in the stomach to determine meal size, she should compare responses to which pair of preloads?

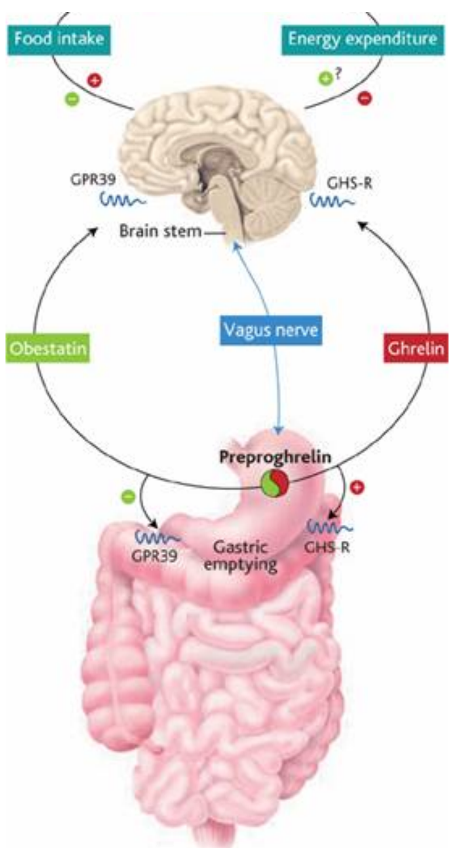
A. 5 versus 10 mL of 10% sugar solution

B. 10 mL of 5% versus 10% sugar solution

C. 100 calories of carb versus 100 calories of fat

D. 10 mL of 5% sugar versus 5 mL of 10% sugar

E. Any of the above



Ghrelin potently stimulates food intake

Useful for cachexia
Weight loss/wasting after
various diseases

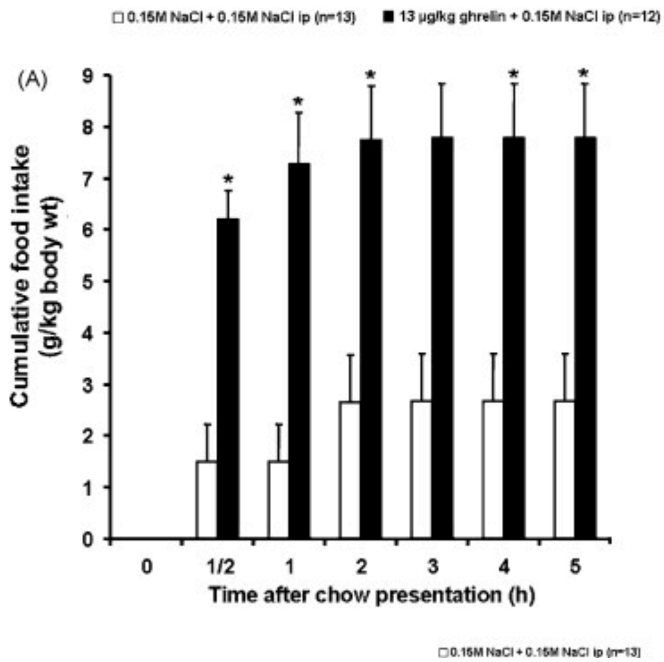
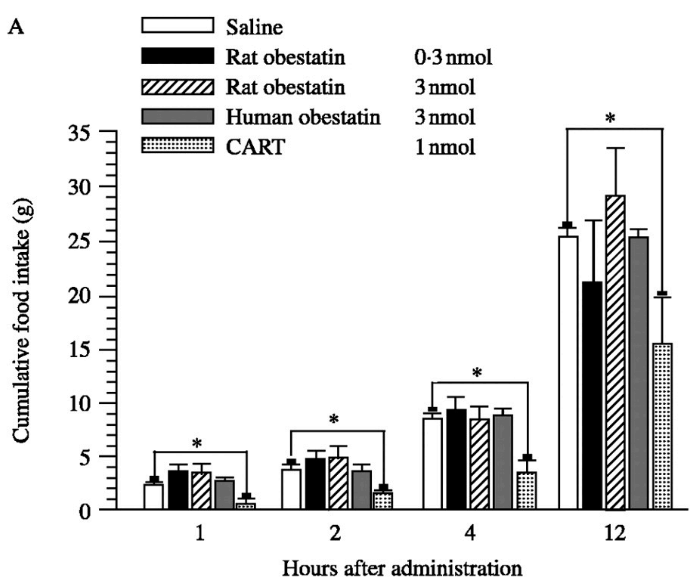


Figure 4
No effect on central or peripheral administration of obestatin on food intake. (A) Cumulative food intake in free-feeding rats in the dark phase (n=6 per group) following i.c.v. administration of saline, rat obestatin (0.3, 3.0nmol), human obestatin (3.0nmol), or CART (1nmol).

Obestatin not what people hoped

CART = cocaine & amphetamine regulated transcript



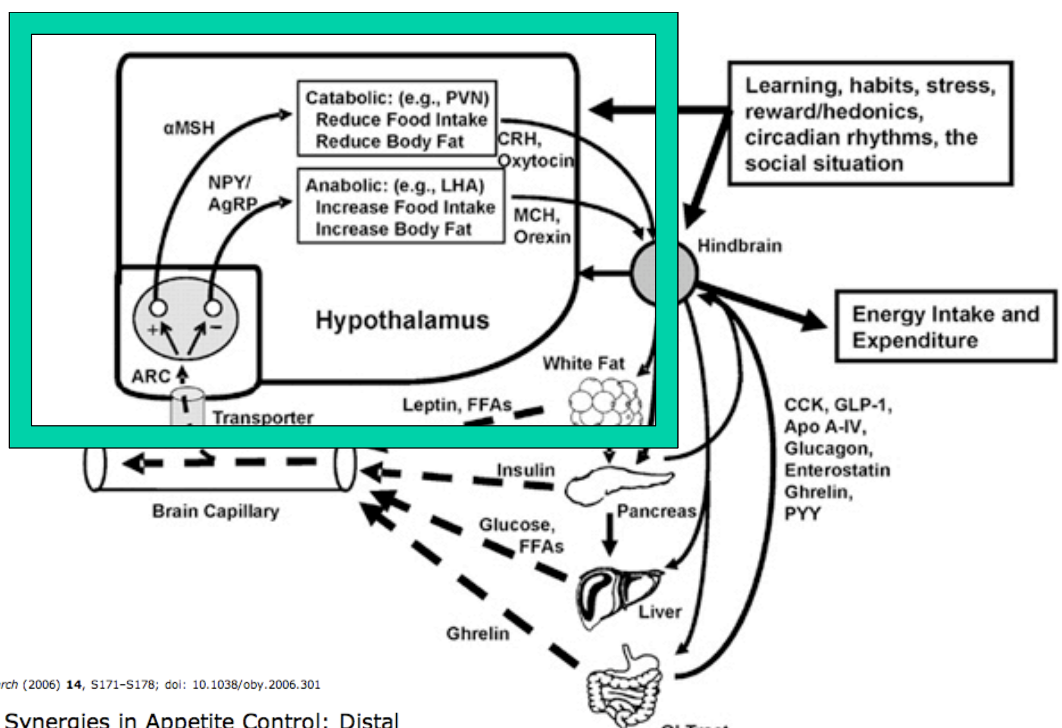
Mouth factors too:

Act of eating/drinking

Palatability

Odor – problem in aging

etc

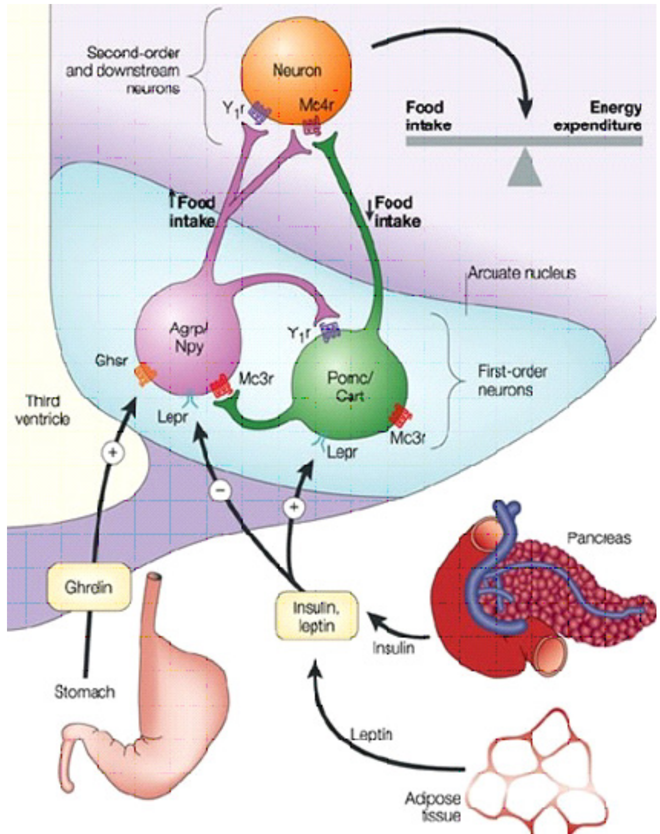


Obesity Research (2006) **14**, S171–S178; doi: 10.1038/oby.2006.301

Dietary Synergies in Appetite Control: Distal Gastrointestinal Tract

Stephen C. Woods*

*Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio.



Barsh and Schwartz, 2002

Silver *et al. Nutrition & Metabolism* 2011, **8**:8
http://www.nutritionandmetabolism.com/content/8/1/8

Nutrition&Metabolism

RESEARCH Open Access

Effects of grapefruit, grapefruit juice and water preloads on energy balance, weight loss, body composition, and cardiometabolic risk in free-living obese adults

Heidi J Silver[1*], Mary S Dietrich[2], Kevin D Niswender[3,4]

Abstract

Background: Reducing dietary energy density has proven to be an effective strategy to reduce energy intakes and promote weight control. This effect appears most robust when a low energy dense preload is consumed before meals. Yet, much discussion continues regarding the optimal form of a preload. The purpose of the present study was to compare effects of a solid (grapefruit), liquid (grapefruit juice) and water preload consumed prior to breakfast, lunch and dinner in the context of caloric restriction.

Methods: Eighty-five obese adults (BMI 30-39.9) were randomly assigned to (127 g) grapefruit (GF), grapefruit juice (GFJ) or water preload for 12 weeks after completing a 2-week caloric restriction phase. Preloads were matched for weight, calories, water content, and energy density. Weekly measures included blood pressure, weight, anthropometry and 24-hour dietary intakes. Resting energy expenditure, body composition, physical performance and cardiometabolic risk biomarkers were assessed.

Results: The total amount (grams) of food consumed did not change over time. Yet, after preloads were combined with caloric restriction, average dietary energy density and total energy intakes decreased by 20-29% from baseline values. Subjects experienced 7.1% weight loss overall, with significant decreases in percentage body, trunk, android and gynoid fat, as well as waist circumferences (-4.5 cm). However, differences were not statistically significant among groups. Nevertheless, the amount and direction of change in serum HDL-cholesterol levels in GF

Lose Weight with a Preload

healthhabits | February 8, 2011 | 2 Comments

Tweet 55 | Like 17 | 1 | +1 0

"Preload that Sunny D and you'll get wicked abs like mine"

Let me introduce you to the simplest weight loss trick of all time

Preloading.

The next time you are on diet (calorie restriction), I want you to preload your tummy (20 minutes before a meal) with either:

1. 1/2 a normal sized grapefruit (GF), or
2. 127 grams / 4.5 oz of unsweetened grapefruit juice (GFJ), or
3. 127 grams / 4.5 oz of water

If you do this, you should expect to see these kind of results over the next 2 weeks.

- average calorie intake decreased by 21% in GF group, 29% in GFJ group, and 28% in water group
- an increase in "good cholesterol" HDL-C from baseline by 6.2% in the GF group and 8.2% in the GFJ group
- an average weight loss across all groups of 7.1% of initial body weight – *minimal diff between groups*
- 5.8 ± 3.9 kg weight loss for the GF group,
- 5.9 ± 3.6 kg weight loss for the GFJ group and
- 6.7 ± 3.1 kg weight loss for the water group

All thanks to drinking or eating 127 grams of unsweetened grapefruit juice or water 20 minutes before each meal.

Pretty cool.

For more info, here's a link to the study as published in Nutrition & Metabolism.

Self-test question

What is the ultimate factor that determines whether one gains or loses weight?

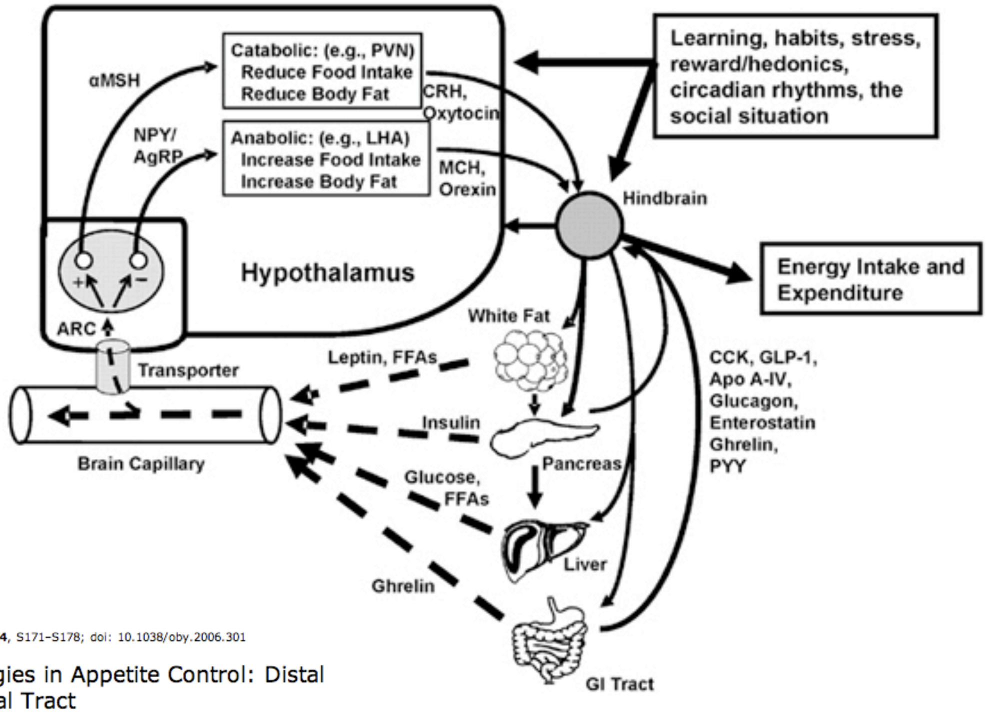
A. Activity of arcuate and PVN neurons

B. Amount of leptin

C. Balance of energy intake versus expenditure

D. Combination of multiple genes

E. We simply don't know

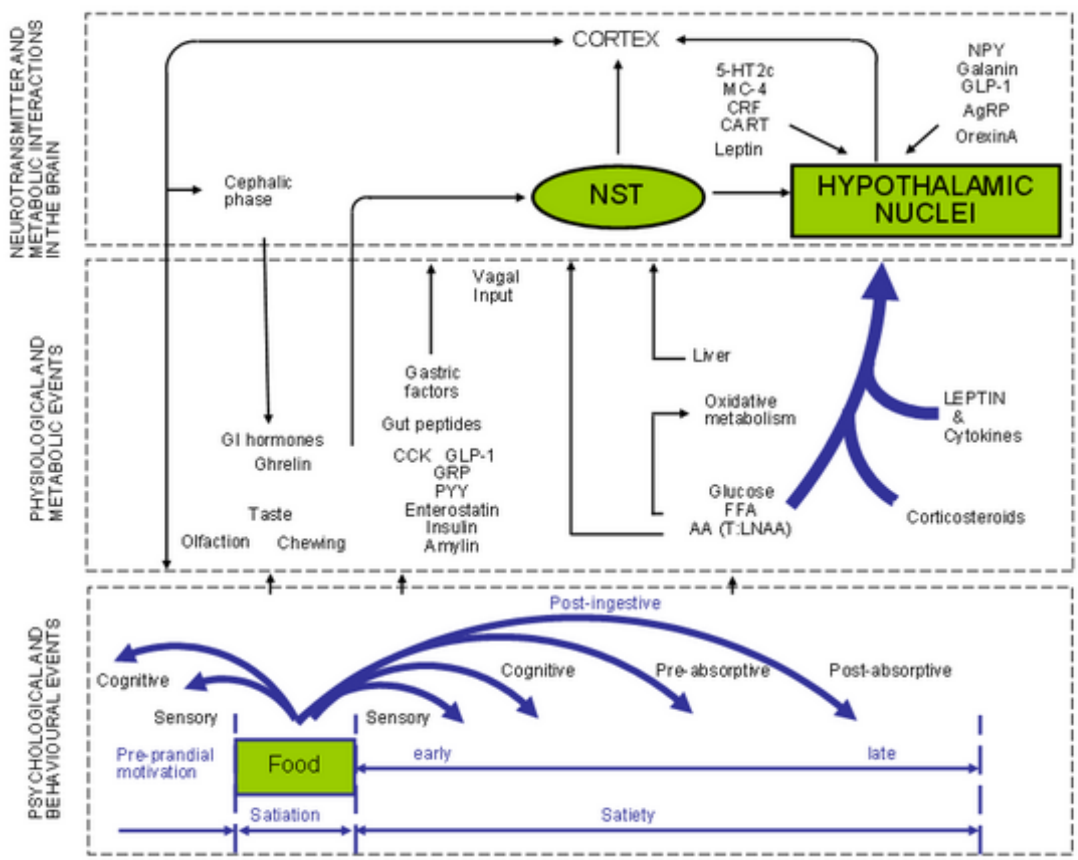


Obesity Research (2006) **14**, S171–S178; doi: 10.1038/oby.2006.301

Dietary Synergies in Appetite Control: Distal Gastrointestinal Tract

Stephen C. Woods[*]

[*]Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio.



Summary

Distributed system

gut, liver, brain etc

Multiple players

Inhibition vs stimulation

Nature hasn't had to deal with selection pressure of too much energy

Easier to break than to control

Required Reading: Chapter 9.1

Study Questions:

1. Describe several kinds of evidence that argue for and against the idea that the SCN is "the clock".

2. How does light affect the circadian clock?

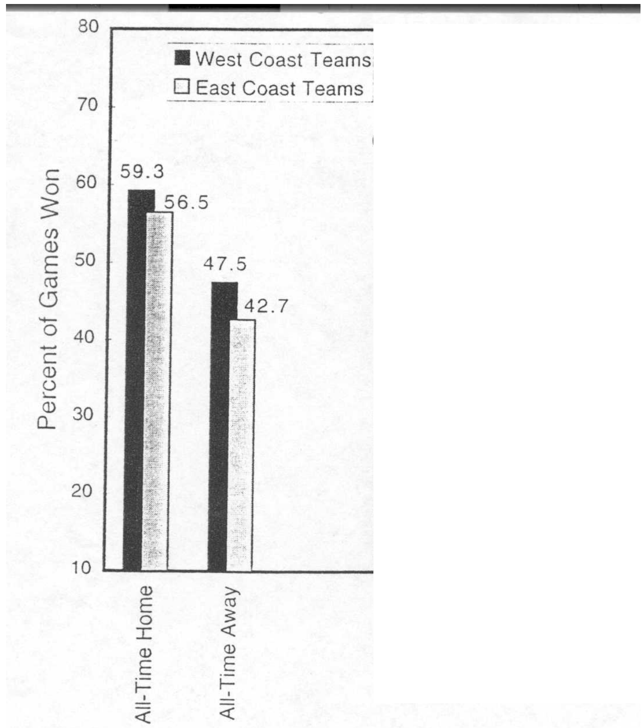


FIG. 1. MNF, Monday Night Football games; W/E, West Coast teams versus East Coast teams; H, home games; A, away games.

Football

MNF always starts around 8:30 Easterr Time

or 5:30 Pacific Time

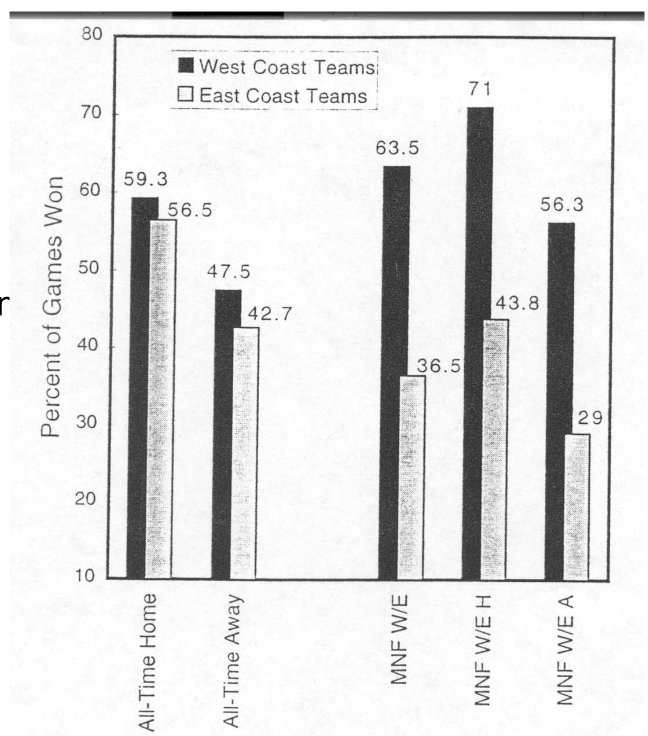


FIG. 1. MNF, Monday Night Football games; W/E, West Coast teams versus East Coast teams; H, home games; A, away games.

Self-test question

What explanation do you think is likely explains the MNF advantage for west coast teams?

A. West coast teams are just better

B. Flying across the country impairs performance

C. Teams do better at home

D. Athletic performance is better in the afternoon than in the evening

E. It is easier to fly east than west

Everything exists in time:

Ultradian rhythm

- 2-4 h vole feeding cycle
- 90 minute BRAC, REM

Circadian

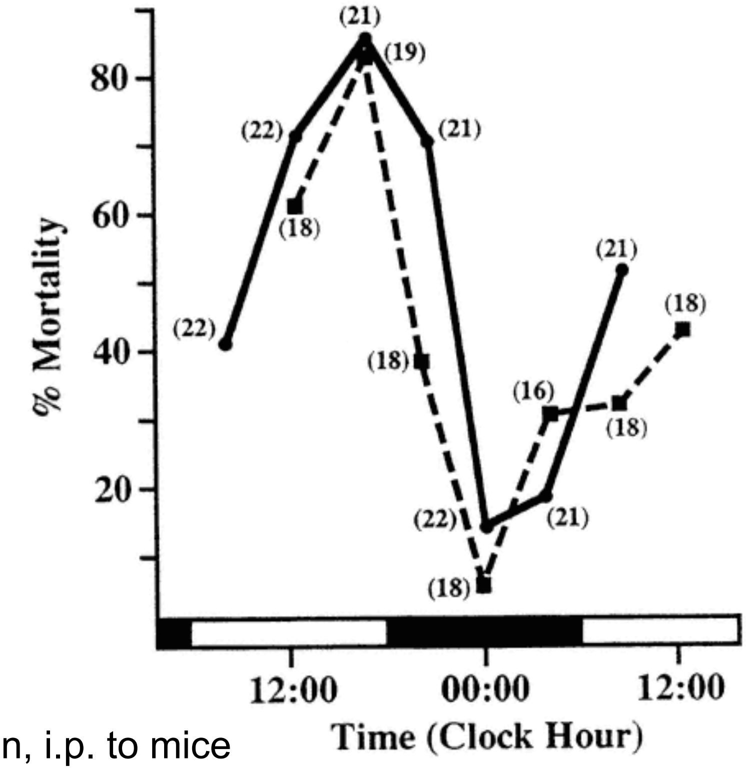
- today's lecture

Infradian

- estrous, menstrual cycle

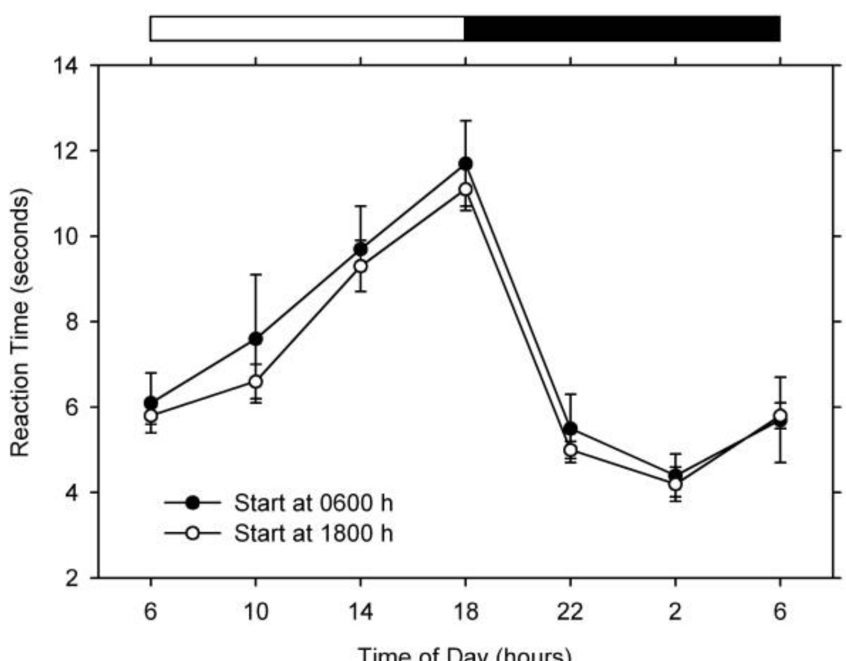
Circannual

- squirrel body weight,
- hibernation
- Seasonal Affective Disorder (SAD)

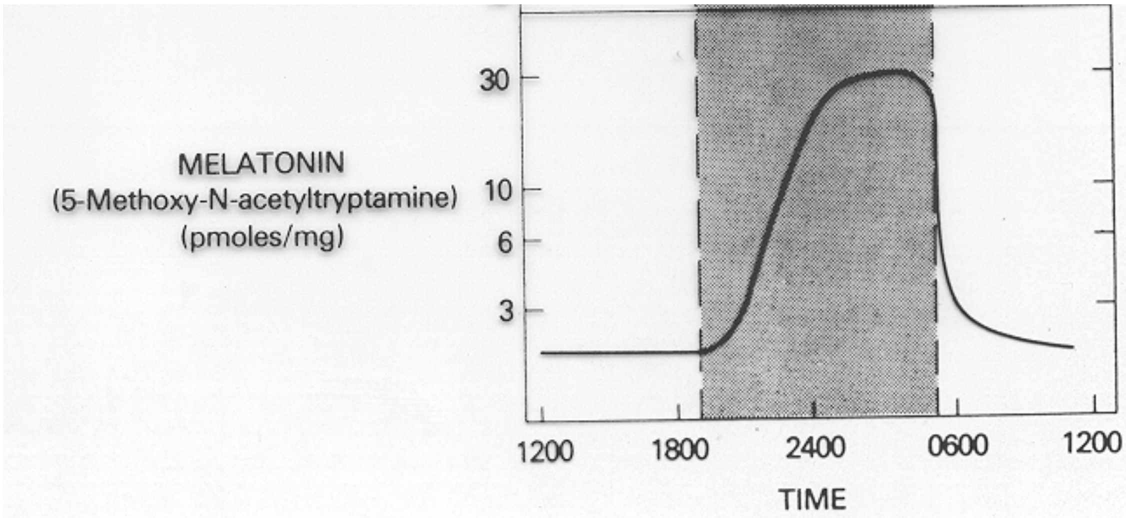


E. Coli endotoxin, i.p. to mice

Pain sensitivity of rats
Reaction time to move tail from hot surface

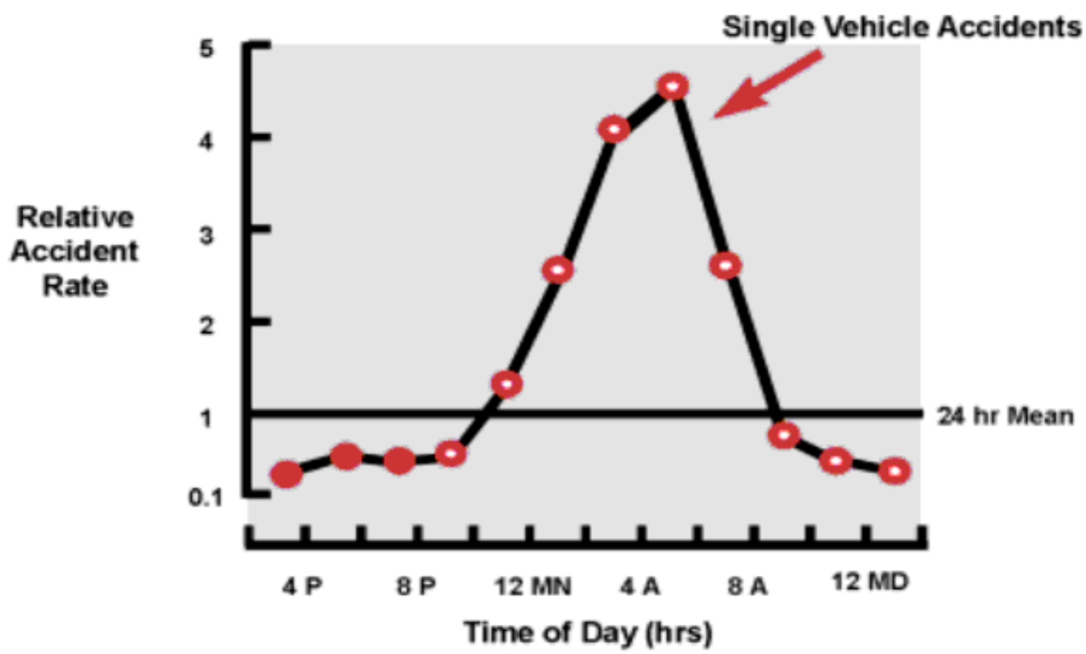


Christina et al., 2004

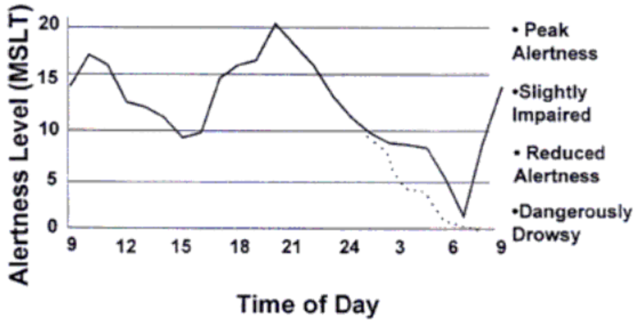


Melatonin rhythm

Accidents

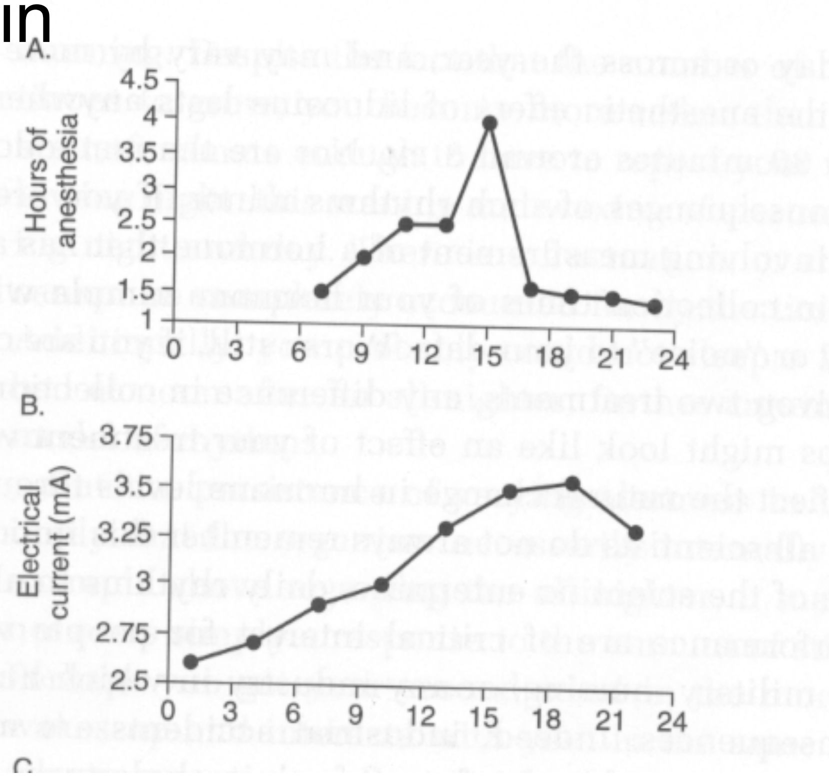


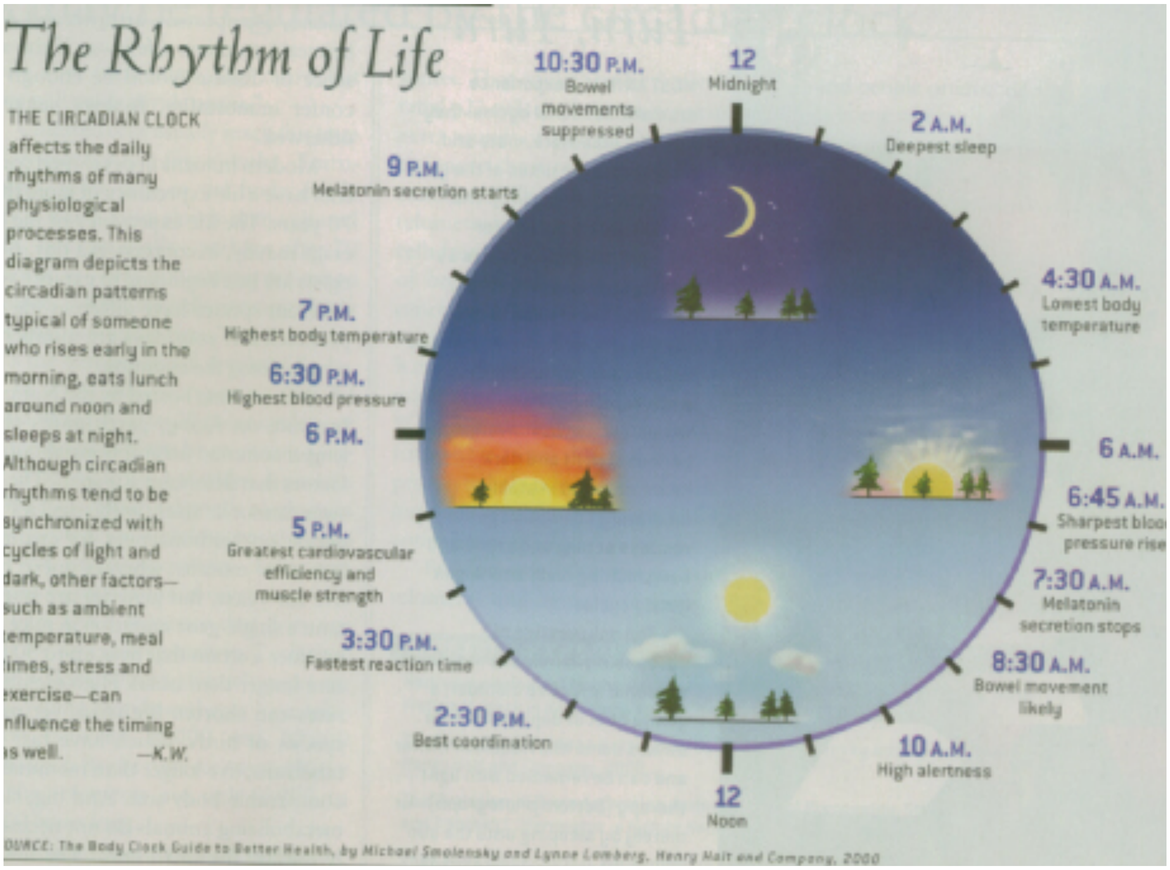
Human alertness



Dental pain

Pain Threshold





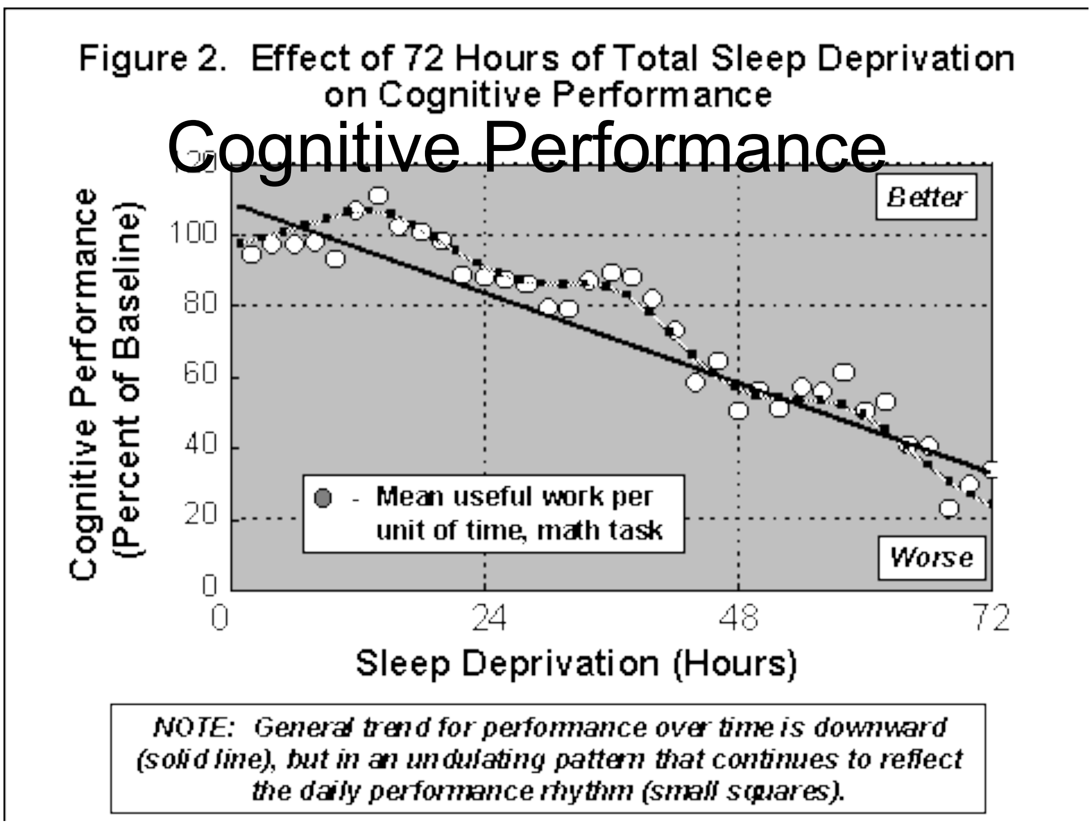
Consequences:

- Public safety
- Medical interventions
- Experimental controls
- Educational policy
- Shift-work

How do you know that there is a “clock”?

Maybe all of the above are just due to the day/night environment

Cognitive Performance



Flies and mice

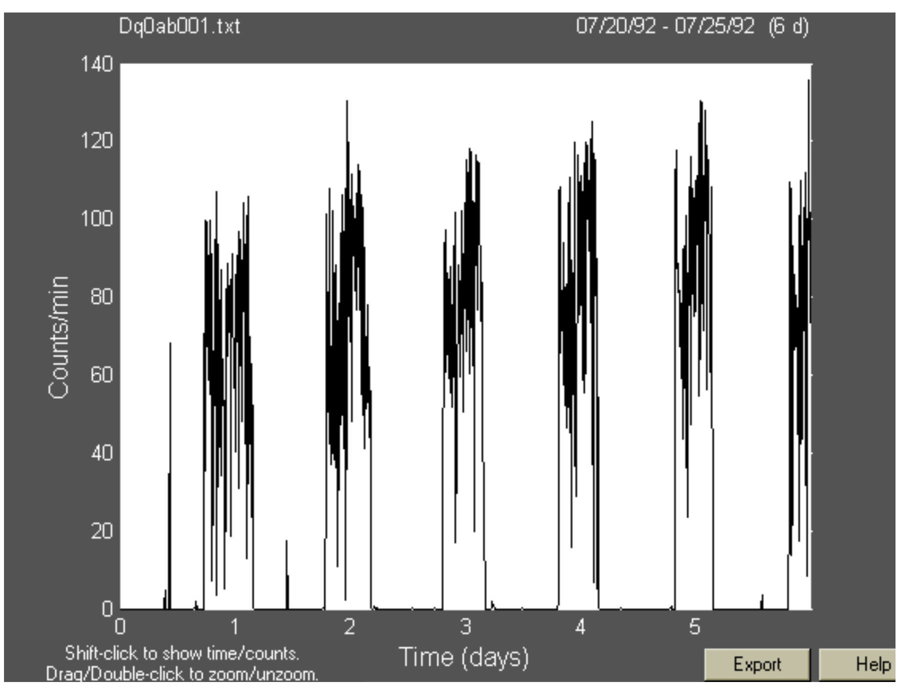
a 

Drosophila

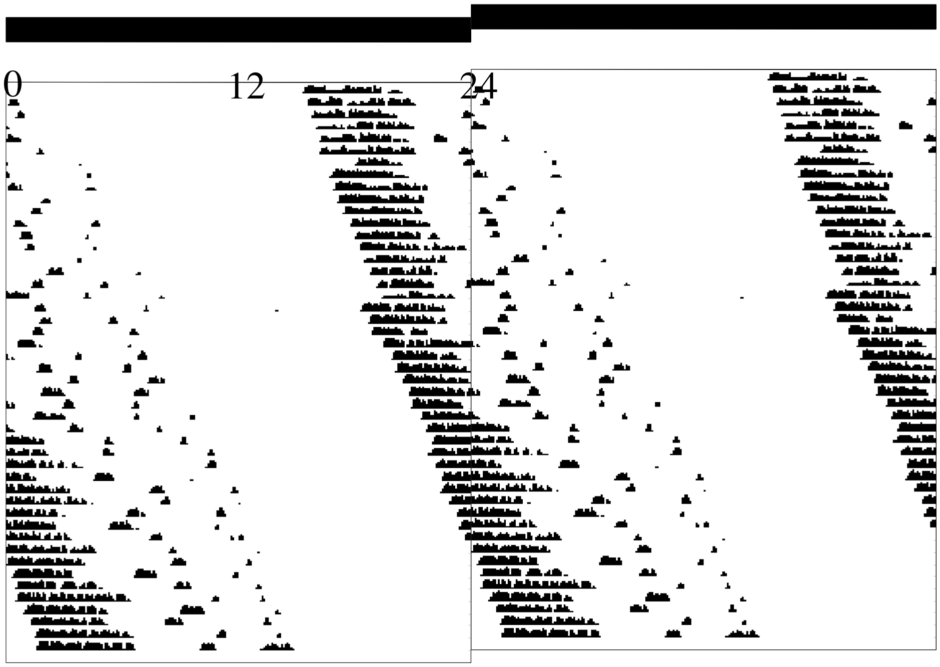
d 

Mus

Hamster wheel-running activity over several days



Wheel-running rhythm in constant darkness (DD)
=ACTOGRAM



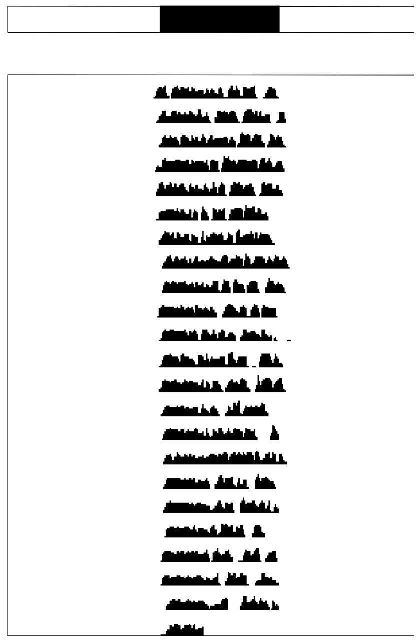
Free-running period (FRP, tau)   phase shift halfway through

Proves that there is an *endogenous* self-sustained oscillator

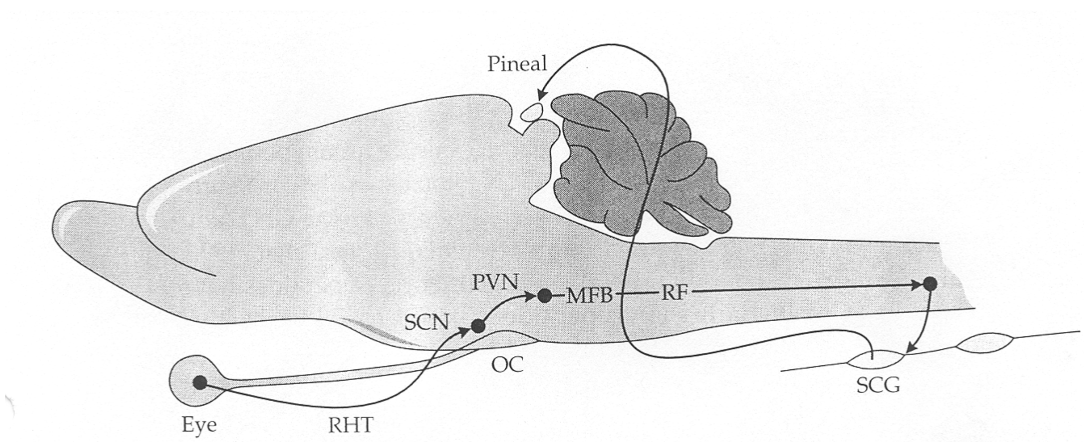
True of rest/activity but countless other things

e.g., temperature, learning, sensation, motivation etc

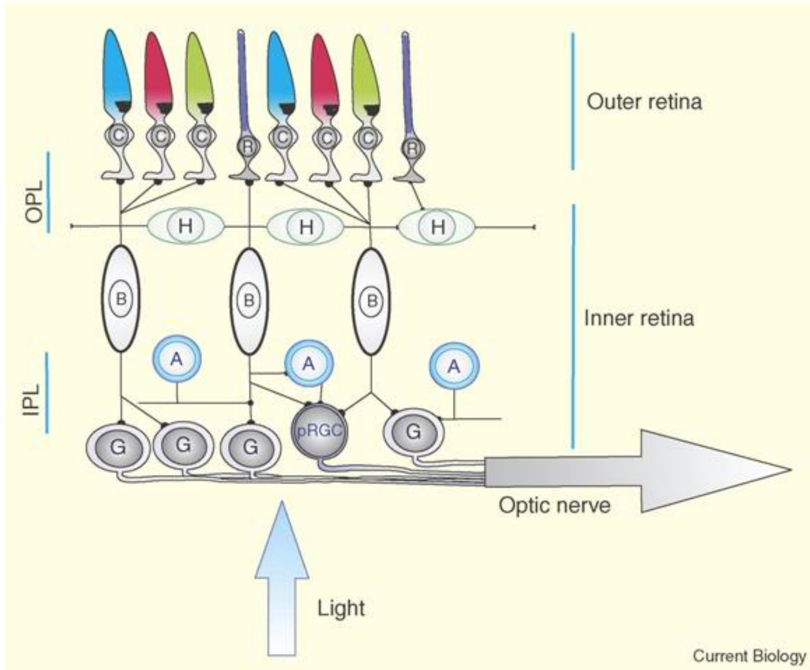
Entrainment by light
Onsets line up vertically



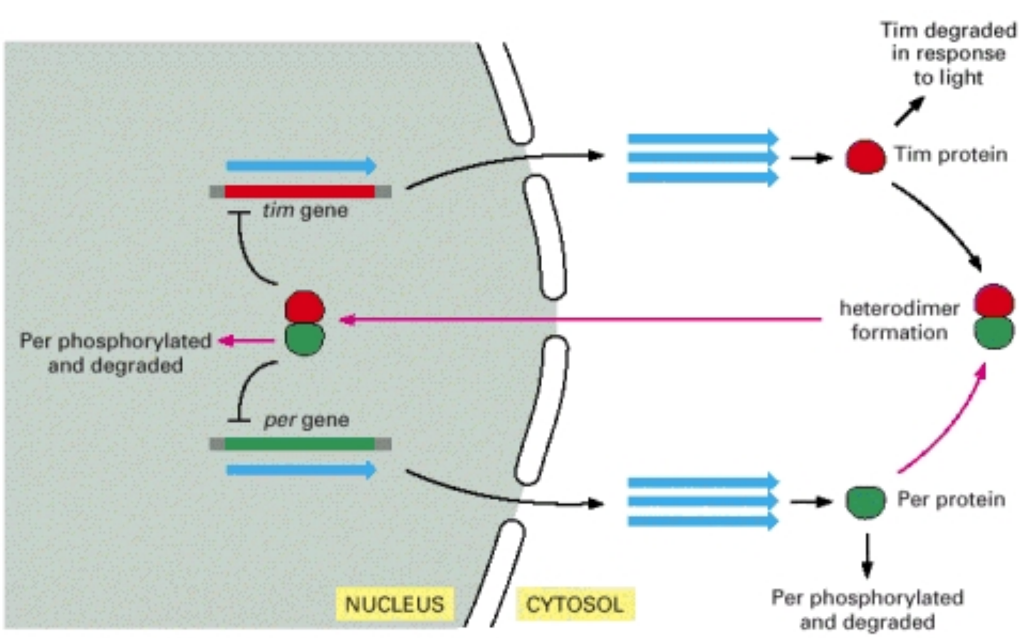
Suprachiasmatic nucleus
OC=optic chiasm
Pineal release melatonin

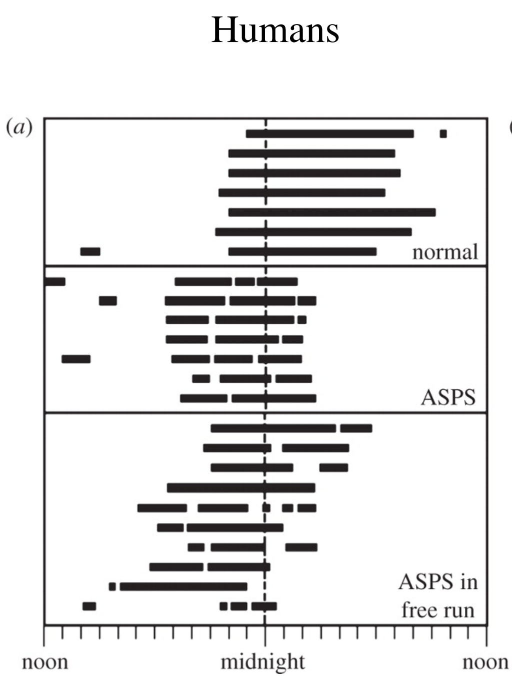


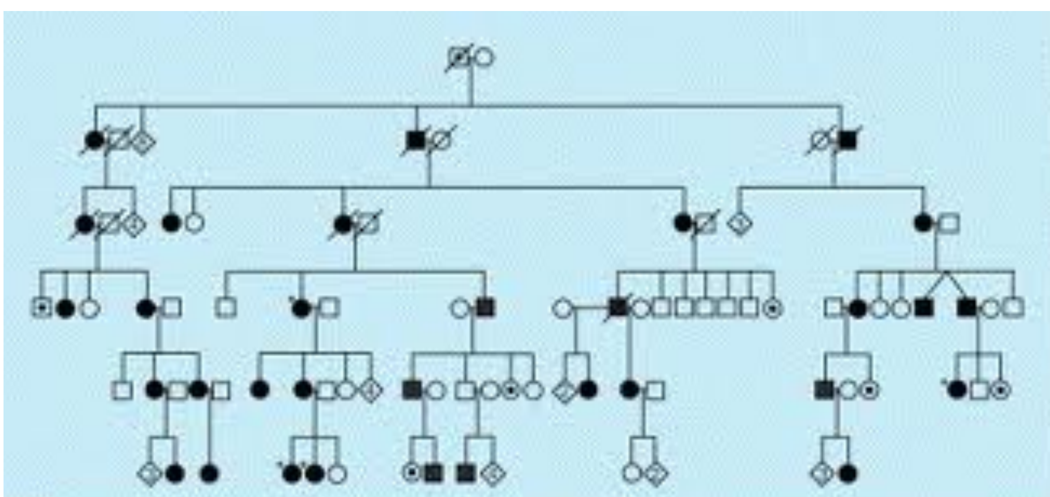
Specialized visual system
ipRGC=intrinisically photosensitive retinal ganglion cell
Contains melanopsin



Transcription-translation feedback loop (TTFL)
components are "clock genes" e.g., per1, per2
Takes about 24 h to cycle

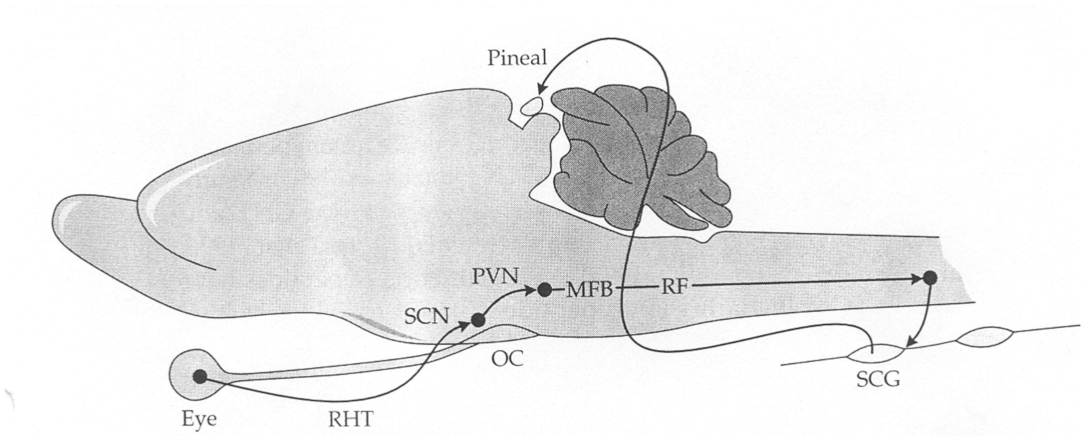




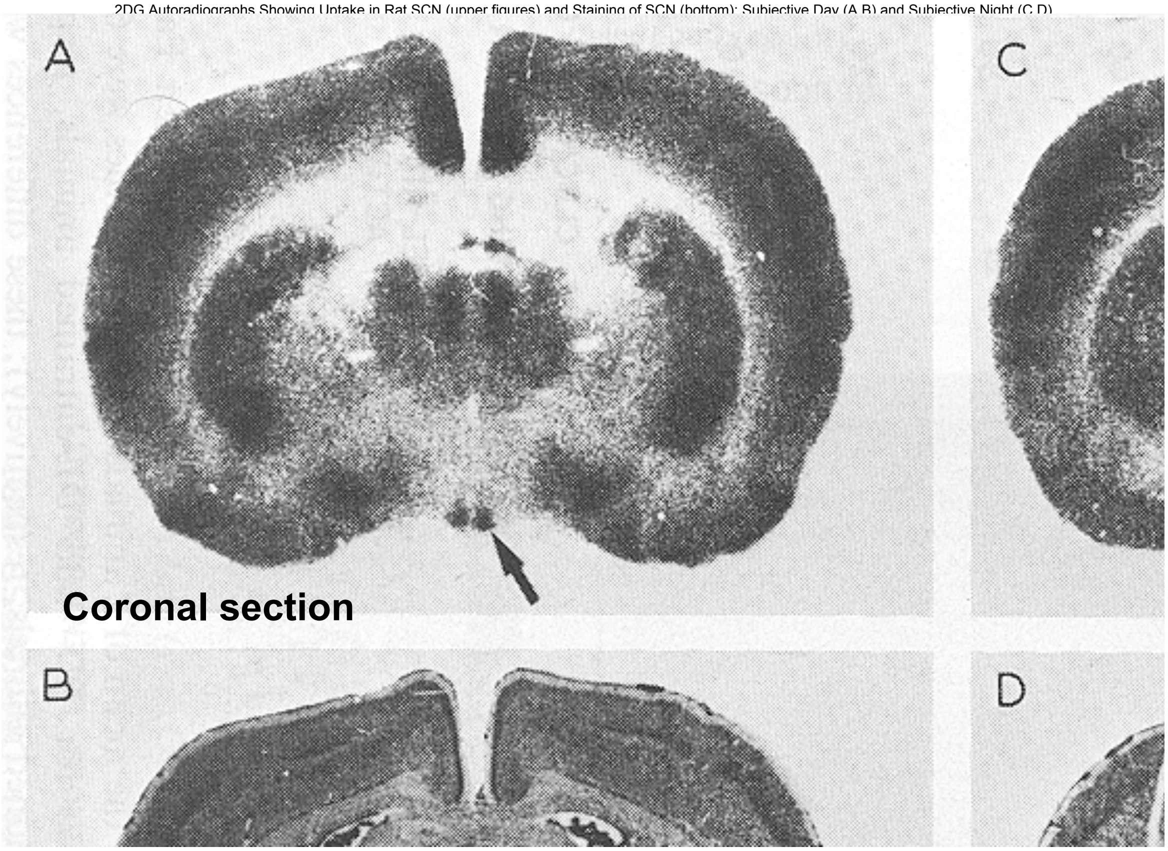


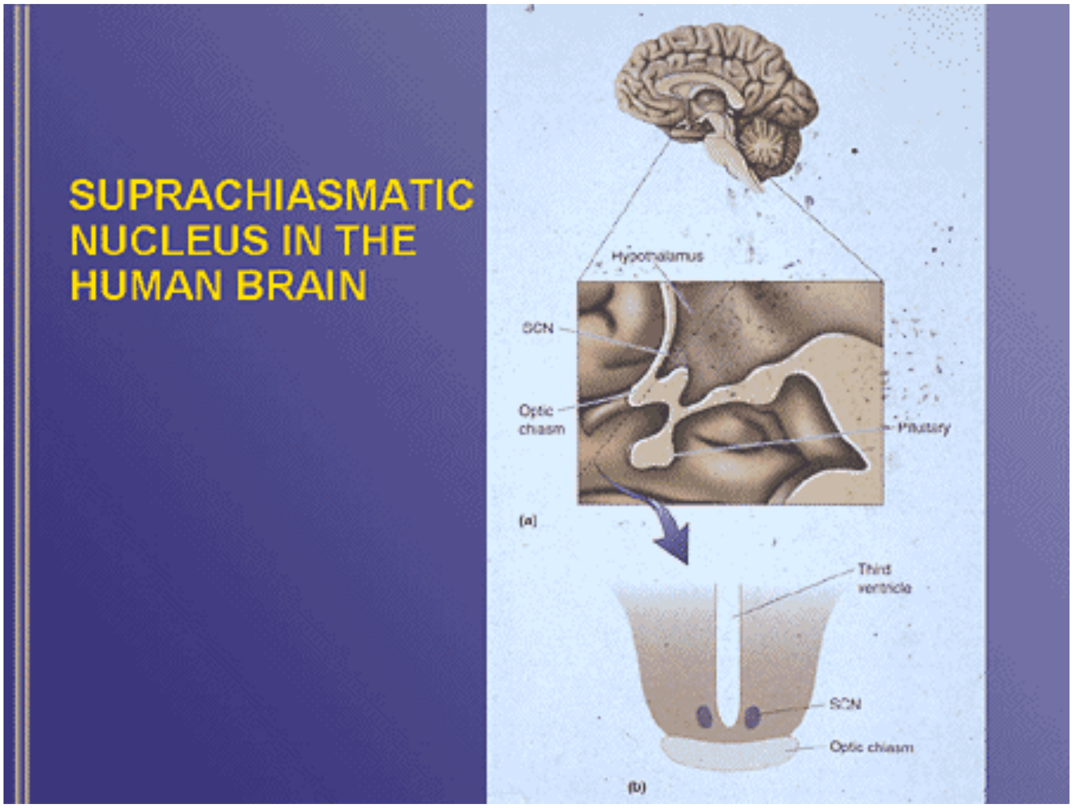
Presence of ASPS (advanced sleep phase syndrome)
Dark symbols are affected
found mutation in hPer2 gene (dominant autosomal)

SCN is tiny – only 10,000 cells
How was it found to be important for the clock?



2DG Autoradiographs Showing Uptake in Rat SCN (upper figures) and Staining of SCN (bottom): Subjective Day (A,B) and Subjective Night (C,D)

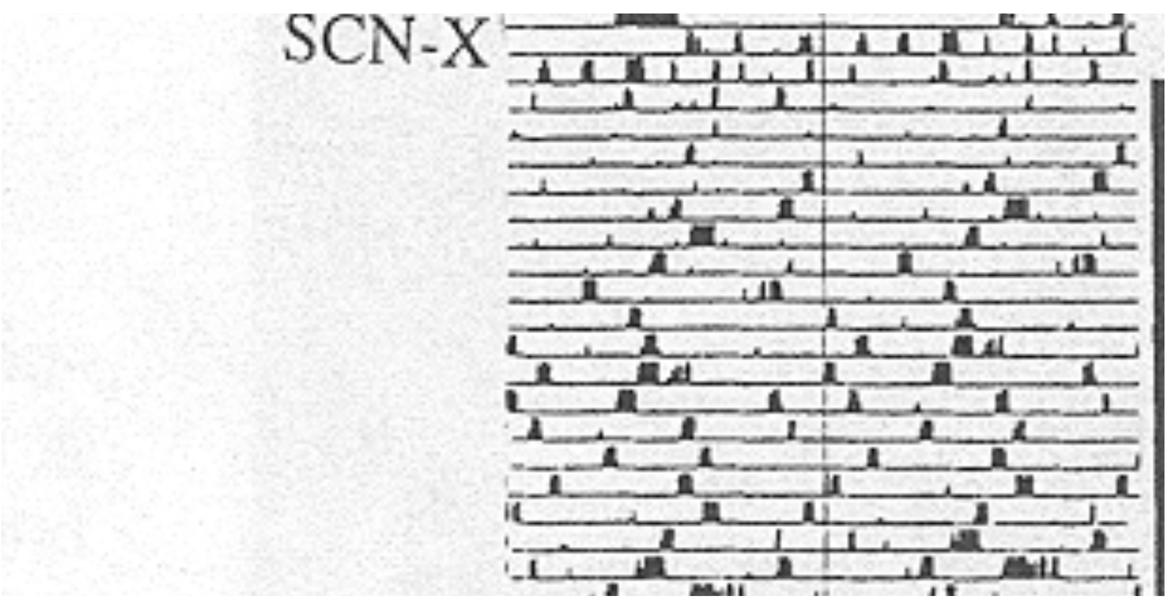




Around 1970, saw that the eye projected to this structure

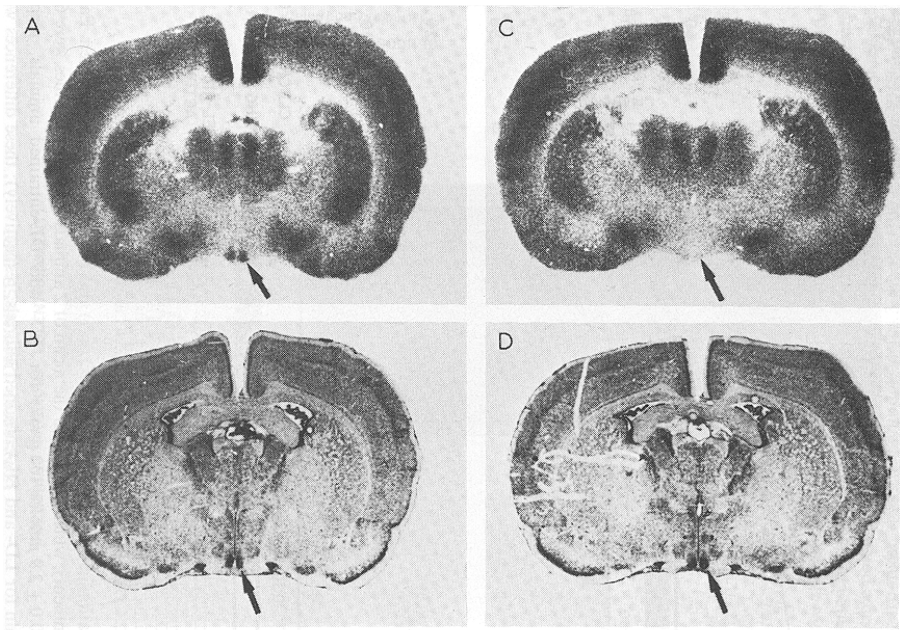
Lesioned it (SCN-X) to see if sensitivity to light disappeared

Instead, found arhythmicity



2DG Autoradiographs Showing Uptake in Rat SCN (upper figures) and Staining of SCN (bottom): Subjective Day (A,B) and Subjective Night (C,D)

DAY **NIGHT**

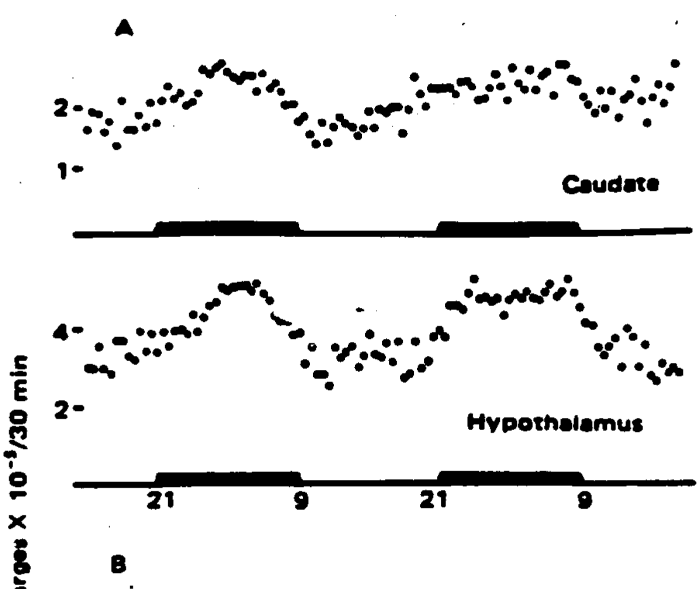


2-DG shows how much energy used

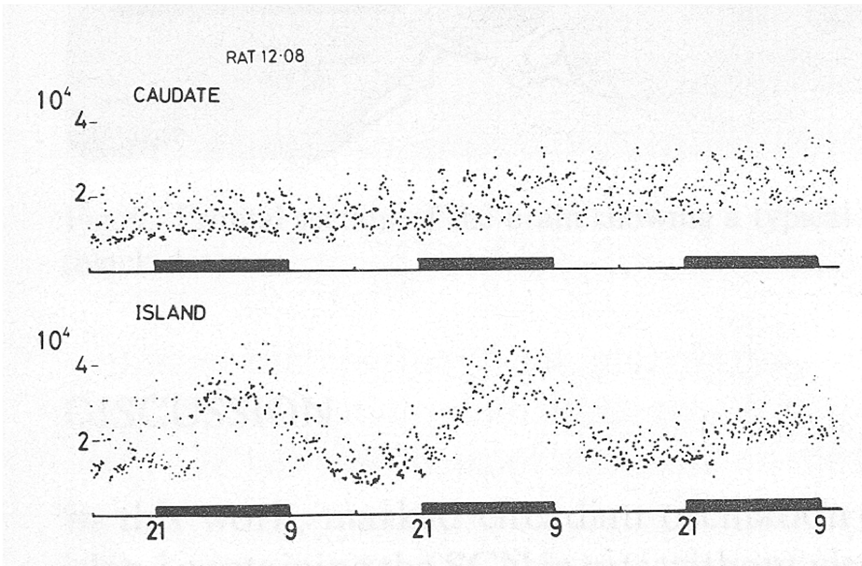
Stain for structure

But lots of parts of brain are rhythmic
Measuring electrical activity (action potentials)

Proc. Natl. Acad. Sci. USA 76 (1979)



Rhythmicity logically arises from within the hypothalamic island made with knife cuts



Can even study clock function in a petri dish = *in vitro*

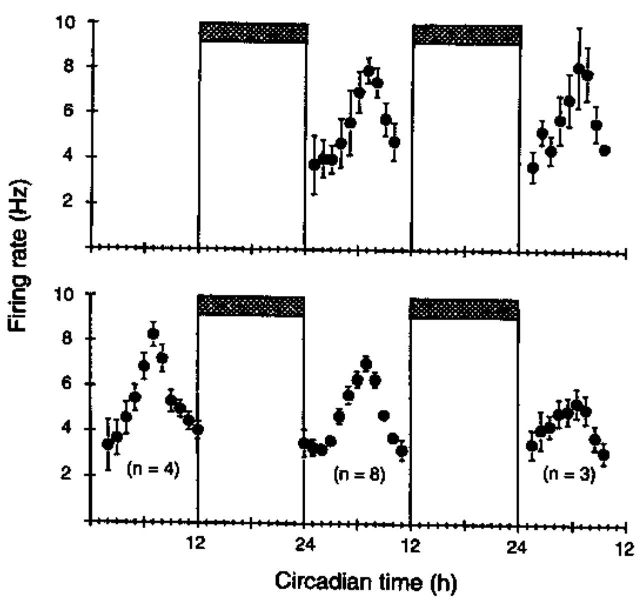


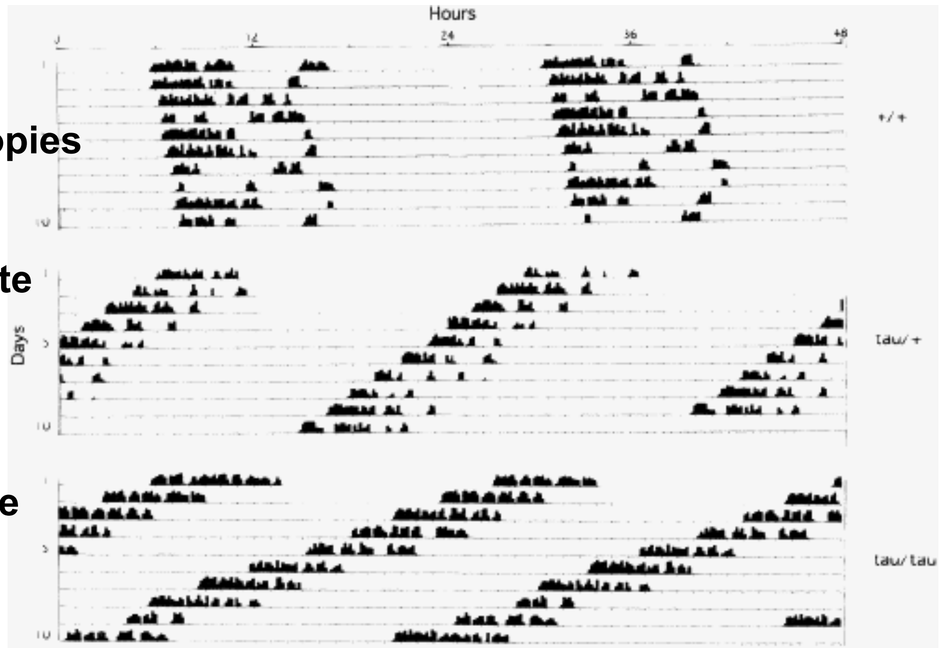
Figure 2. Circadian rhythm of neuronal activity *in vitro*. Top: Recording from a single SCN on day 2 (peak = CT7.0) and day 3 (peak = CT6.5). Lower: Mean of firing rates on successive days from several animals (*n* equals the number of animals). The means (±SEM) of all single units recorded from 2-hour intervals are plotted with 1-hour lags. Horizontal bars represent subjective night. (Adapted from Prosser & Gillette, 1989.)

There are clock gene mutants – tau mutation

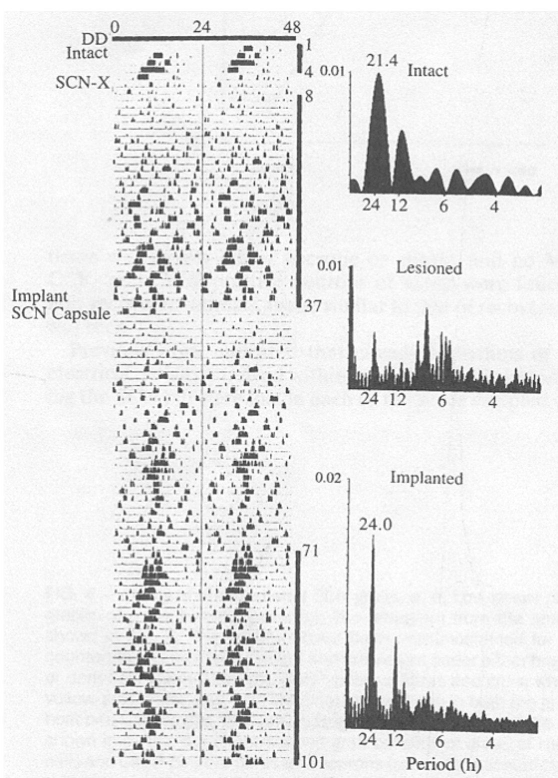
Wild-type
2 normal copies
~24.1 h

Heterozygote
1 normal
1 mutant
~22 h

Homozygote
2 mutant
~20 h



Restoration of Activity Rhythm by SCN Transplant From Wild-Type Hamster to SCN-Ablated Tau-Mutant Hamster



transplants
Free-run tau = 21.4
SCN-X = arhythmic
add fetal SCN cells in 3rd ventricle

rhythm comes back

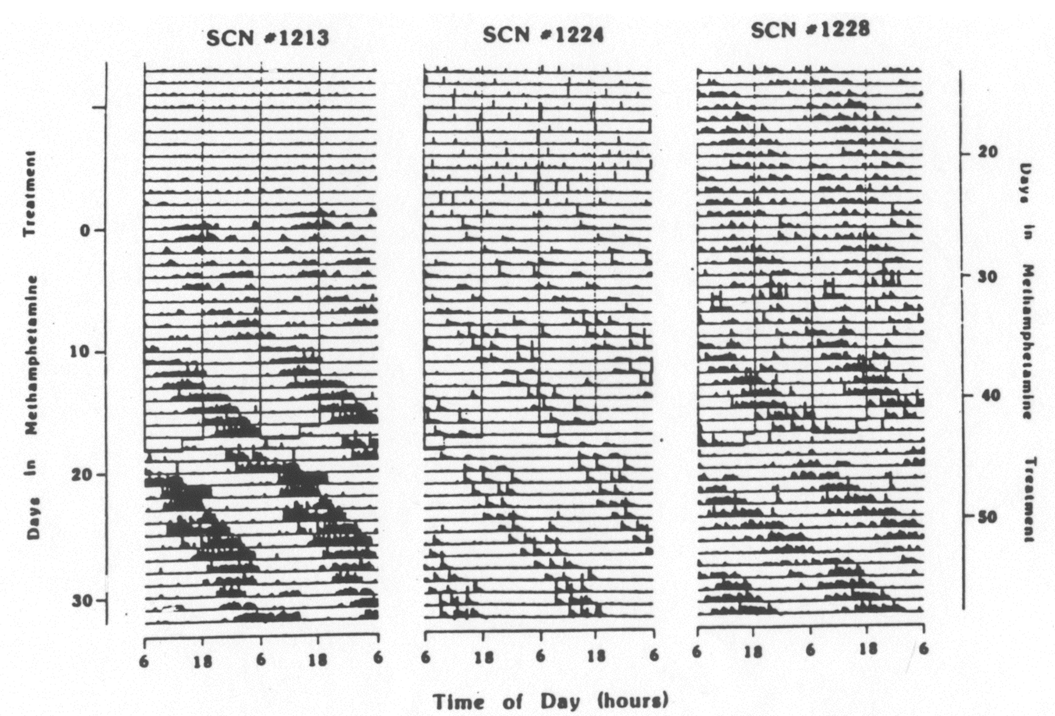
has period of donor tissue

neural connections not needed for activity rhythms

Lesions
Metabolic studies
Hypothalamic Islands
In vitro studies
Transplant studies

All suggest CRITICAL ROLE of SCN

Unexpected result:
Methamphetamine in water of SCN-X rats



Self-test question

What is the period of the circadian rhythm after methamphetamine was given?

A. Less than 24 h

B. 24 h

C. More than 24

D. Impossible to tell from actogram

Self-test question

What can we conclude from the finding that SCN-X rats show circadian activity rhythms if they have methamphetamine in their water?

A. That the SCN is not a clock

B. That there are clocks outside of the SCN

C. That the SCN was not properly lesioned

D. That circadian rhythms are not endogenous

E. Choices A and B

Current Model

SCN sits atop a hierarchy of clocks
    Normally coordinates entire system

Additional, weaker clocks throughout brain/body

Normally dampen without SCN

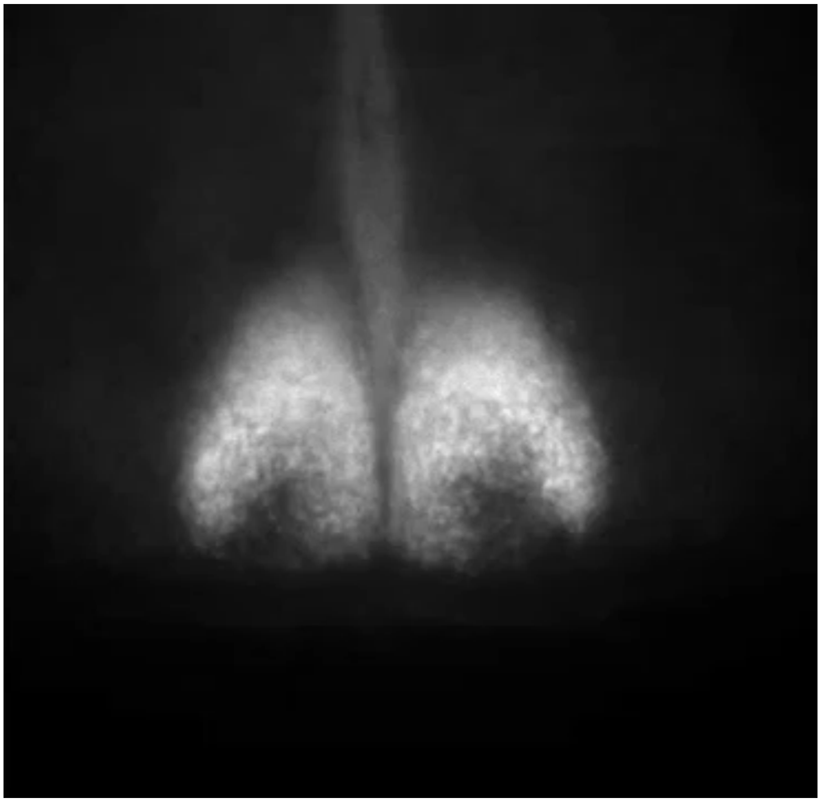
Under permissive conditions, these can be coordinated

Advanced tools make this an incredible model system for understanding how individual neurons work together to control behavior.

~1990 Record from single SCN cells in vitro
- **grow cells on micro-electrode plate**
- **one cell has a circadian rhythm**
- **different cells have different periods etc**

~2005 Switch from electrical recording (a hand or output of the clock) to clock-gene recording (a gear of the clock)

- **use glow-in-the-dark protein from fireflies**
- **attach to a clock gene**



David Welsh

7 days

Football

MNF always starts around 8:30 Eastern Time

or 5:30 Pacific Time

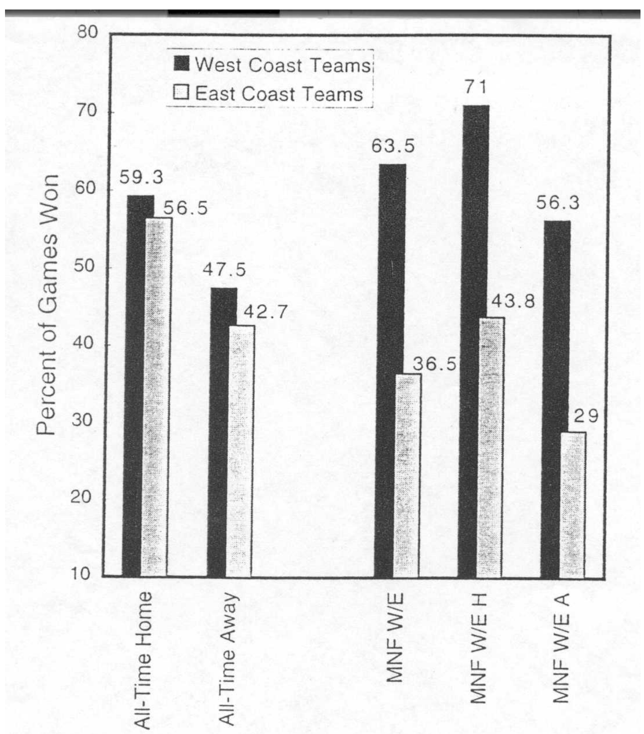


FIG. 1. MNF, Monday Night Football games; W/E, West Coast teams versus East Coast teams; H, home games; A, away games.

Self-test question

What explanation do you think is likely explains the MNF advantage for west coast teams?

A. West coast teams are just better

B. Flying across the country impairs performance

C. Teams do better at home

D. Athletic performance is better in the afternoon than in the evening

E. It is easier to fly east than west