Appetite and Satiety: It’s complicated (and complex)

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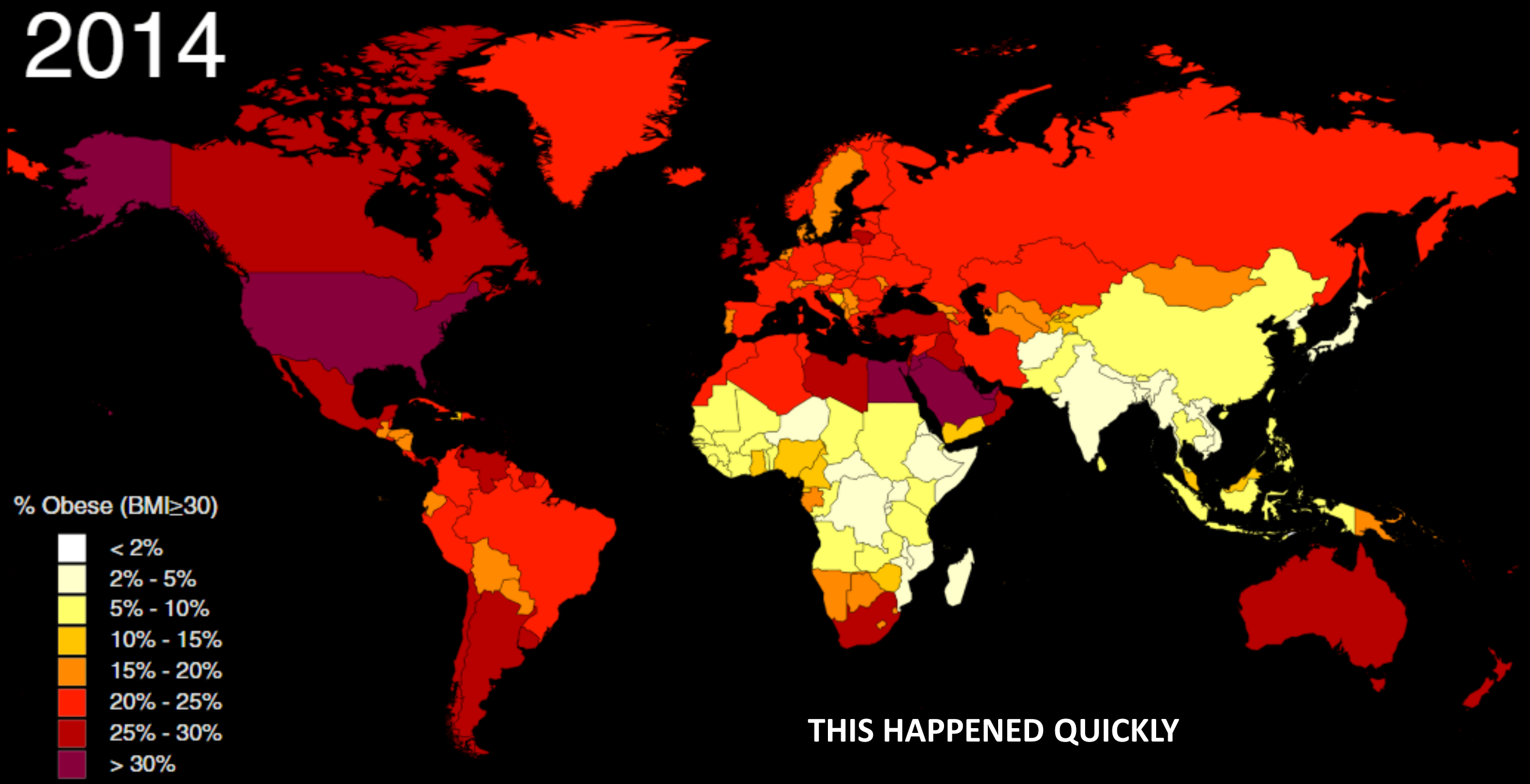
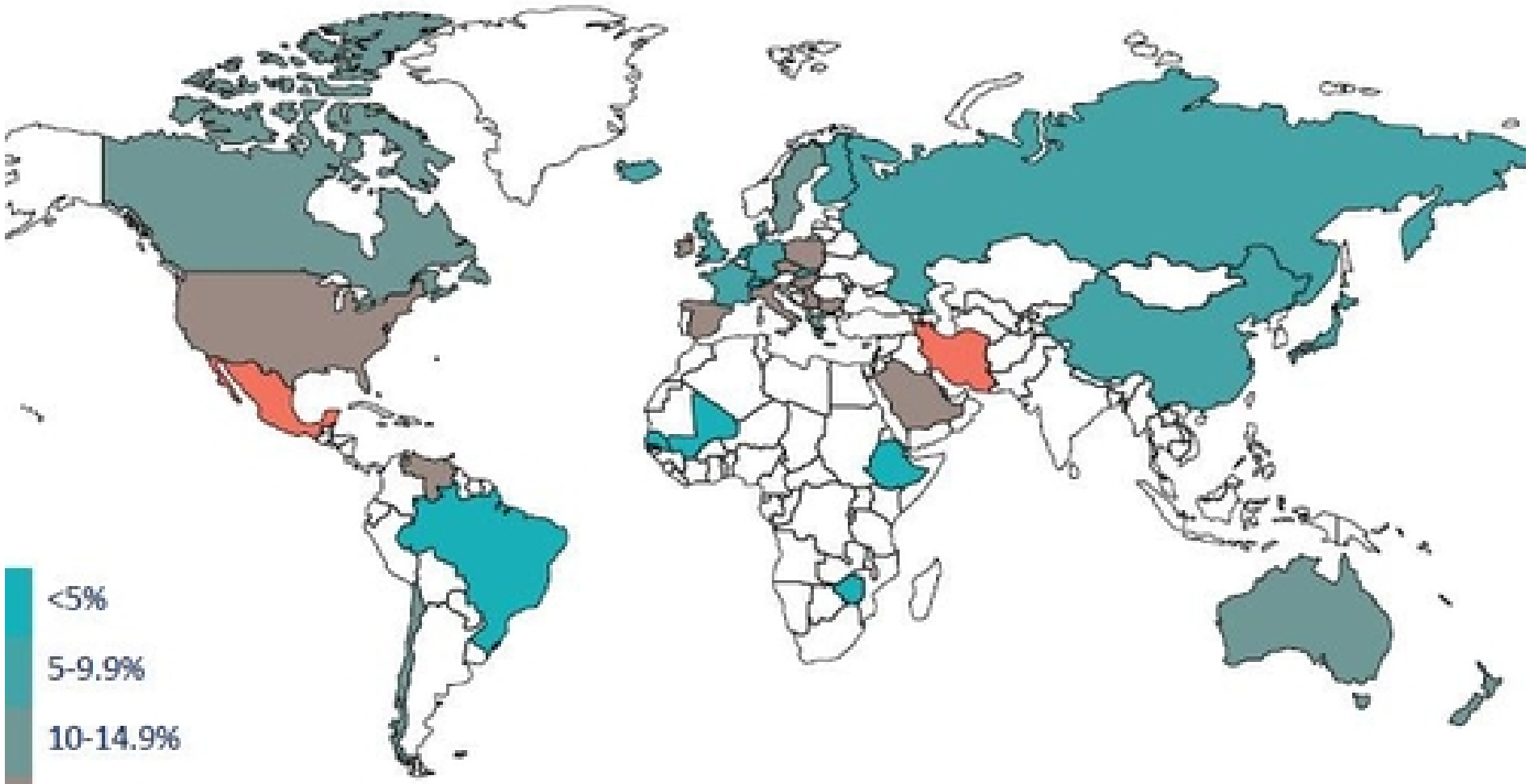
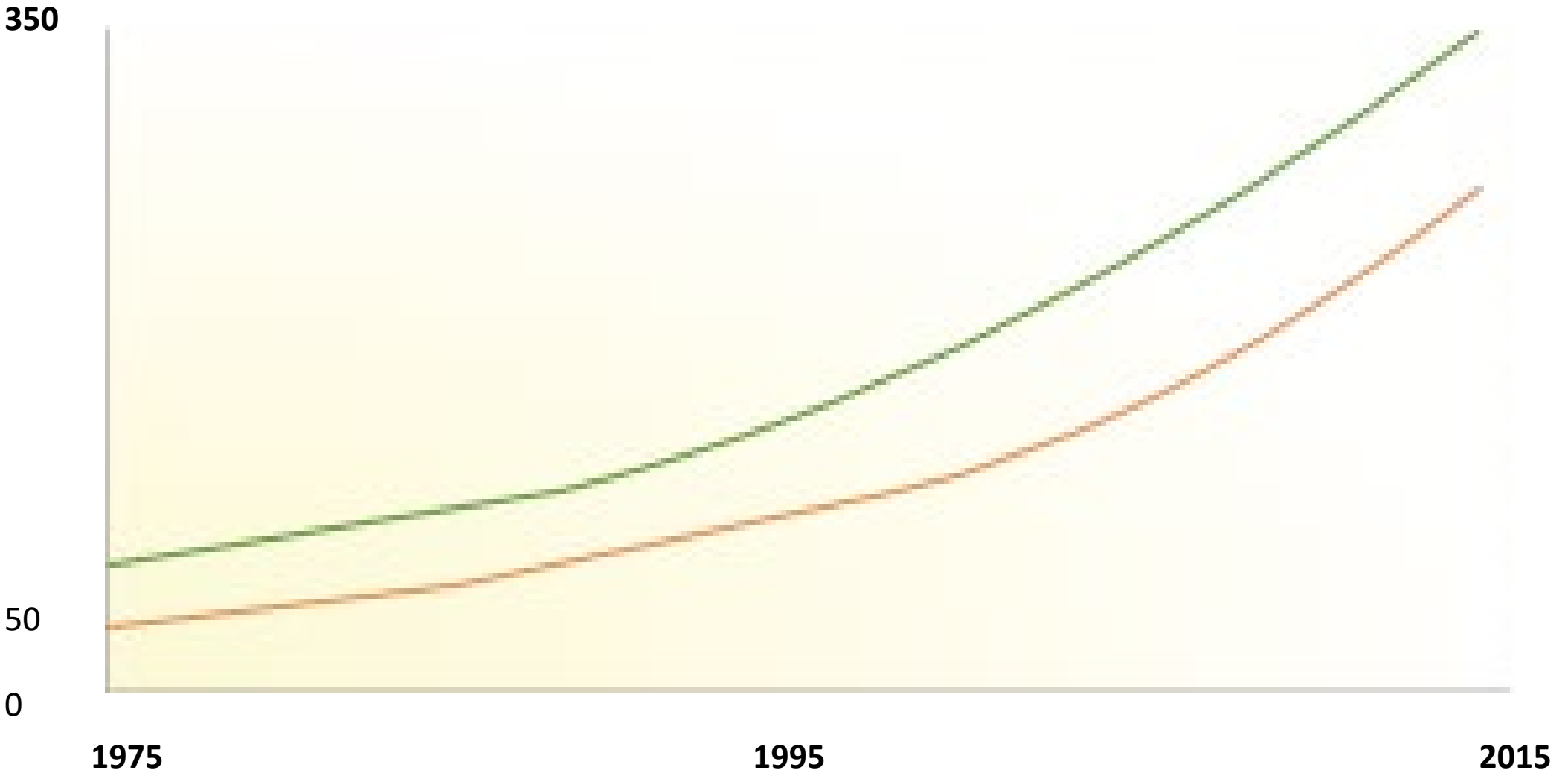

2014
% Obese (BMI≥30)
< 2%
2% - 5%
5% - 10%
10% - 15%
15% - 20%
20% - 25%
25% - 30%
> 30%
THIS HAPPENED QUICKLY

WORLD OBESITY

% Prevalence of Childhood Overweight
1960's – 90's

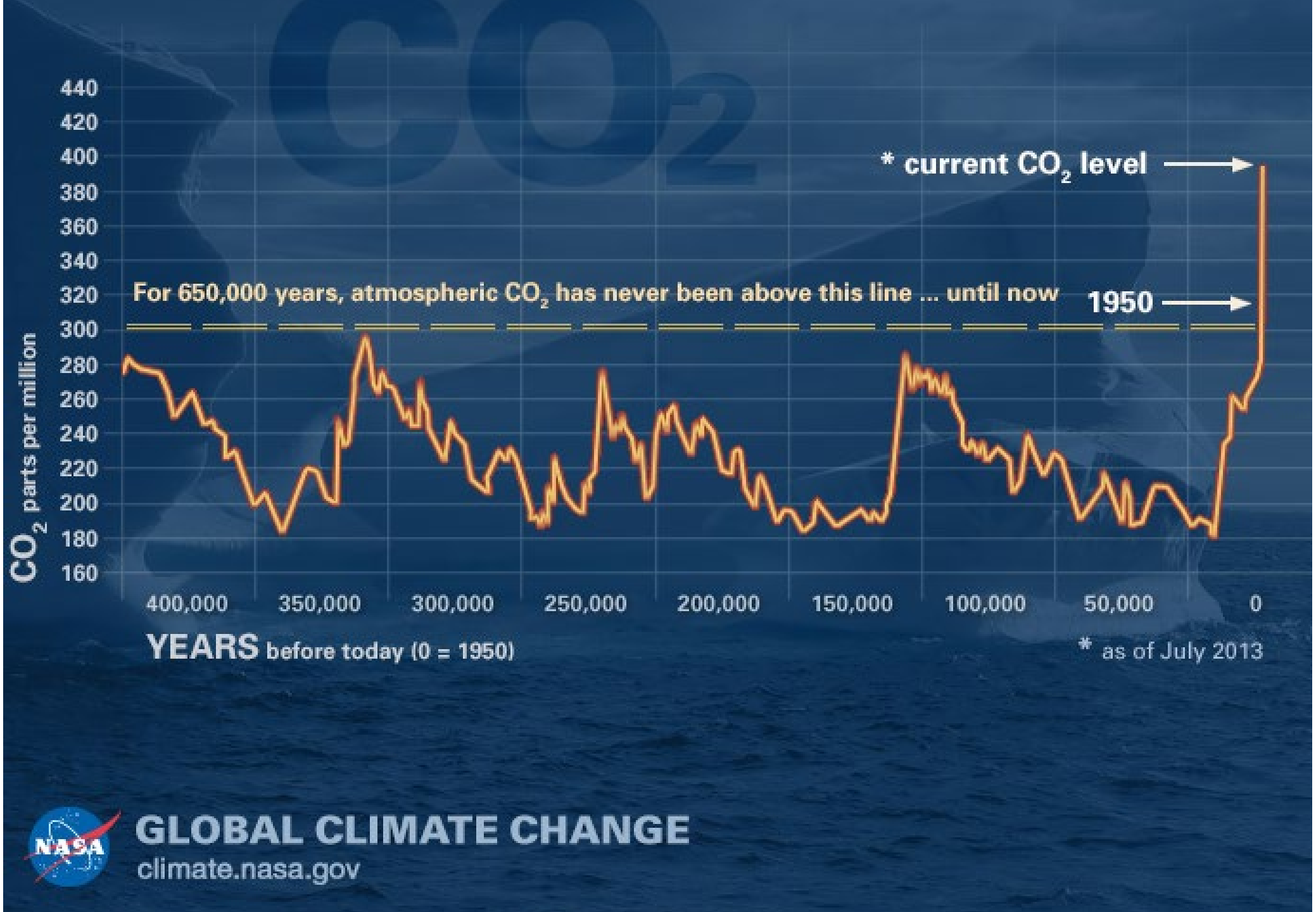


Knowledge Solutions Action



Y axis, obesity prevalence in millions (Women> Men)

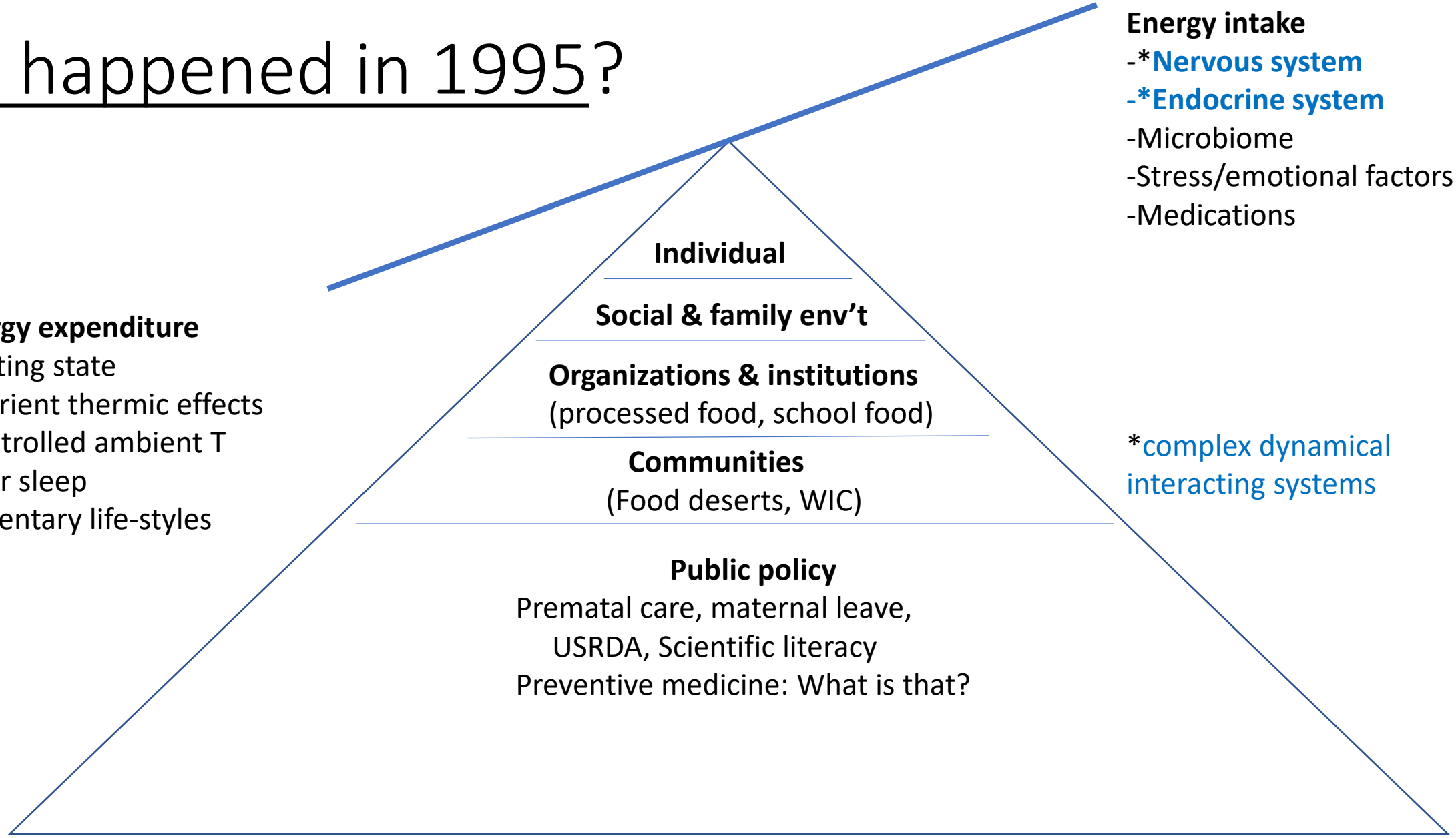
Gonzalez-Muniesa et al, 2017


440
420
400
380
360
340
320
300
280
260
240
220
200
180
160
CO_2 parts per million
* current CO_2 level
For 650,000 years, atmospheric CO_2 has never been above this line ... until now
1950
400,000
350,000
300,000
250,000
200,000
150,000
100,000
50,000
0
YEARS before today (0 = 1950)
* as of July 2013
GLOBAL CLIMATE CHANGE
climate.nasa.gov

What happened in 1995?

Energy intake
-***Nervous system**
-***Endocrine system**
-Microbiome
-Stress/emotional factors
-Medications

Energy expenditure
-Resting state
-Nutrient thermic effects
-Controlled ambient T
-Poor sleep
-Sedentary life-styles



*complex dynamical interacting systems

Gonzalez-Muniesa et al, Nat Rev Dis Primers vol 3, no 17034 with editorial comments

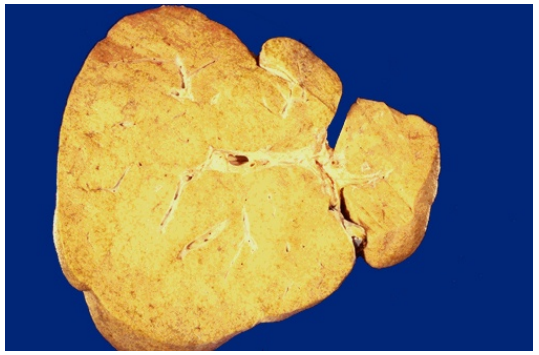
Metabolic syndrome : Unhealthy obesity

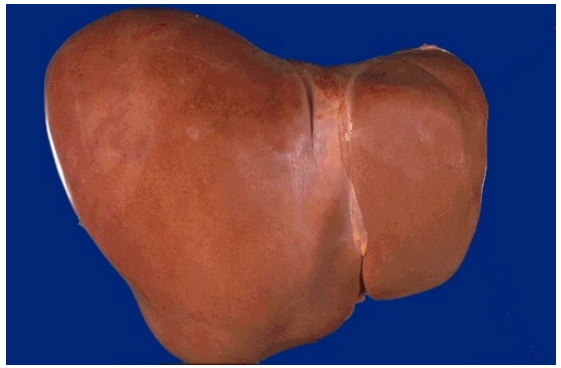
When 3/5 criteria occur simultaneously:

- Visceral obesity: a waist circumference of ≥94 cm in men and ≥80 cm in women
- Hypertriglyceridaemia: ≥150 mg per dl or on triglyceride-lowering medication
- Low levels of high-density lipoprotein cholesterol: <40 mg per dl for men and <50 mg per dl for women
- Elevated blood pressure: systolic blood pressure of ≥130 mmHg, diastolic blood pressure of ≥85 mmHg
- Increased glucose levels: fasting glucose levels of ≥100 mg per dl or drug treatment to lower increased levels of glucose

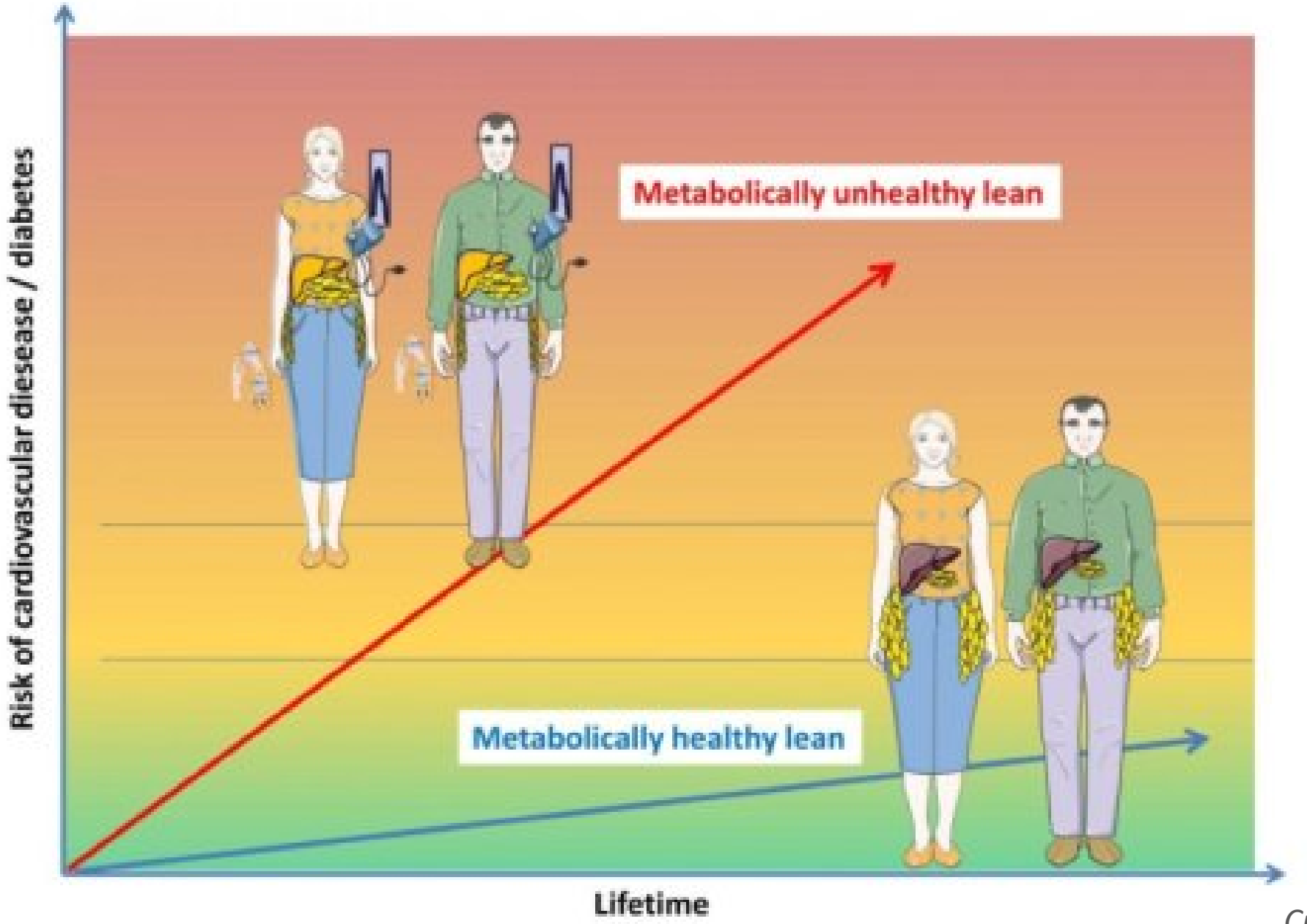
Helps to identify individuals who are likely to have insulin resistance and related metabolic abnormalities, associated with visceral obesity.

Future business for liver transplanters





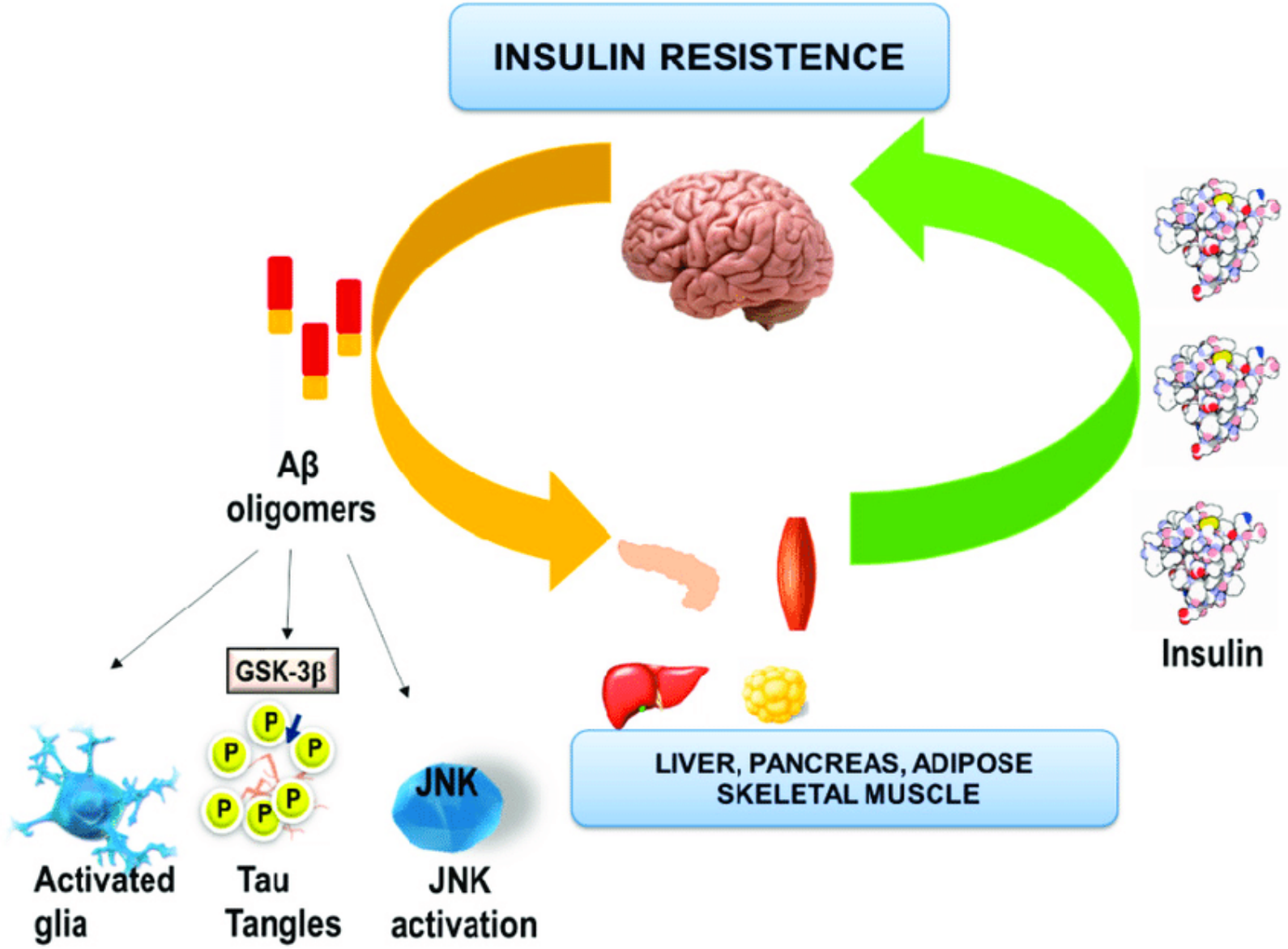
- Obesity epidemic paralleled by
- Non-alcoholic steatohepatitis
- “Fatty liver” : HC turn on PPARγ
- Independently leads to cirrhosis and all its sequelae
- Worsens any other underlying liver disease
- Chronic liver disease associated with DM
- ALF associated with hypoglycemia
- (DRUGS USED NOW TO TREAT OBESITY LIKELY WILL HELP NASH)

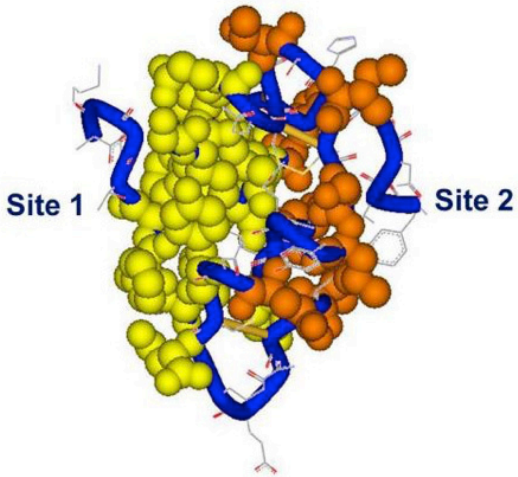

Risk of cardiovascular diesease / diabetes
Metabolically unhealthy lean
Metabolically healthy lean
Lifetime

Credit: IDM

Obesity is a state of insulin resistance

-Traditionally CV effects emphasized
-Increasingly AD





Processes

Anabolism
Glucose homeostasis
Lipid metabolism
Protein metabolism
Growth/mitogenesis
Reproduction
Lifespan
Cognition

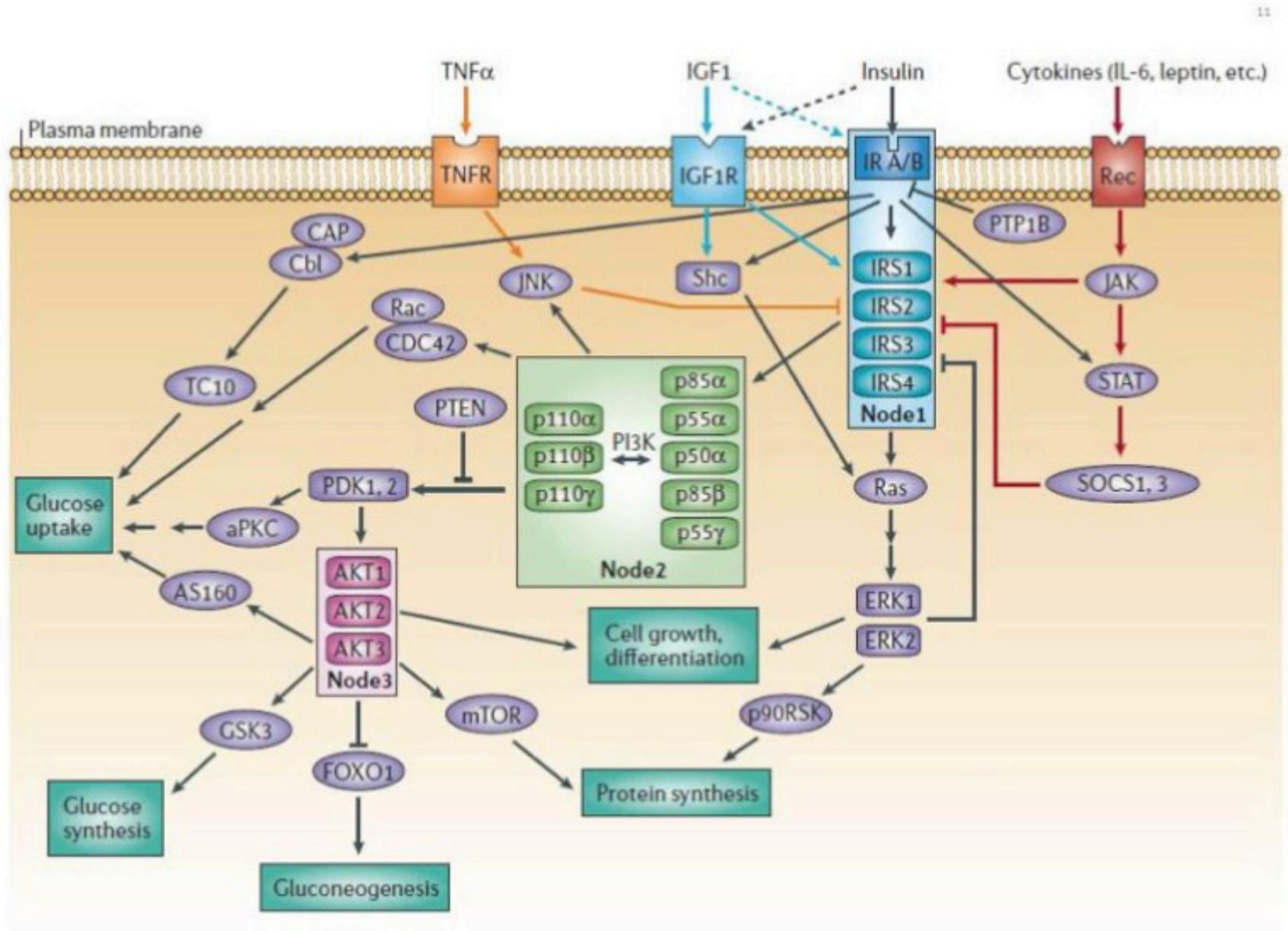
Pathways

Increases
Decreases

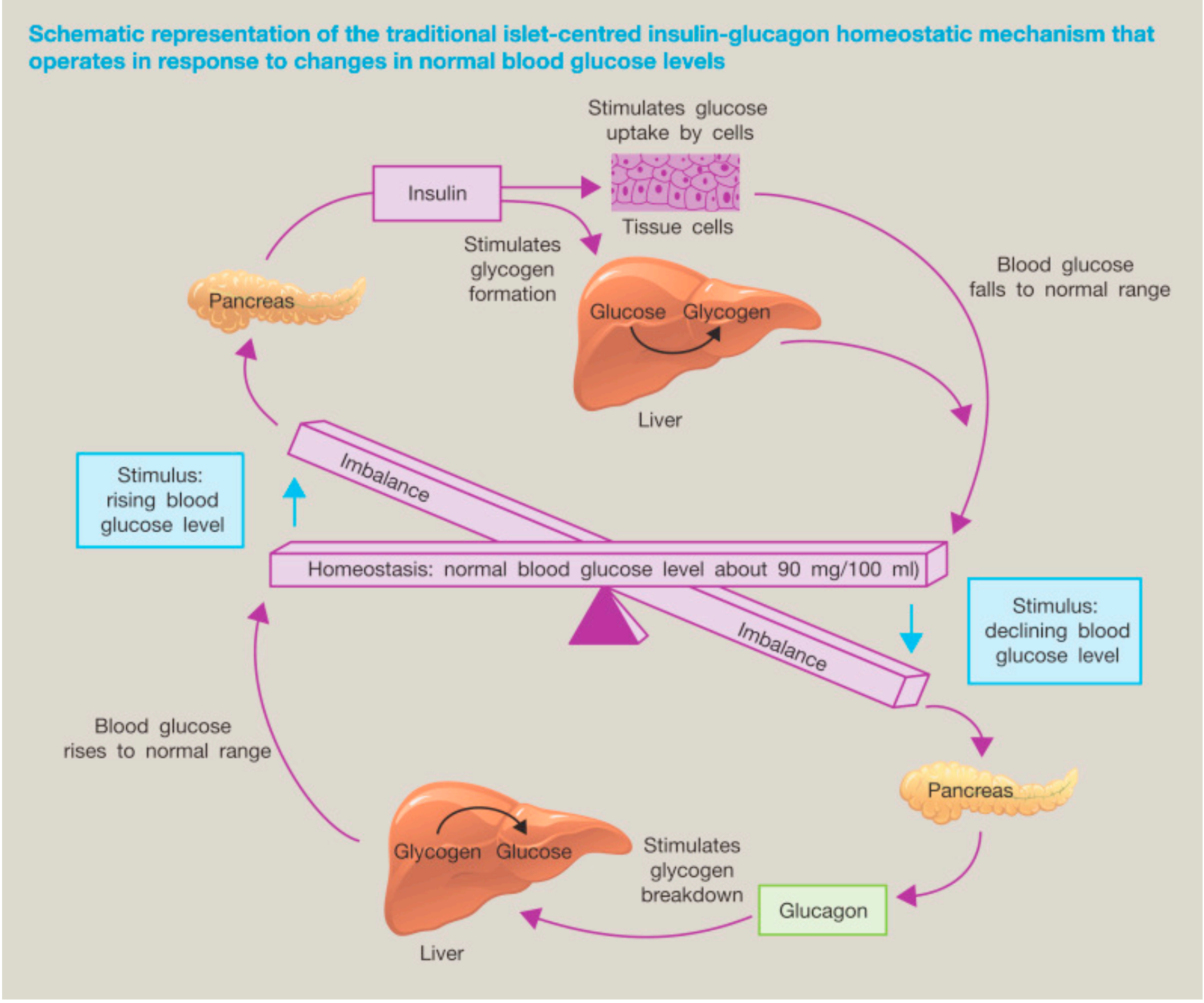
Glucose uptake
Glycogen synthesis
Gluconeogenesis
Lipogenesis
Lipolysis
Protein synthesis
Gene expression
DNA synthesis
Amino acid uptake
$(Na^+ K^+)$-Pump
Apoptosis
Autophagy

De Meyts, 2016 (Novo Nordisk)

Canonical (idealized, generalized) insulin receptor signal transduction network



De Meyts, 2016 (Novo Nordisk)



Feedback network regulating glucose

ADIPOKINES: Mediators of fat cells as active endocrine organs (vs. storage depots)

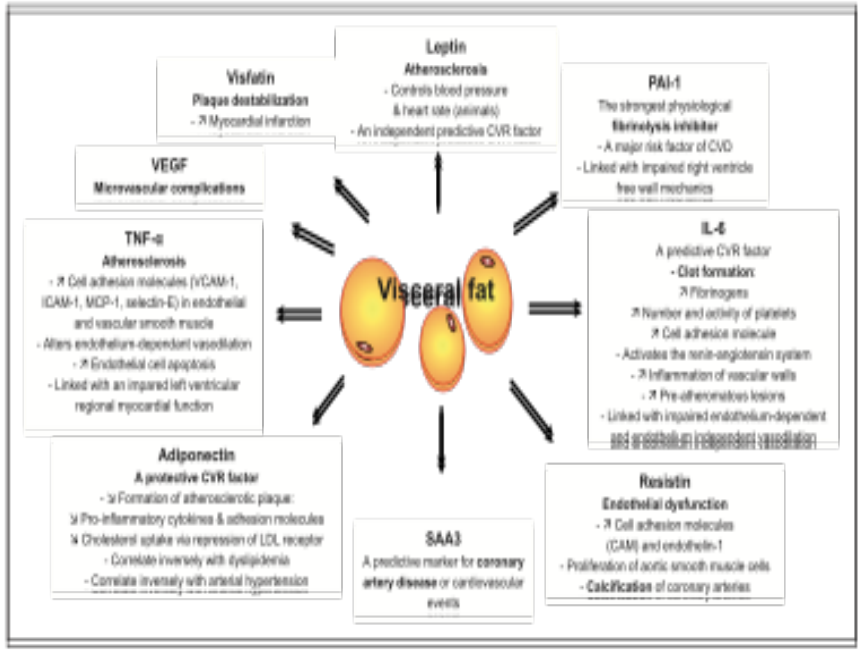
- Adiponectin*
- Insulin
- Interleukin-6
- Leptin*
- PAI type I*
- Resistin
- TNF-alpha

*CLINICAL TRIALS SUGGEST SIGNIFICANT WEIGHT LOSS ASSOCIATED W/REDUCED CIRCULATING LEVELS

VISCERAL VS. PERIPHERAL FAT

SENESCENCE PHENOTYPE: PROINFLAMMATORY, CAN BE REDUCED BY EXERCISE

With aging: Marrow, liver, skeletal muscle accumulate fat



Schaffer et al, Diabetes 2016; 65:1606; Dutheil et al, 2018

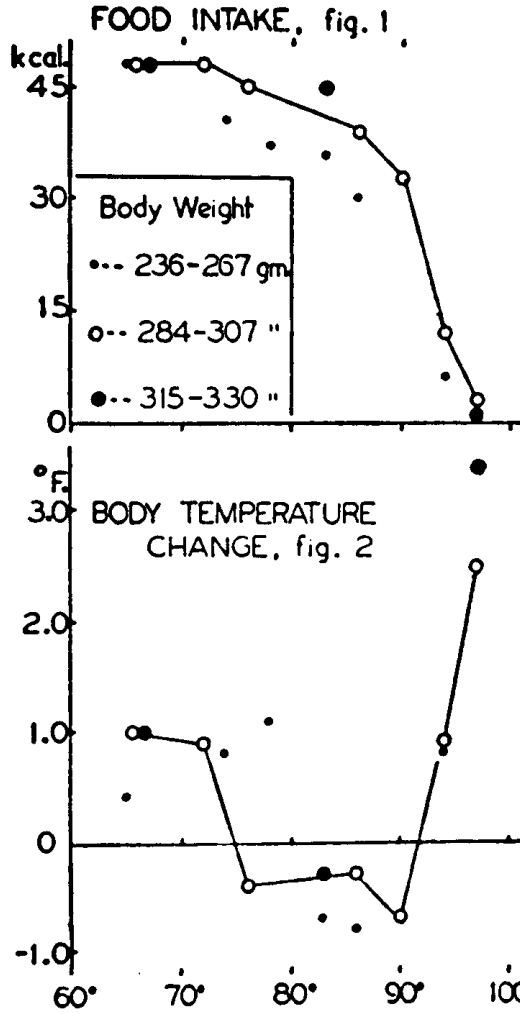
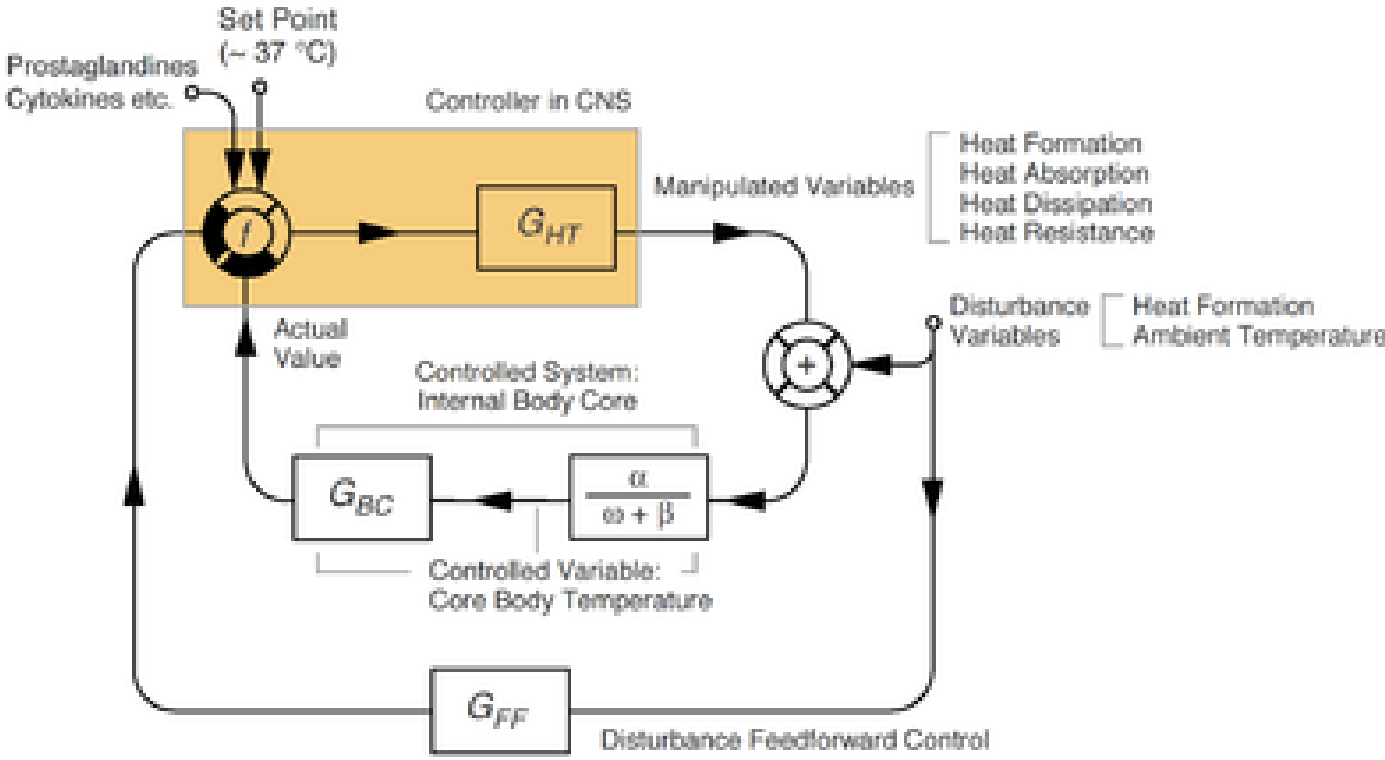


FIG. 1. Relationship between food intake environmental temperature (upper graph) body temperature change and environmental perature (lower graph) in rats exposed to lected temperatures for 18 hours. Each represents a group of 5 or 6 rats. (From Brobeck, Yale J. Biol. Med., 1948, *20*, 545.)

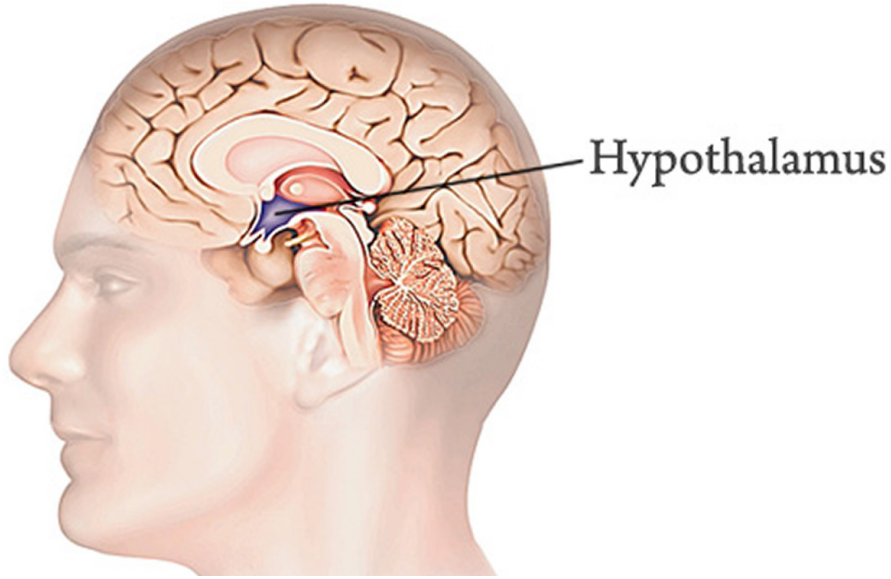
First brain control system connected to food Intake (before obesity epidemic): Temperature control

-Measurable in 1948
-More food intake—>more heat generated
-Feedback control on intake via hypothalamus



Also at this time…

- Decerebrate cats → reflex chewing, swallowing
- “Quantitative” control of intake by temp control in hypothalamus
- Lateral hypothalamus lesions→animals don’t eat
- Medial hypothalamus lesions→overeating and obesity
- Stimulation of medial hypothalamus→satiety
- Cortex involved but unclear role



Hypothalamus: Homeostasis Central/Allostasis Central

Links CNS with endocrine system

- HR, BP
- Temperature
- Fluid/electrolytes: THIRST*
- Appetite (weight)
- GI hormone responses
- Sleep cycle
- Influences pituitary hormone release
  - Anterior: ACTH, TSH, LH/FSH, PRL, GH, MSH
  - Posterior: ADH, Oxytocin

*Caltech.edu Yuki Oka video on brain regions regulating thirst

History, hunger, appetite & satiety

1950's view: Problems of the digestive system
Late 1950's: Neurologic control looking at lesioned animals
But in med school (1970's): Bias toward obesity as a psych disorder

Sensory basis

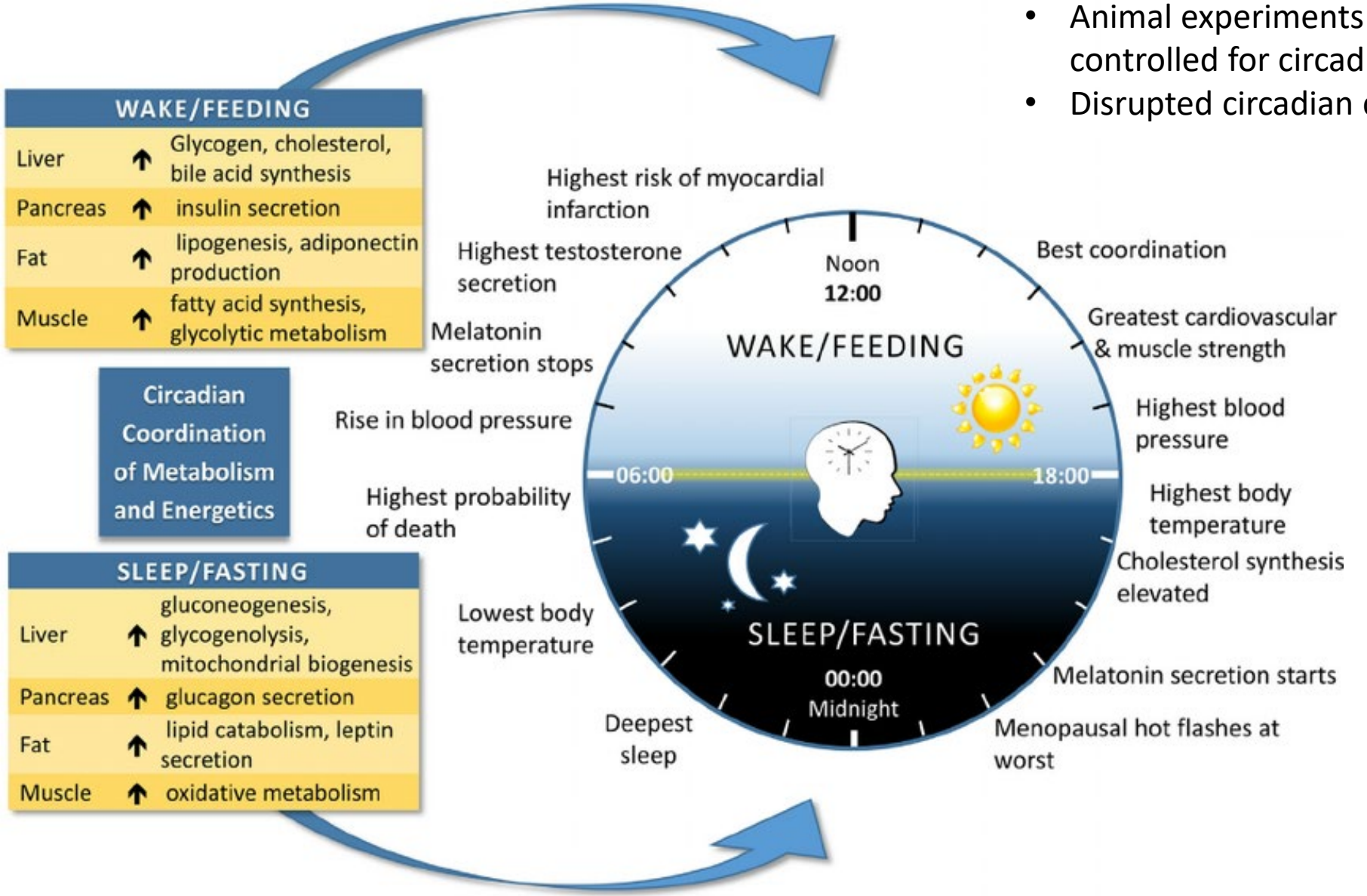
Visual reflexes
Olfactory reflexes
Tactile reflexes
Gustatory reflexes
Enteroceptive reflexes

Behavioral basis

Reflexes of attention
Reflexes of examination
Reflexes of incorporation
Reflexes of rejection

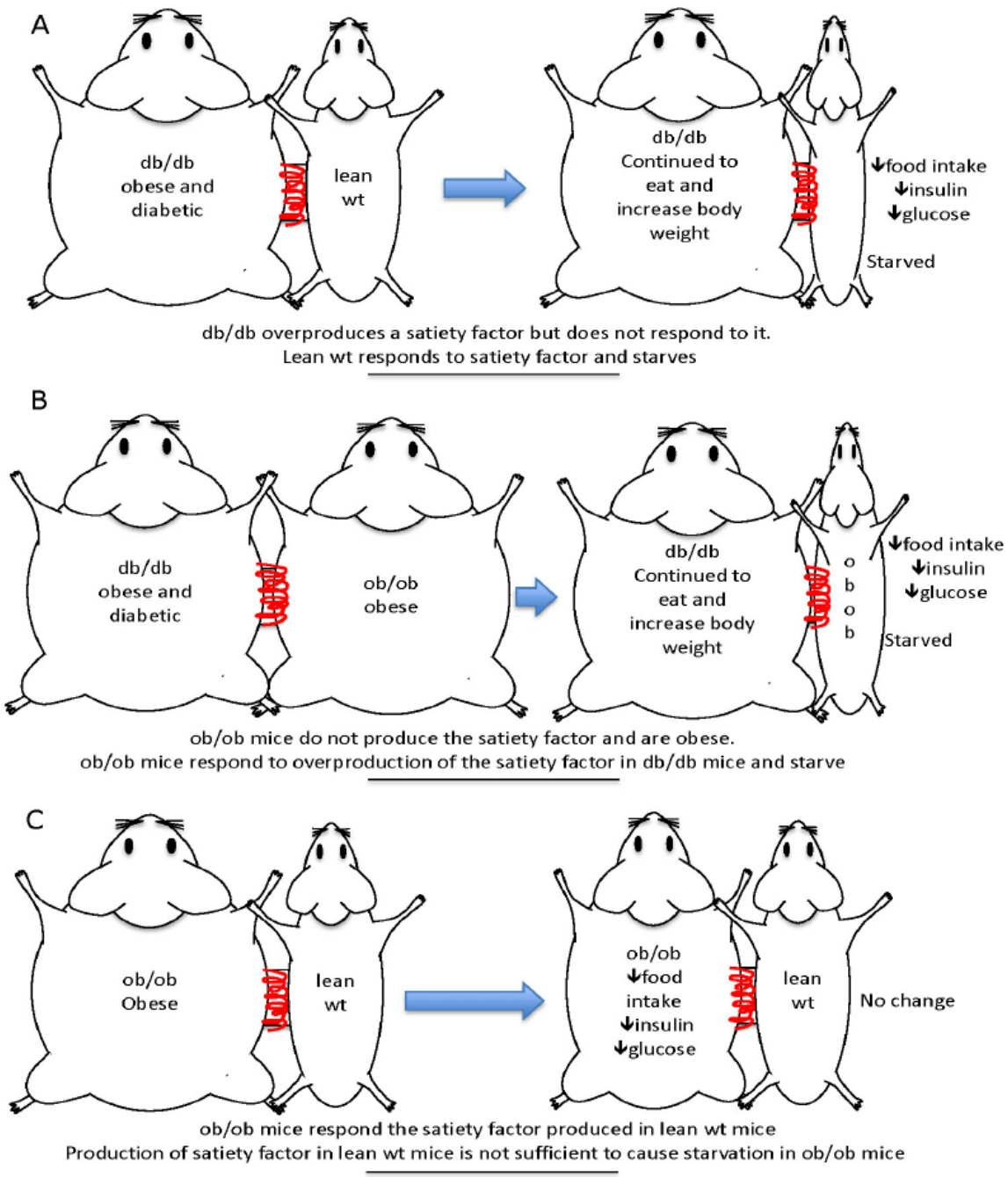
JR Brobeck papers from 1946-1959

- When you eat is important for weight
- Animal experiments often not controlled for circadian clock
- Disrupted circadian clock→weight

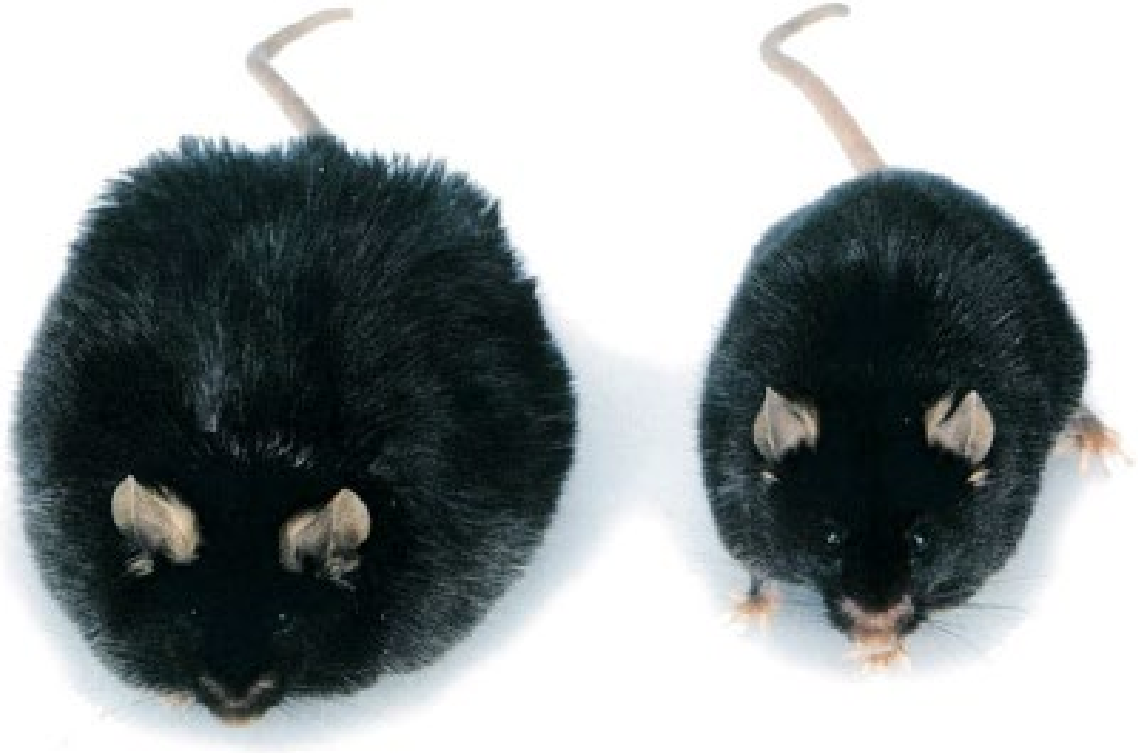


ob/ob and db/db mice

Hard to breed ob/ob mice



ob/ob -- leptin and db/db -- leptin receptor



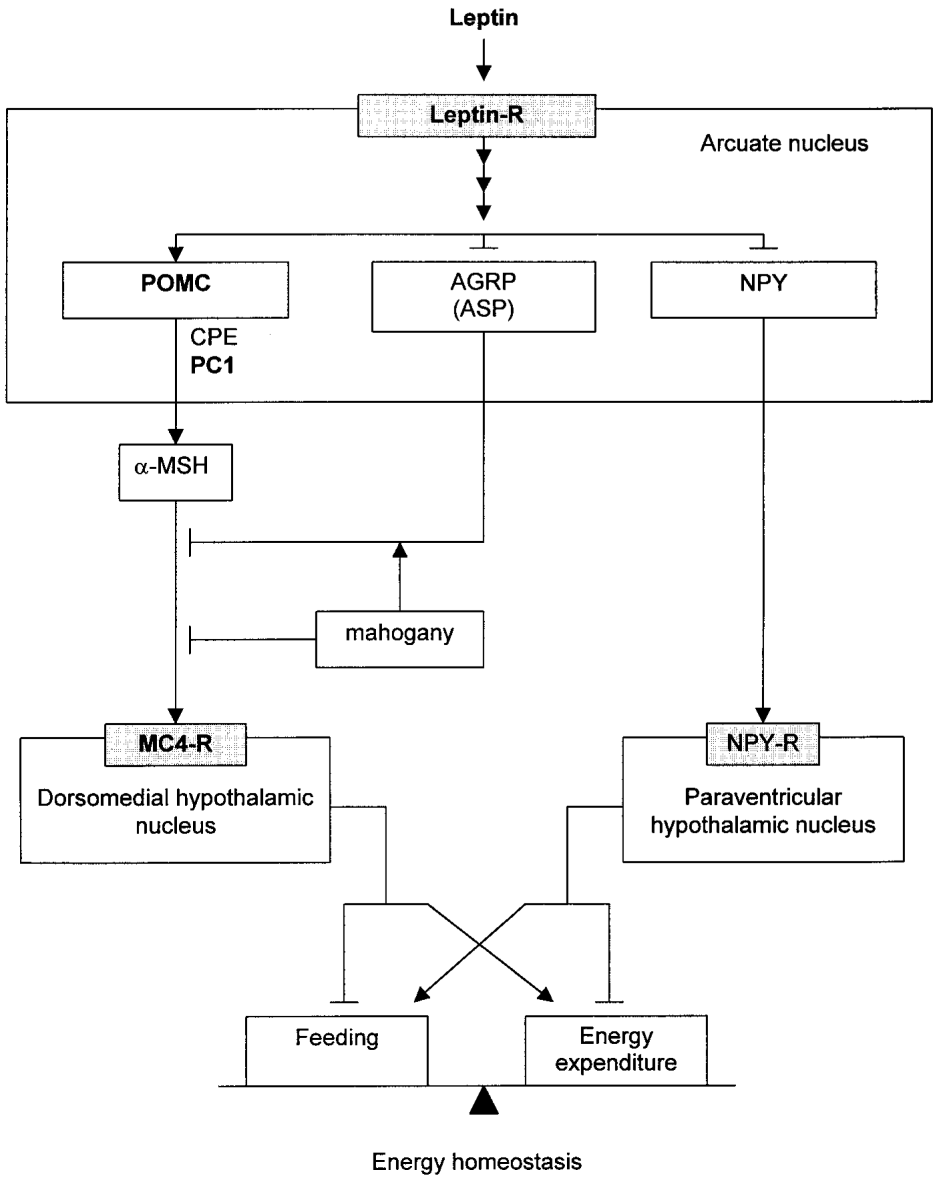
***ob/ob* mouse**
67 g

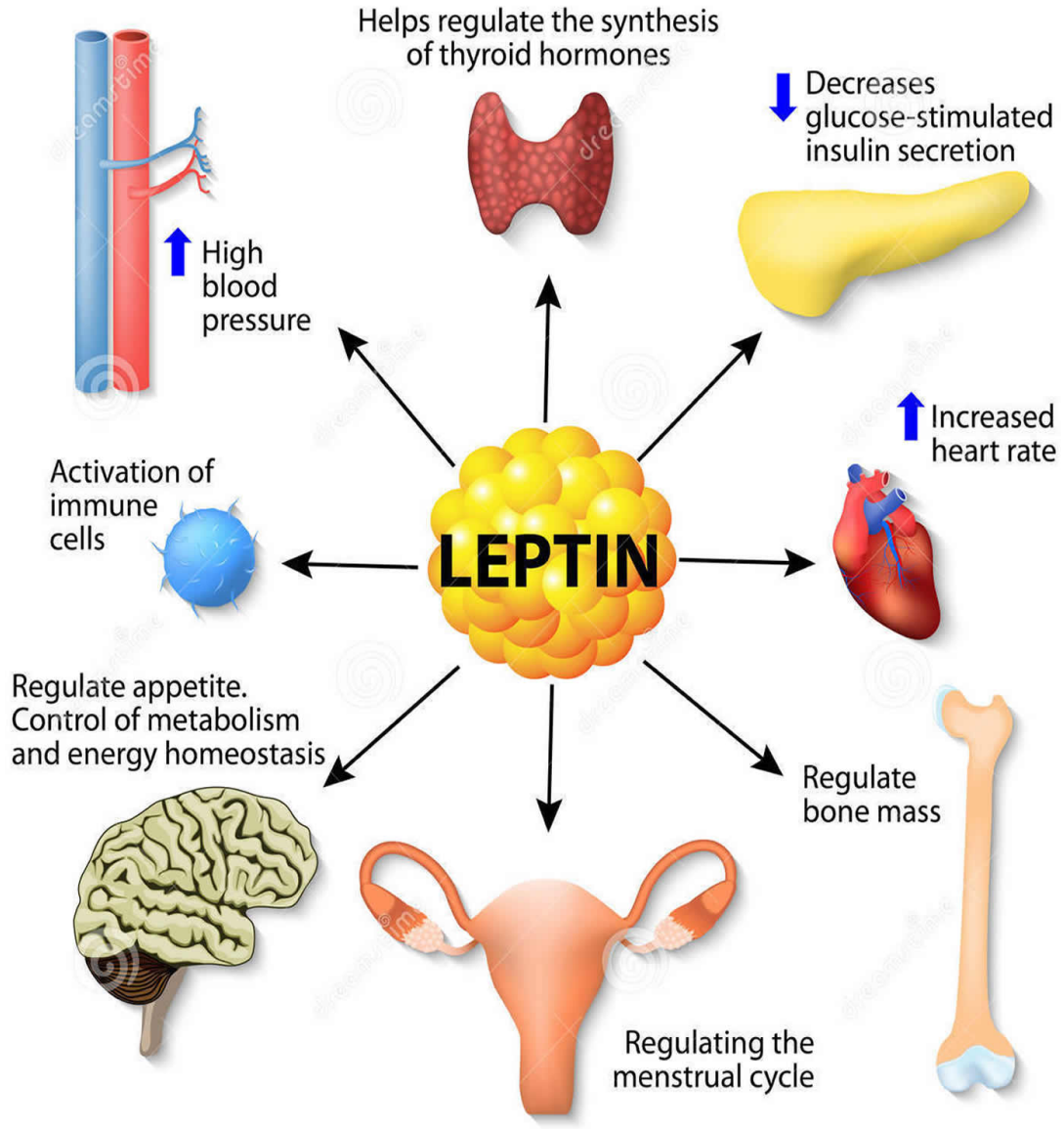
***ob/ob* mouse**
+ Leptin
35 g

Leptin supplementation:

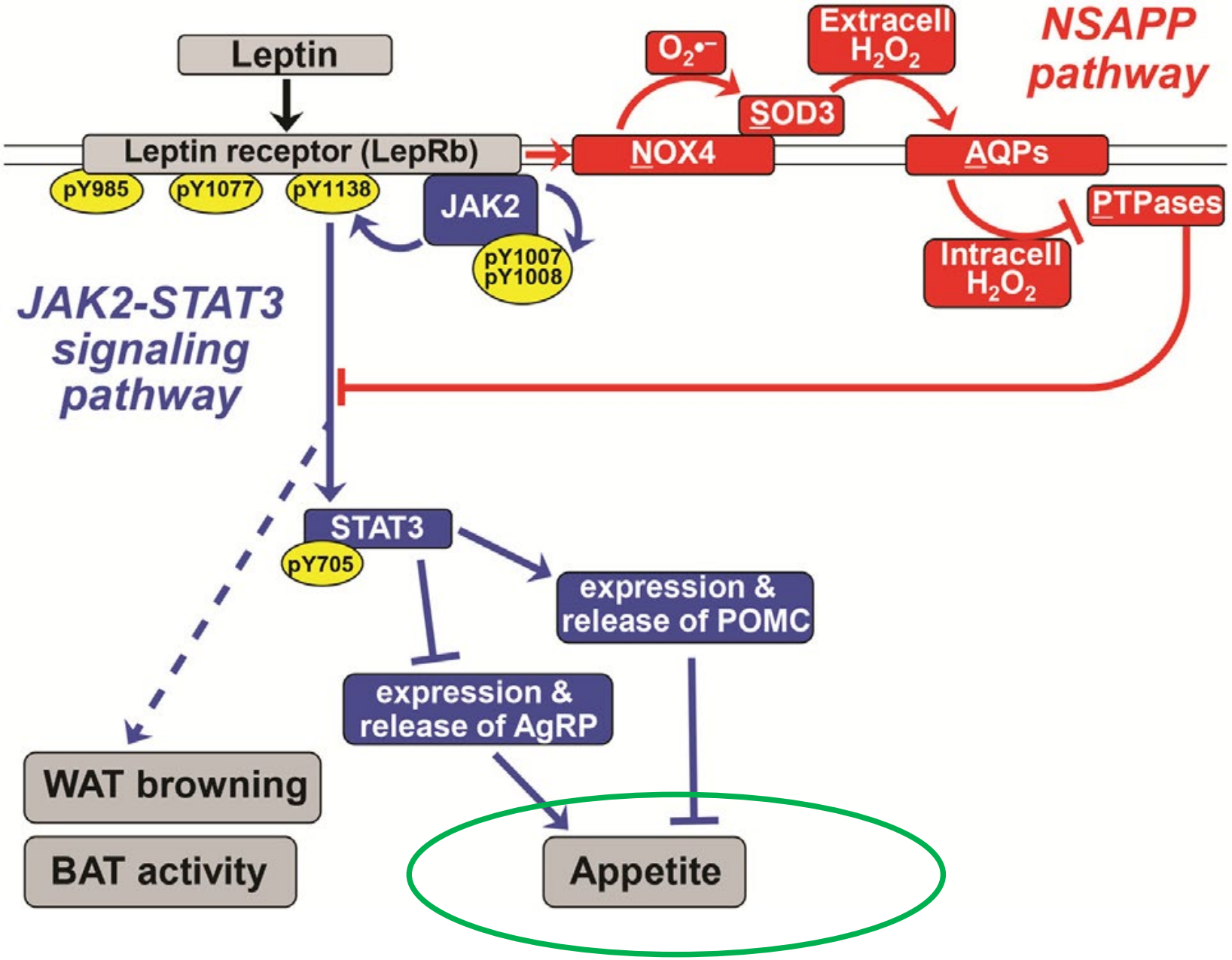
A cure for obesity!

Obese gene: Zhang et al, 1994





WHY LEPTIN SUPPLEMENTATION CAN HAVE MYRIAD SIDE-EFFECTS



Leptin helps true leptin-deficiency
- -Infertility
- -Lipodystrophy (lack of adipose)

In obese animals decreases food intake and weight

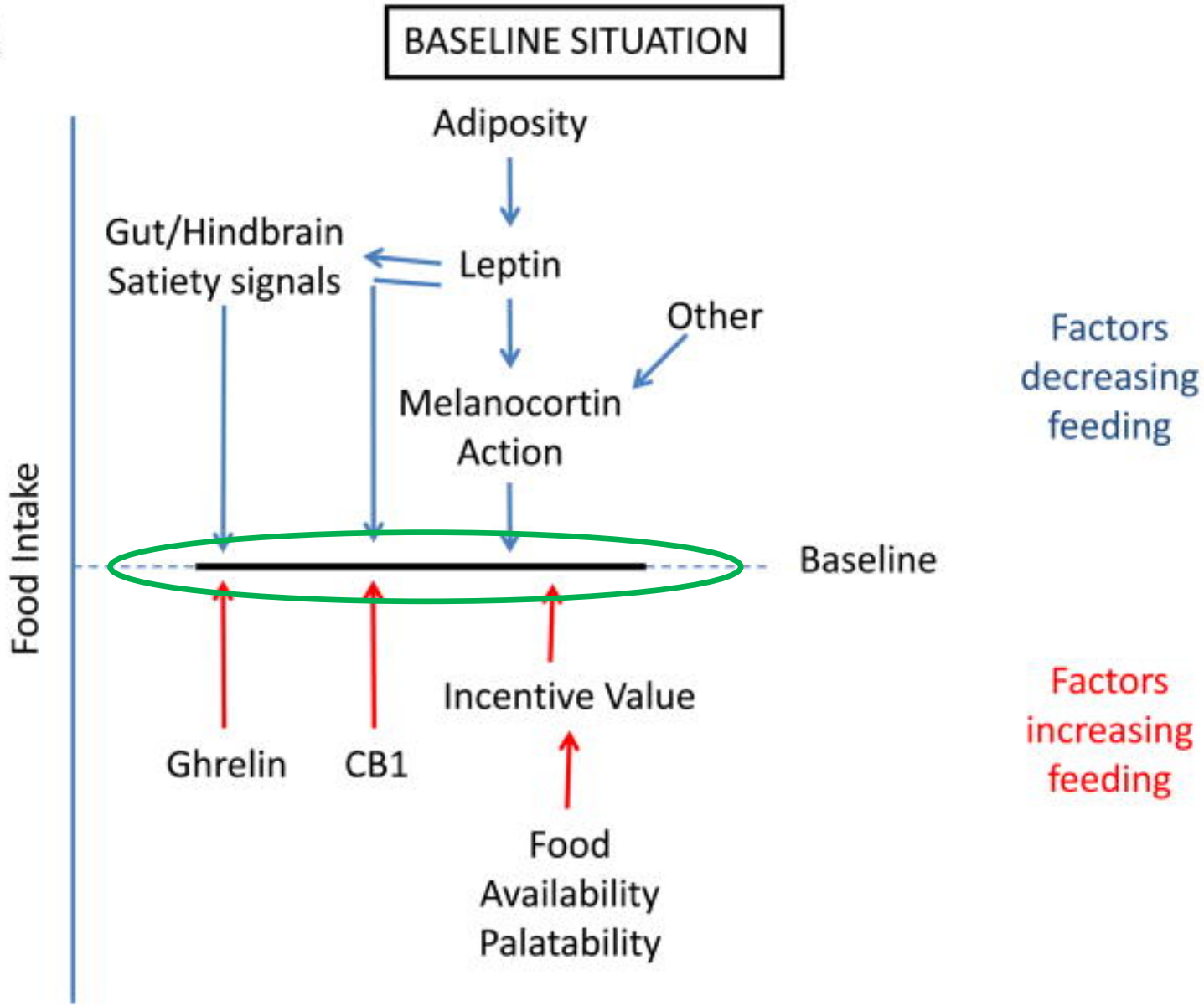
Humans—W/ prolonged leptin rx weight rebounds after fat stores depleted

Acute leptin action not well-studied in chronic obese models

Myers et al, Trends Endocr Metab, 2010

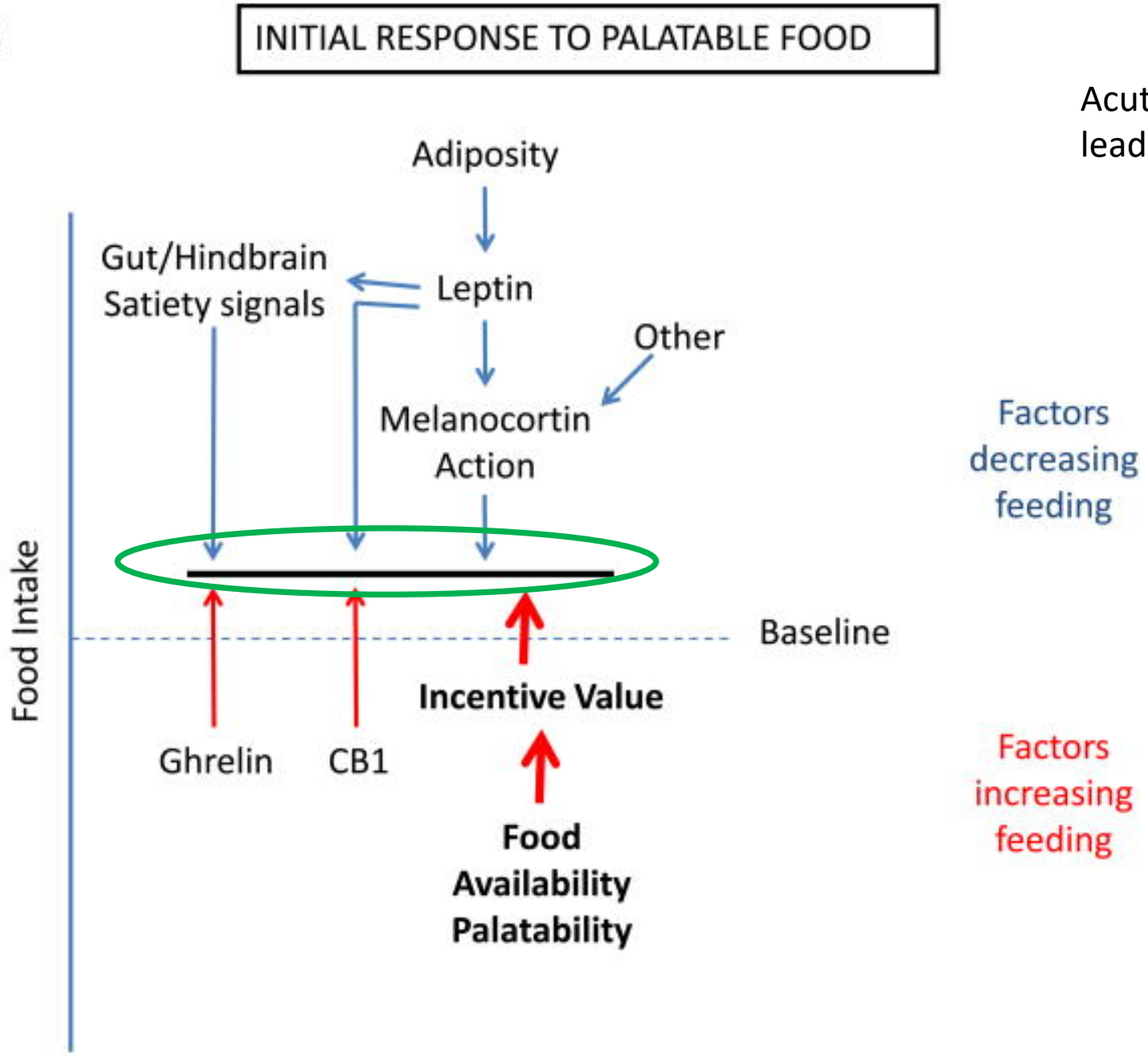
LEPTIN CONTINUES TO SURPRISE

Figure 2A



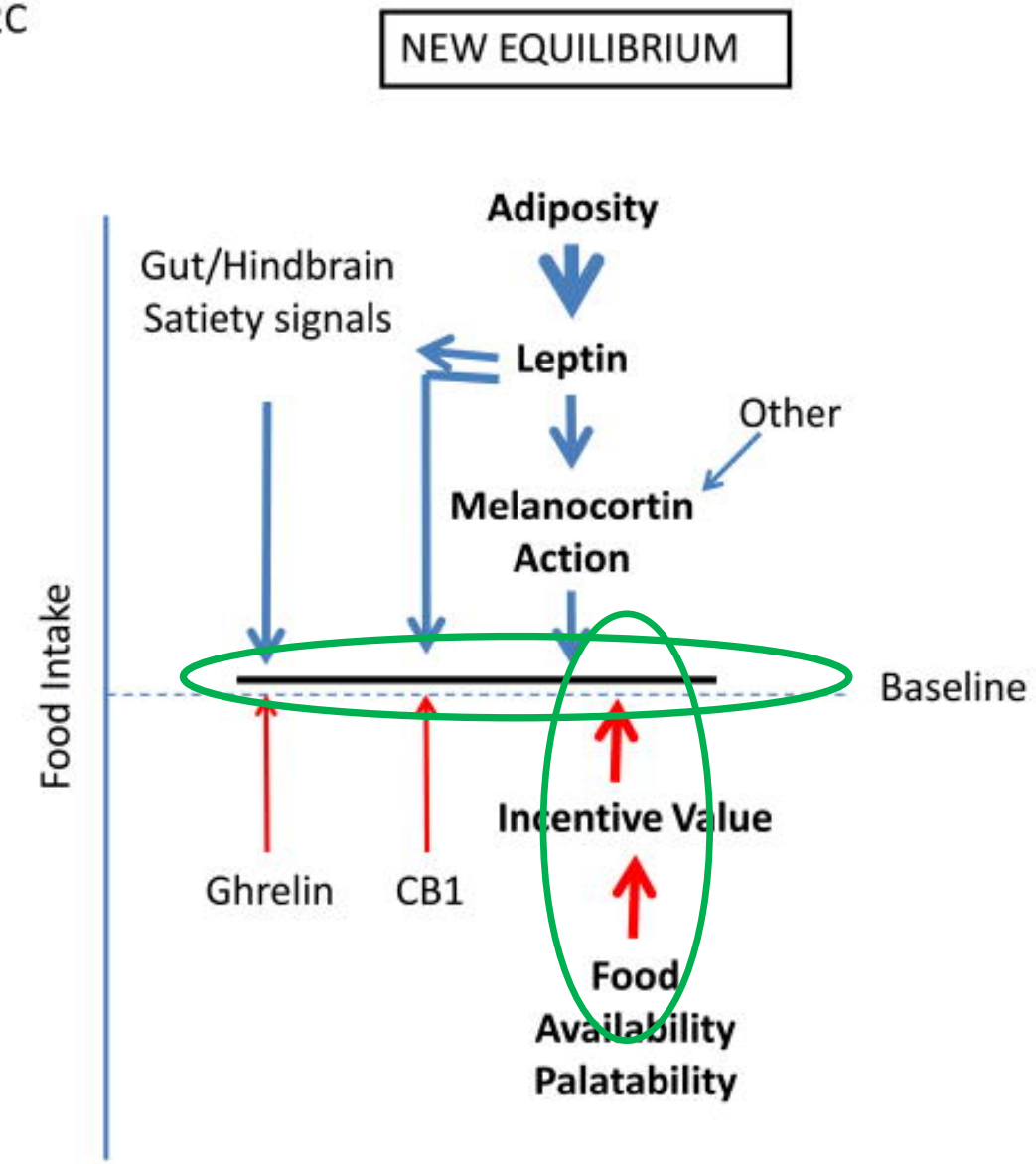
Myers view (Umich)

Figure 2B



Acute responses—
leading to adiposity

Figure 2C



(Chronic) adiposity increases leptin levels, keeping balance in favor of increased feeding

1º role for leptin: limit obesity

Factors decreasing feeding

Factors increasing feeding

WHY LEPTIN DOESN'T WORK FOR TREATING COMPLEX TRAIT OBESITY

And from “Her Time”

“No Thanks, I’m Full”

Monogenic disorders of obesity (1990's): rare

	Leptin	Leptin-R	PC1	POMC	PPARγ	MC4R
Inheritance	AR	AR	AR	AR	?	D
Early hyperphagia	+	+	?	+	?	+
Serum leptin	low	high	normal	+	?	+
DM/IGT	-	-	-	-	+	_
Hypothalamic hypogonadism	+	+	+	?	?	-
ACTH deficient	-	-	+	+	?	-
Other	TSH up	Growth delay; emotional issues; sympathetic NS	Hypoglyc post prand;proinsulin up, autoimm thyroid dis	Red hair Decreased aMSH		

Adapted from Chen & Garg, J Lipid Res 1999

Primary role of leptin to prevent obesity?

vs.

Primary role as a signal of energy deficit

Decreased leptin→increased appetite but also

→decreased reproduction

→decreased thyroid hormone

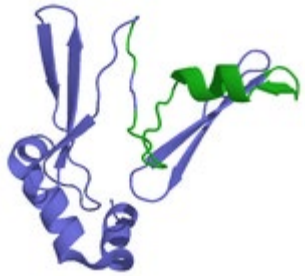
→decreased energy expenditure

To Flier: Suggests more studies are needed

AND

we are missing a player

Ahima et al, 1996; Flier JS and Maratos-Flier Cell Metab 2017



Then along came the ghrelin story

Ghrelin – known about in the 60's, "discovered" in 1999 (Kojima)

-Morphine stimulates GH secretion
-Enkephalins discovered and analogs made that stimulate GH secretion

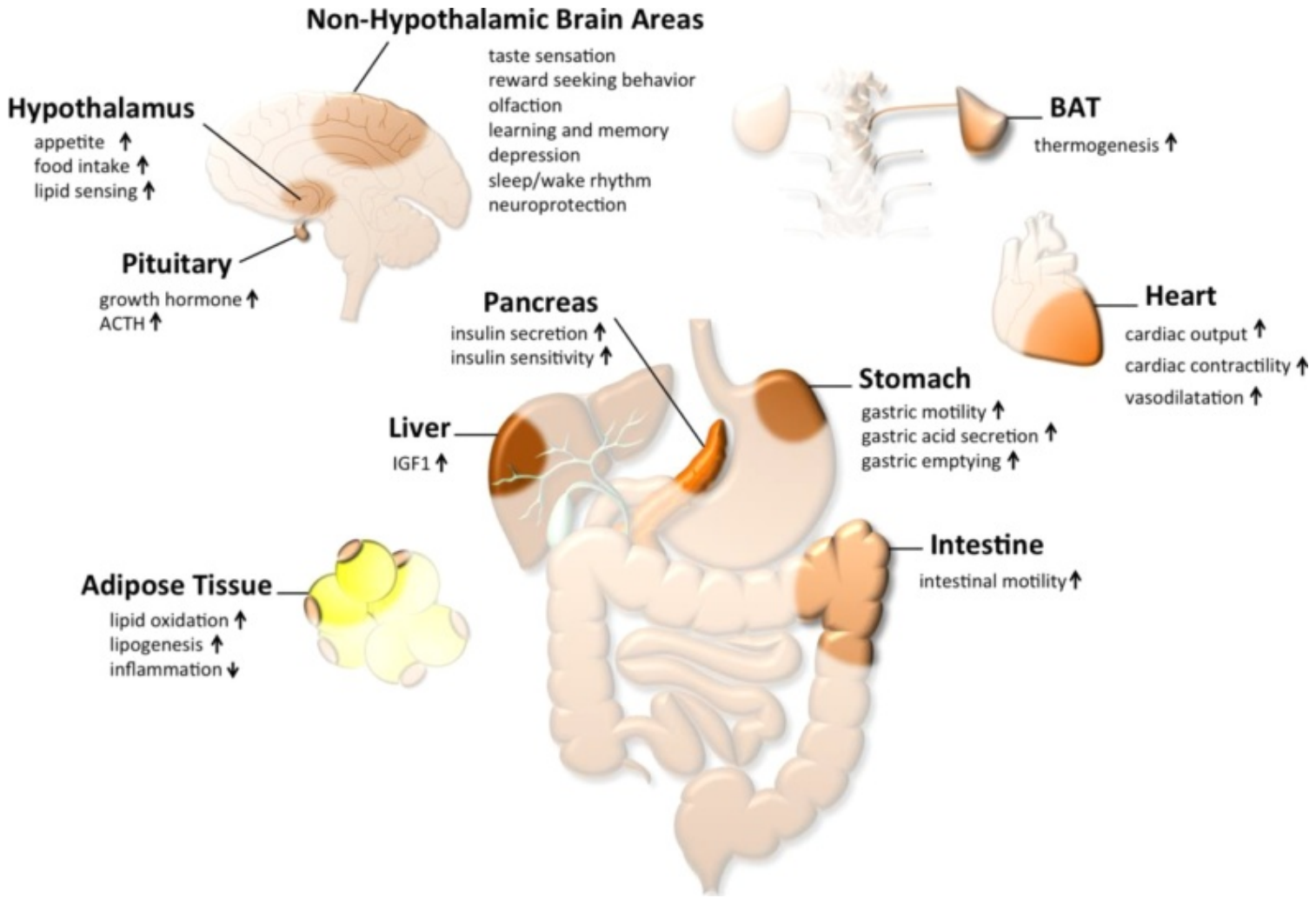
With k/o: Ghrelin necessary for triggering the GH response to nutritional deprivation
-to prevent hypoglycemia

Roles later found (with prolonged nutritional restriction in KO)

-appetite
-GI motility
-glucose and lipid metabolism
-CV function/BP
-immune function
-cell proliferation
-sleep
-anxiety
-memory

Kojima, Nature, 1999

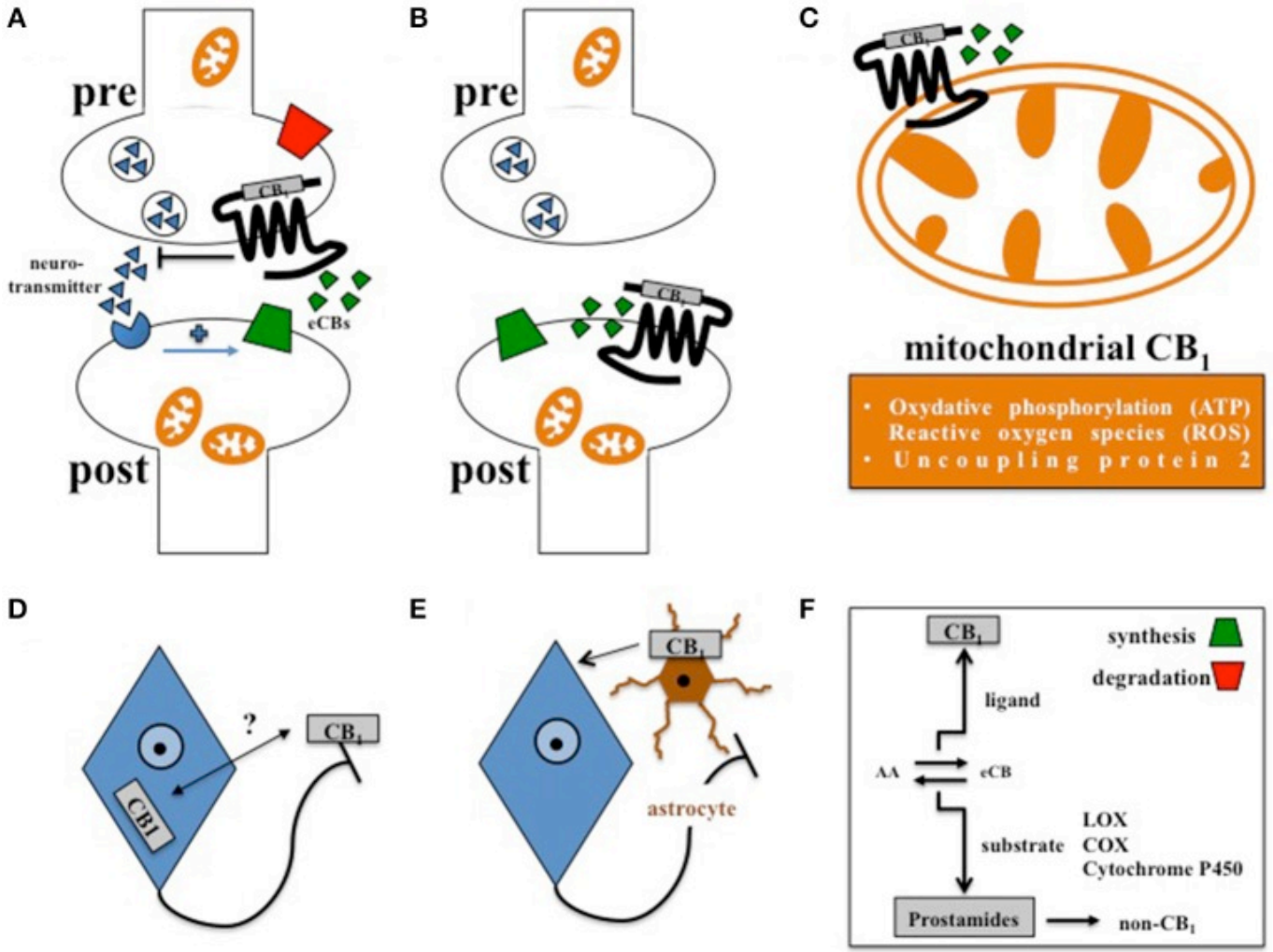
Ghrelin regulation of glucose metabolism



Ghrelin agonism
? DM gastroparesis
? Anorexia associated with pathological underweight, or cachexia

Ghrelin-R antagonism
?weight loss for specific obesity syndromes (PWS)
?improve glucose metabolism in DM

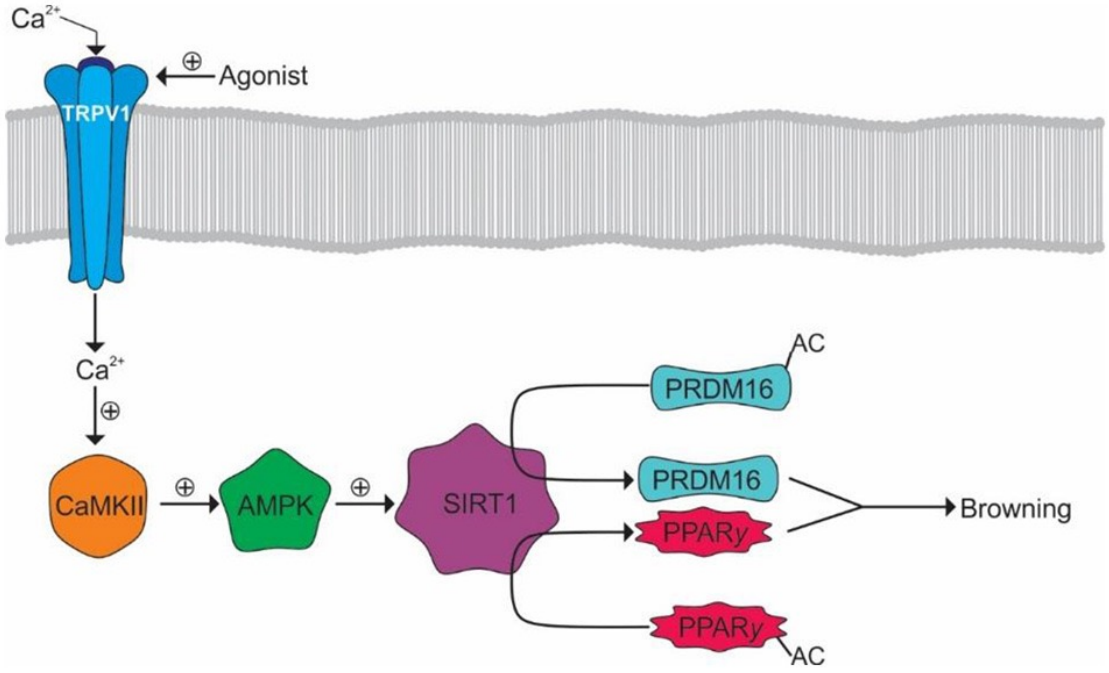
Poher et al, Peptides 2018

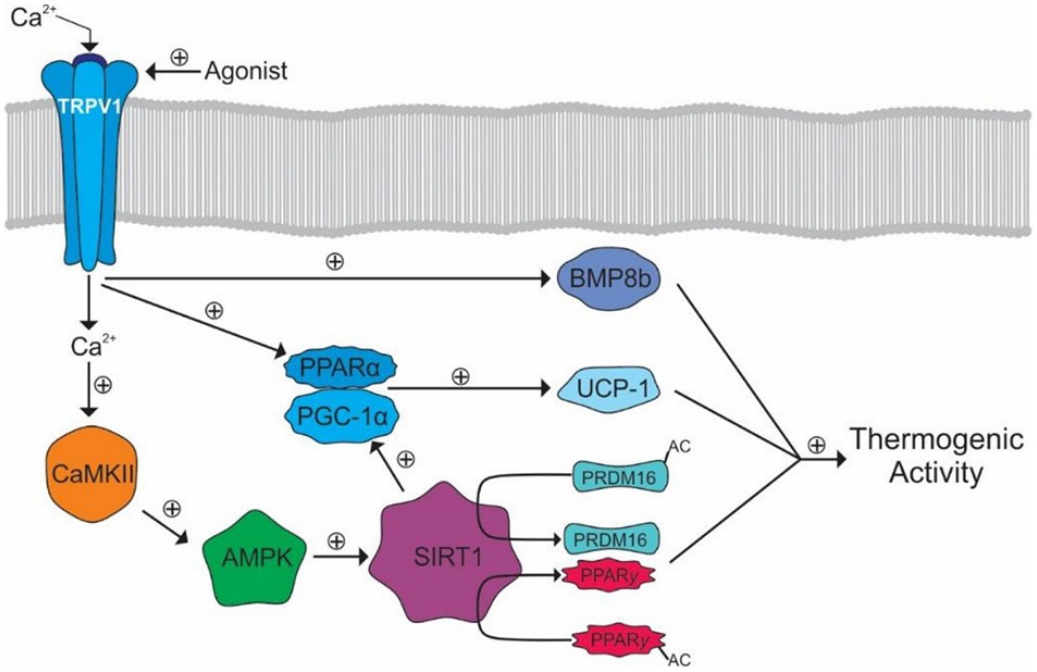


Cannabinoid signaling and feeding behavior

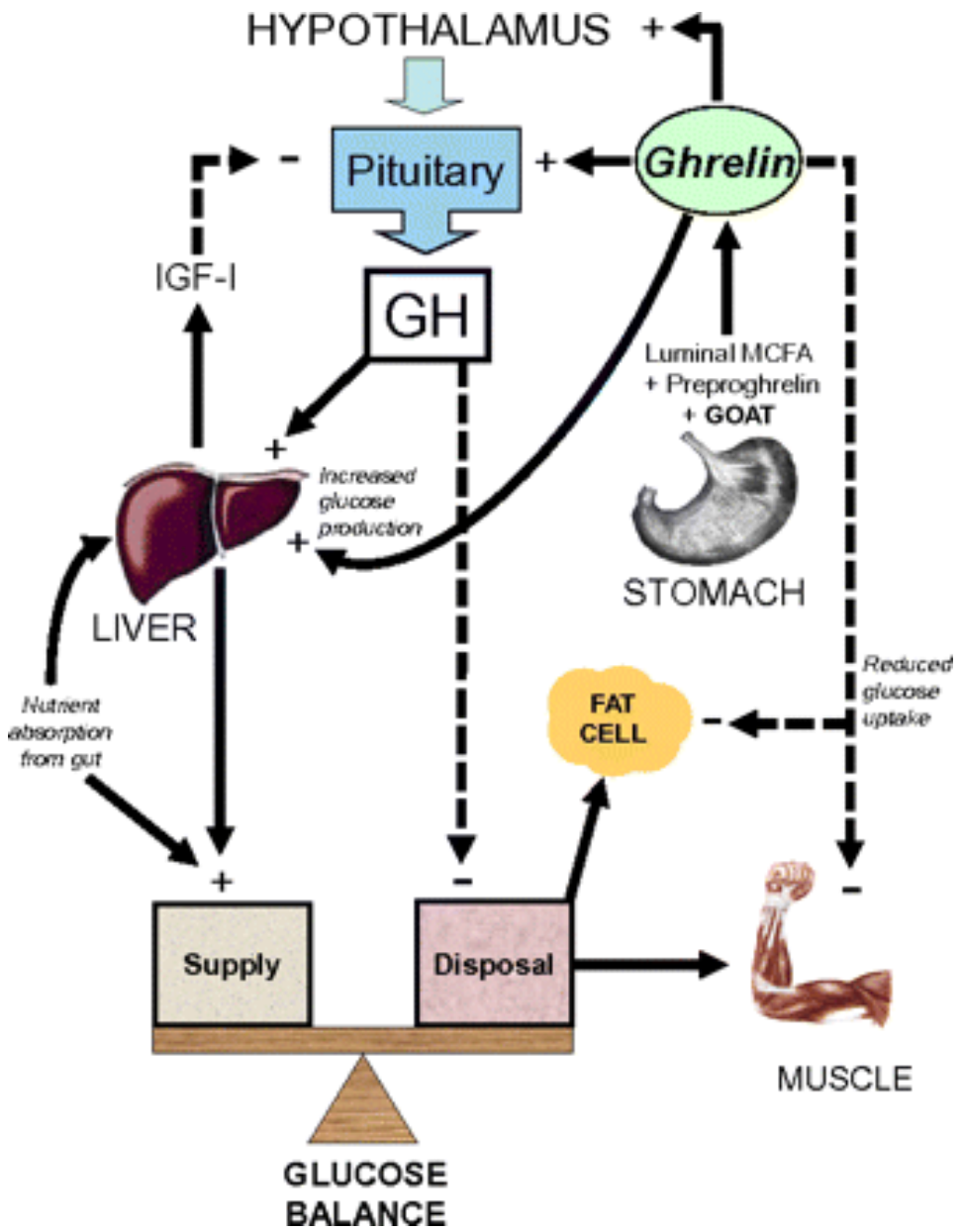
Cannabinoid signaling: More than munchies

In periphery: Contributes to browning of white adipose & thermogenic activity





Role in cancer cachexia?



Regulation of glucose by GH and ghrelin

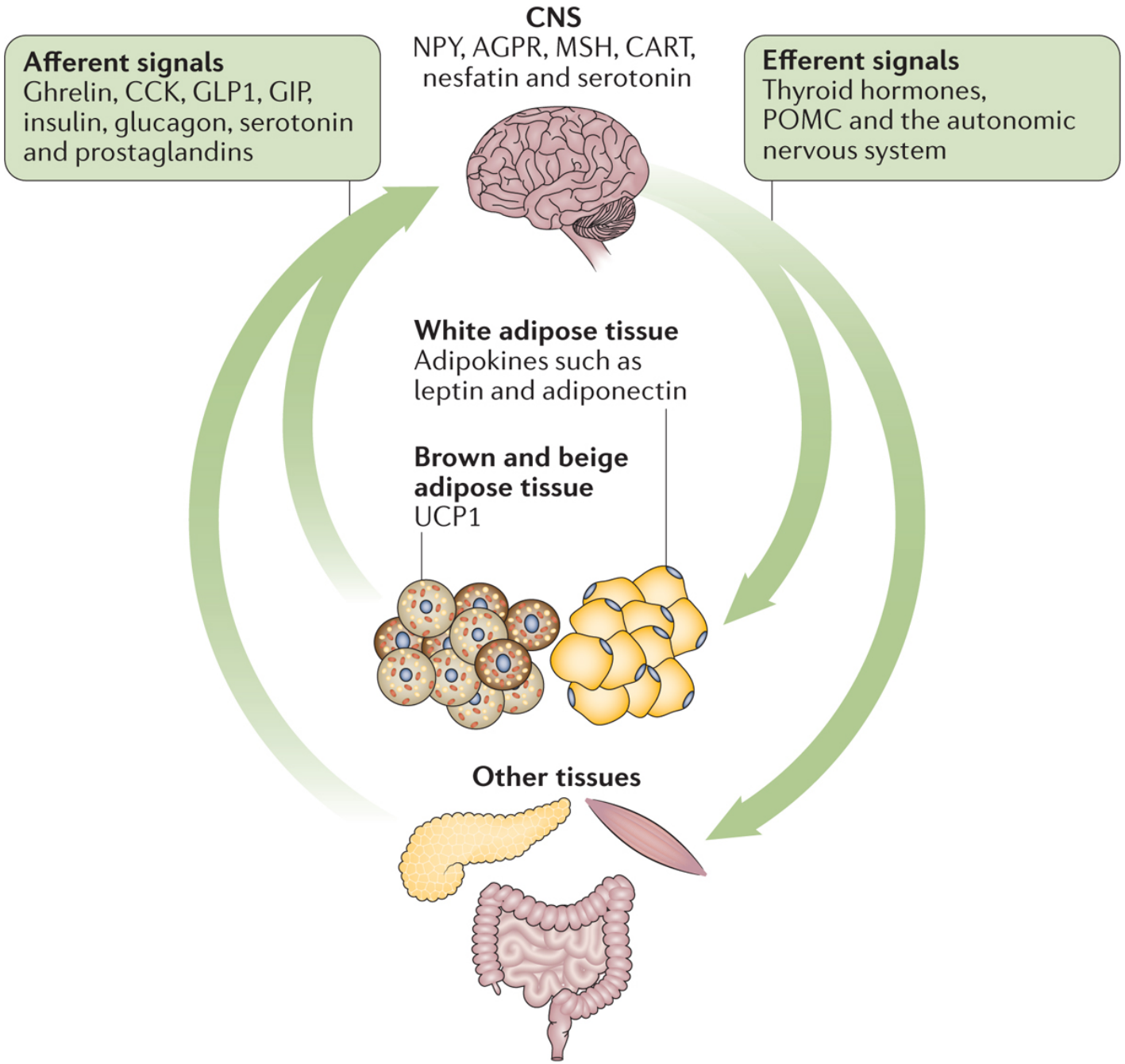
Insulin minute-to-minute

GH/ghrelin for longer-term control when nutrients are scarce

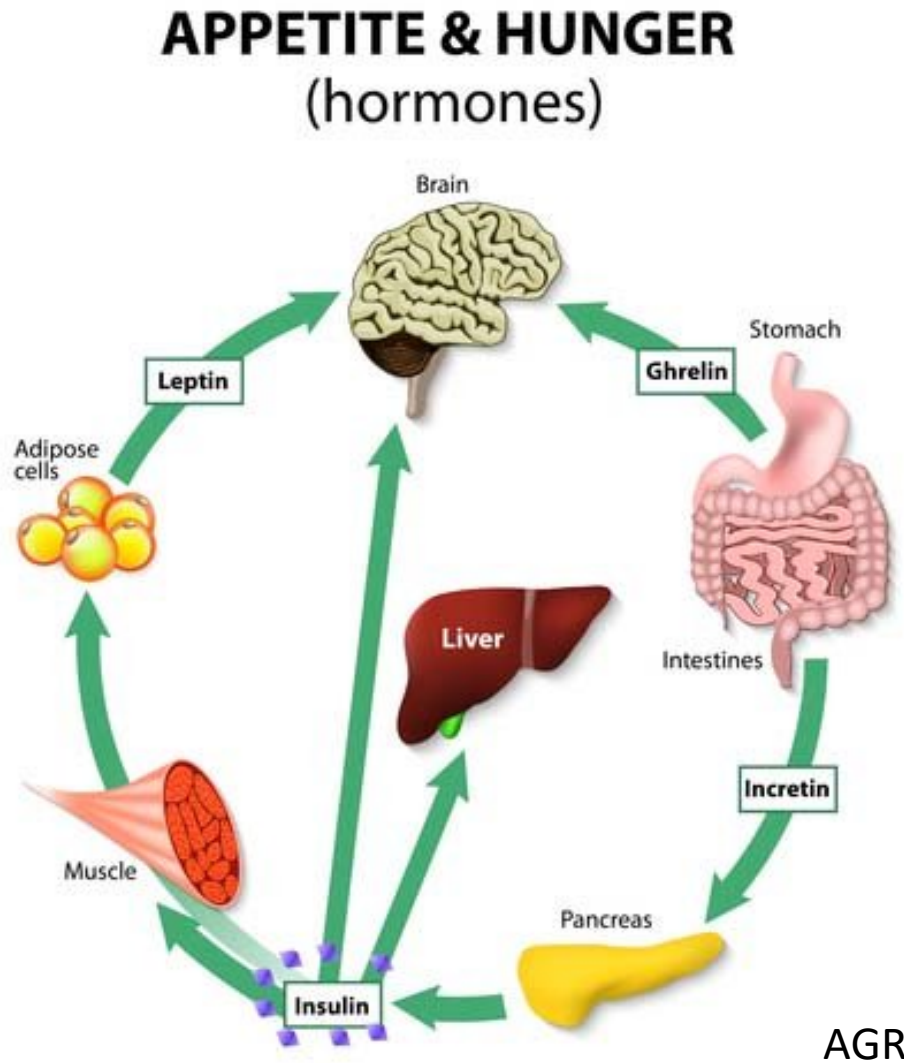
Also involved in glucose control:
-glucagon (pancreas)
-catecholamines
-glucocorticoids (adrenal)

Nass et al, PNAS, 2010

Sun et al, PNAS 2004



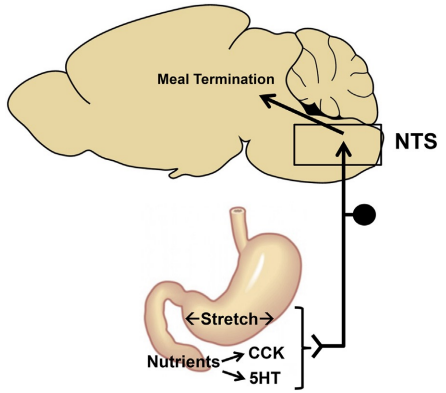
A FAT CENTRIC VIEW of APPETITE & HUNGER

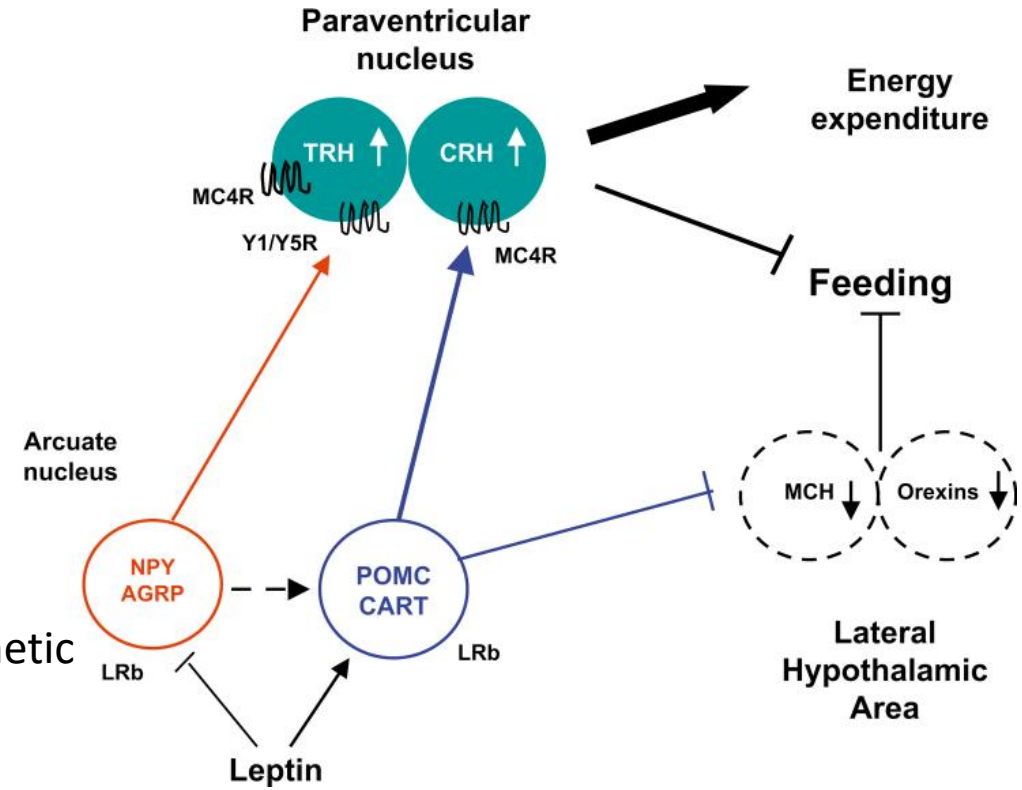


Insulin-R in hypothalamus
-food intake, fat mass and hepatic action

Control of glucose is not control of appetite

Control of appetite and hunger balanced by control of satiety

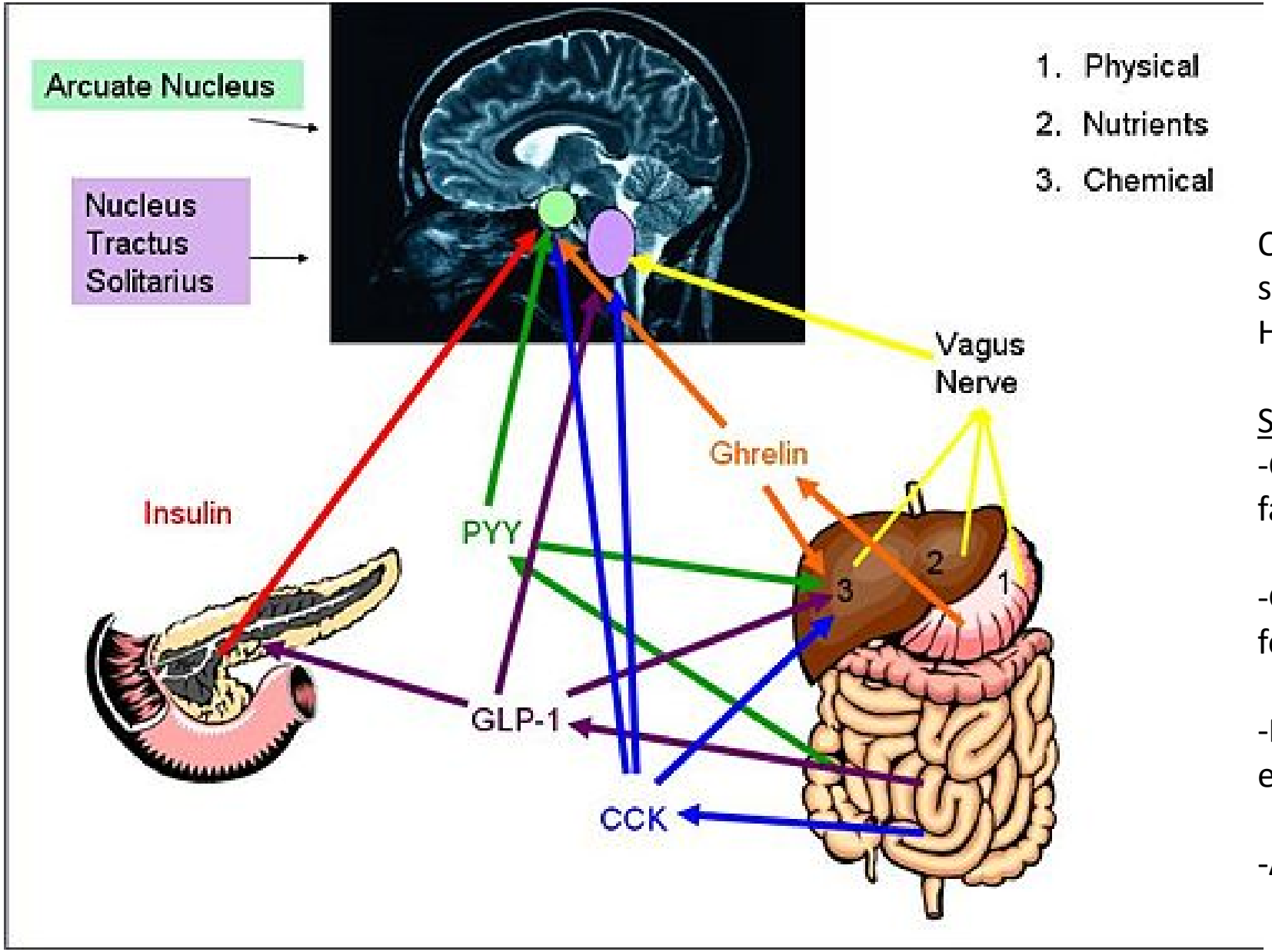




AGRP-sympathetic response to fasting

Ahima & Antwi, 2008

GUT-BRAIN PATHWAY



Overall structure of the pathways similar to those for Hunger

Satiety signals

-**CCK** (SI in response to food, mostly fat & protein)

-**GLP-1** (gut incretin in response to food, mostly CHO)

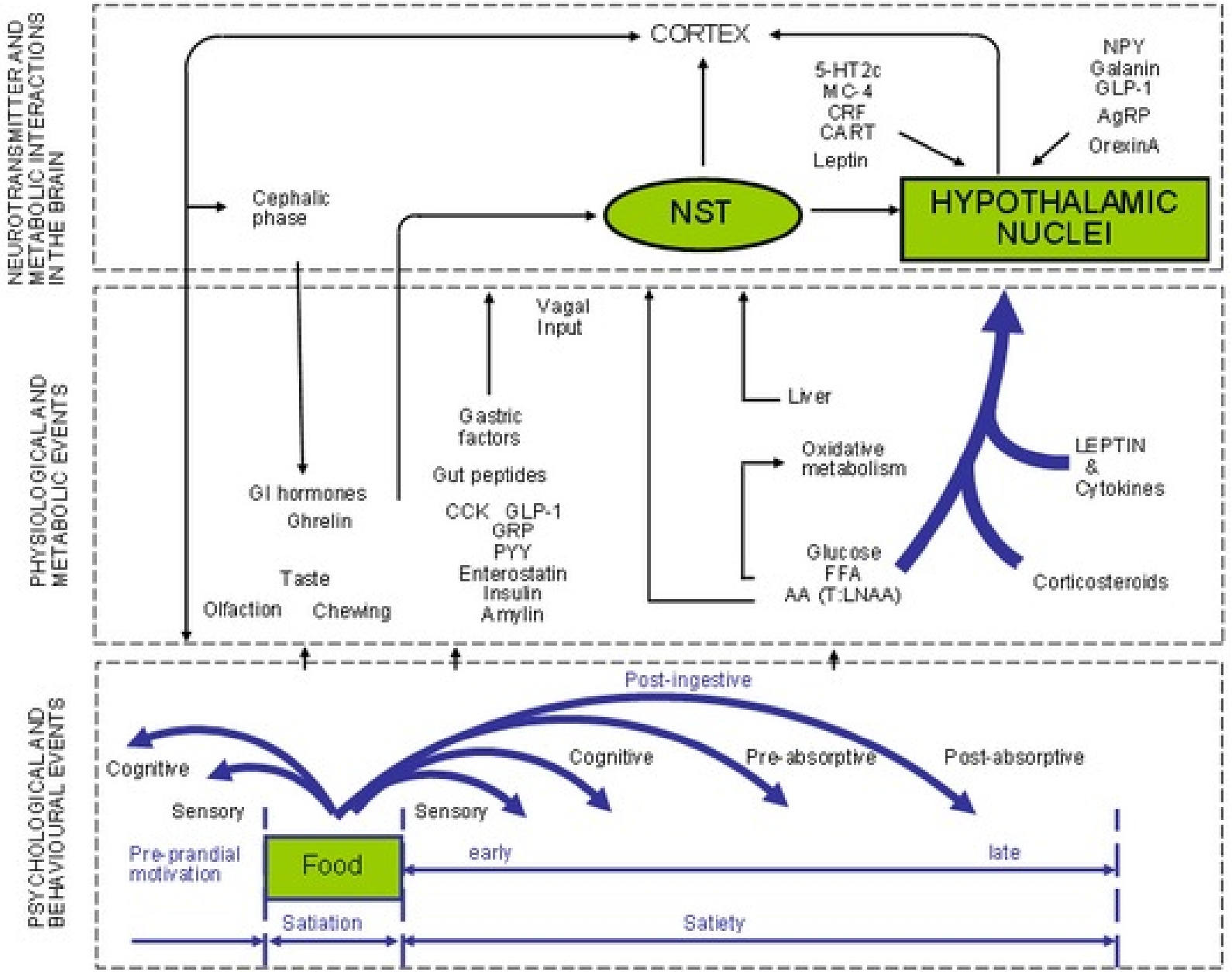
-**PYY*** (SI, LI in response to food especially FFA) and **PYY-R in tongue**

-**Amylin** (pancreatic)

"The overall strength or weakness of the action of these peptides will help to determine whether individuals are resistant or susceptible to weight gain" (Hopkins)

*Batterham NEJM 1997

FDA- approved DRUG	MoA	Wt loss (%)	Side effects
Orlistat	Panc. lipase inibitor, blocks fat absorption	4	GI: diarrhea, bloating; blocks fat-sol vitamin absorption
Lorcaserin	Serotonin-R agonist, reduces food intake	3	Mild: HA, dizziness, nausea, dry Mouth, constipation, avoid other similar MoA drugs
Liraglutide	Glucagon-like-R1 agonist, reduces intake Lower doses for DM	6	**N/V common**; acute pancreatitis, gallbladder dis; hypoglycemia w/ other DM drugs; (avoid in MEN2) **MEDIATES REDUCED CV & ALL CAUSE MORTALITY**
Diethylproprion, Pnentermine, Phendimetrazine, benzphetamine	Noradrenergic, Appetite suppressing	NA	Dizziness, dry mouth, constipation, irritability, CV stimulant
Phentermine- Topiramate ER	Appetite suppression via DA, NA, serotonin release	9 (MOST)	Paresthesias; taste changes; rare: met. Acidosis, glaucoma; avoid MAOI; avoid pregnancy
Natrexone- Bupropion SR	Decrease appetite, Inhibit DA, NA uptake, Block u-opioid R. Activate POMC	6	Nausea, constipation, HA; avoid opioids & MAOI, hx seizures



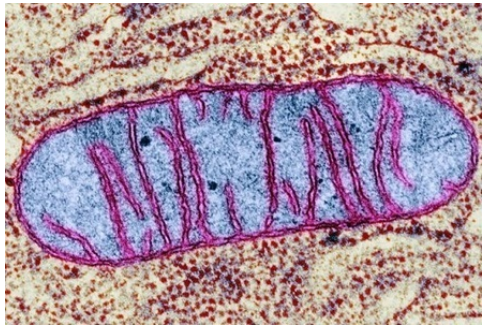
Neurotransmitter level

Physiology/metabolic events

Psychological level

Hopkins et al, Endotext, 2016

ONLY TOUCHES THE SURFACE



Missing players

Missing control/regulatory loops

Missing interactions between subsystems

Missing: Evolutionary explanation

Missing: Good tools to treat obesity, and/or. to reinforce lifestyle changes

<u>How do these regulatory systems interact?</u>

Mitochondrial signaling and energy homeostasis

Psychological/emotional state/pain/sleep/circadian
TrpV1-nociception AND energy homeostasis

Reward systems (DA)

Gut ← →brain axis (and tongue-brain axis)

Adipocyte← →brain axis

Liver ← →brain axis

Cognitive over-rides
(error correction?)