VII CONGRESO URUGUAYO DE OBESIDAD

1º Congreso Regional de Obesidad y Trastornos Alimentarios

Balance Energético y Regulación Siconeuroendócrina de la Ingesta

Dr Fernando M. Escobar
Médico Endocrinologo Universitario
Ex Presidente de la Sociedad Argentina de Obesidad y Trastornos Alimentarios
Docente Adscripto en Medicina Interna

- El relator de la conferencia no presenta conflictos de interés.

Daniel Lambert

1770-1809

335 kg

"The most corpulent man of whom authentic records exist"

Died age 39, Heart Disease

"A Voluptuary under the Horrors of Digestion"

1792, James Gillray

Prince Regent (Future King George IV of England)

Etiología de la Obesidad

Gasto Calórico

Sedentarismo

Ingreso calórico

Alimentos de alta densidad calórica azúcar y grasas

Susceptibilidad Genética

Mecanismos del ingreso alimentario

Influencias familiares y sociales

Factores cognitivos

- Control conciente
- Creencias alimentarias
- Advertencias

Factores sensoriales

- Sabor
- Olor
- Textura
- Efecto visual

- **Efectos de**
- Variedad
- Saciedad al estímulo
- Sensorial
- Palatibilidad
- Tipo de alimento
- Disponibilidad real

Mecanismos cerebrales

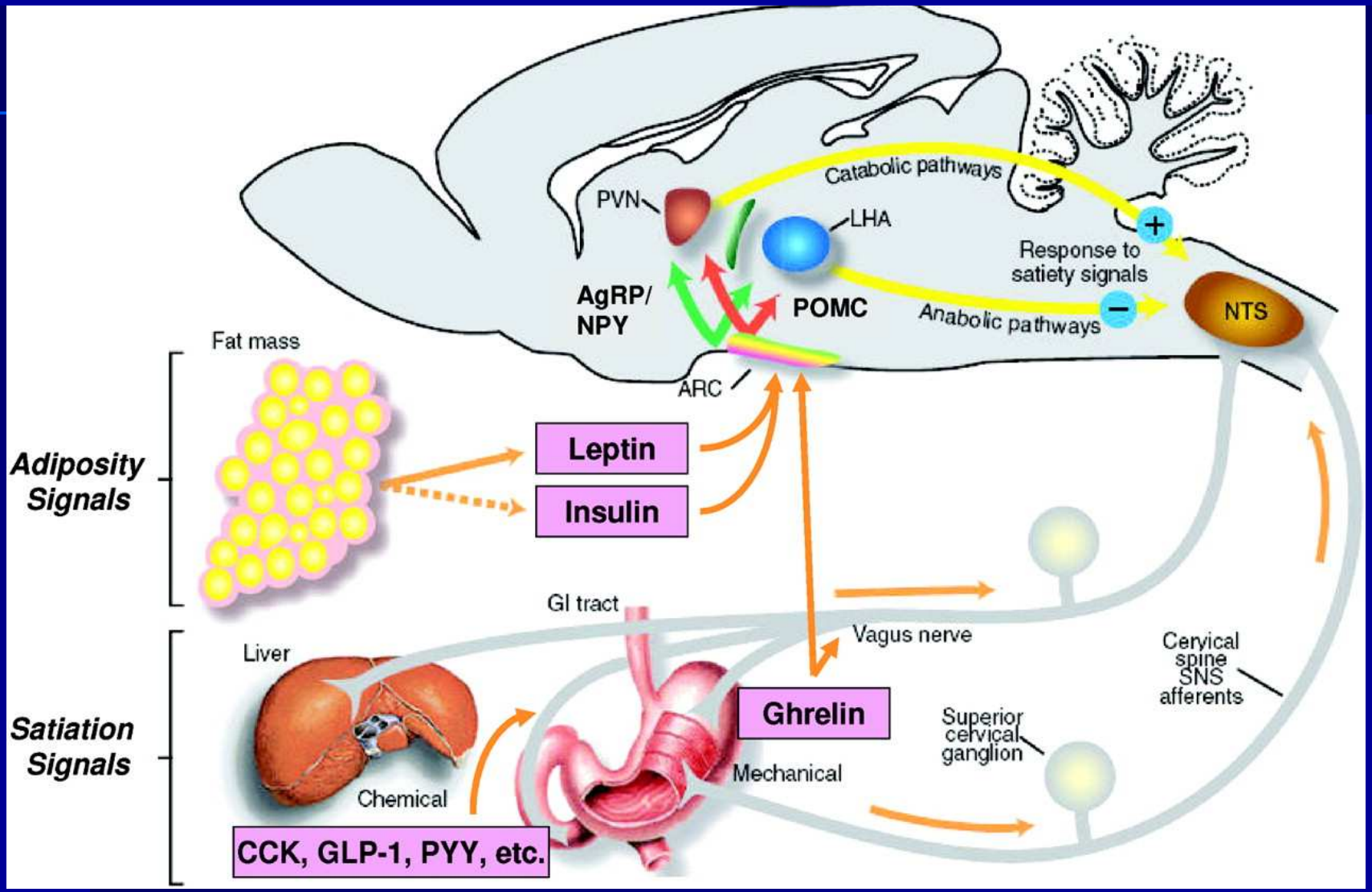
- Modula factores sensoriales mediante señales de saciedad para producir sensación de recompensa y regulación del apetito.

Ingesta

Señales de Saciedad y Apetito

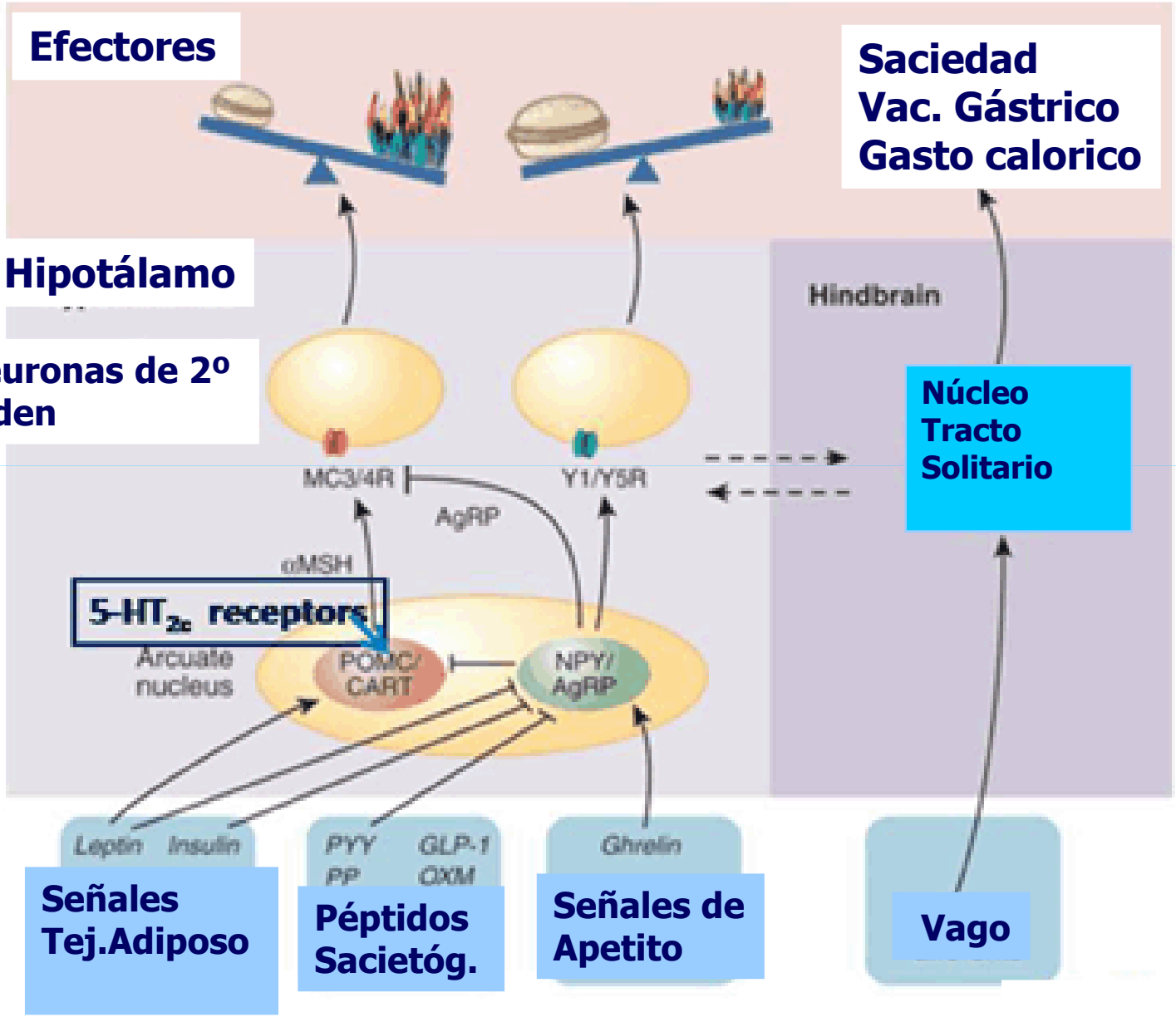
- Hormonas del tej.Adiposo
- Hormonas intestinales
- Distensión gástrica

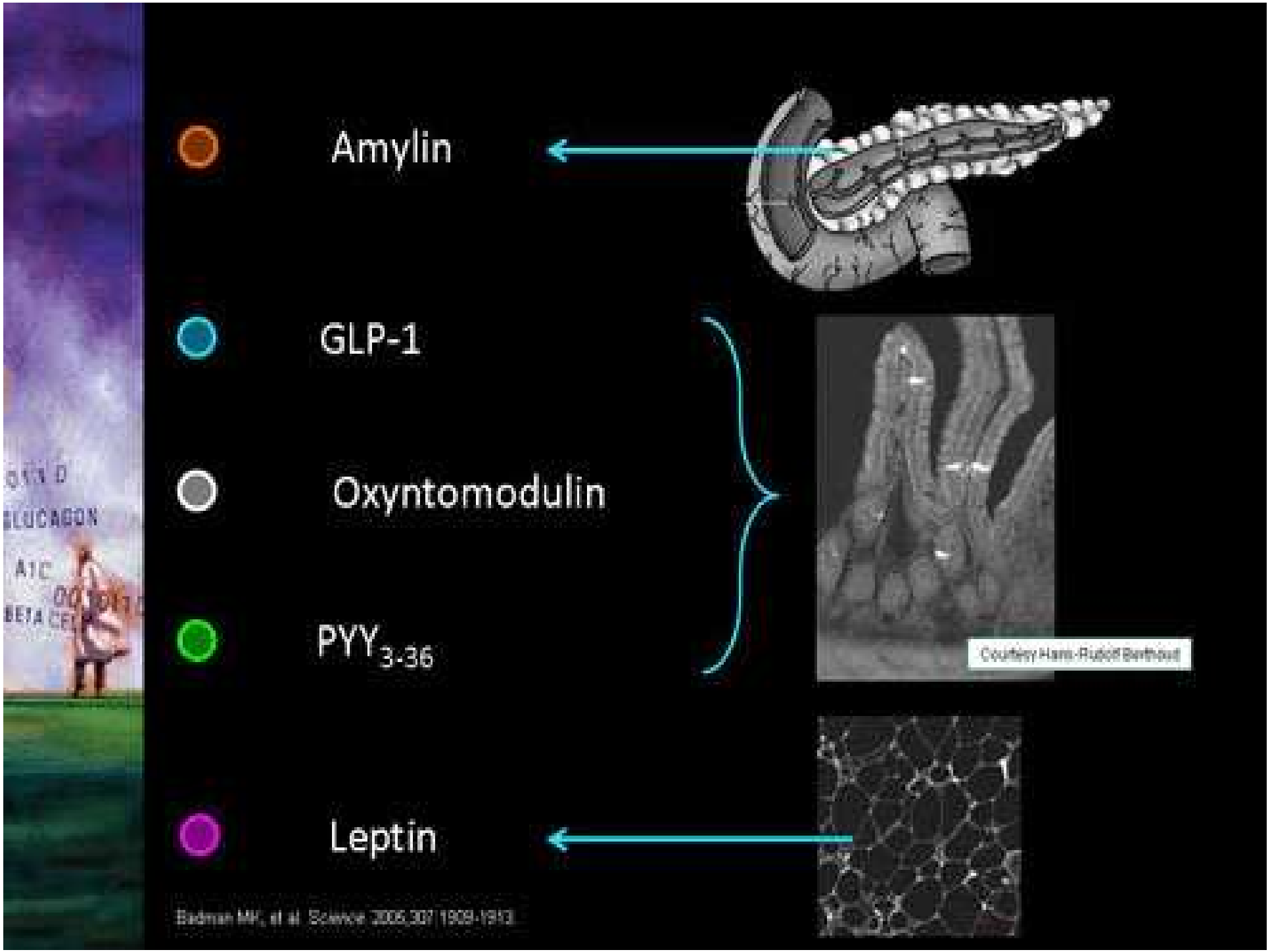
Los diferentes niveles de control del apetito



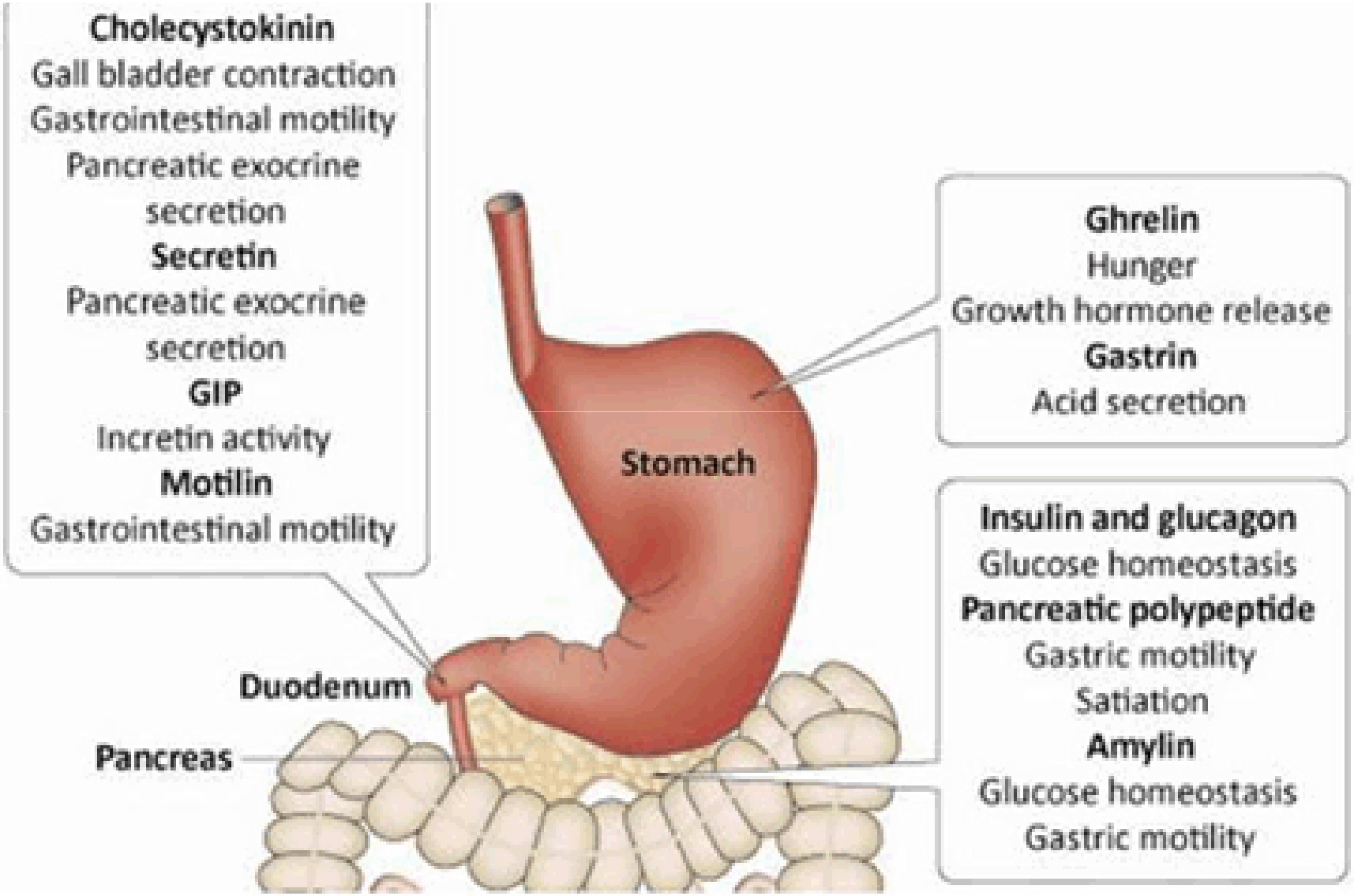
Woods SC, et al. *J Clin Endocrinol Metab.* 2008;93(suppl1):S37-S50.

Neuroregulación del balance energético



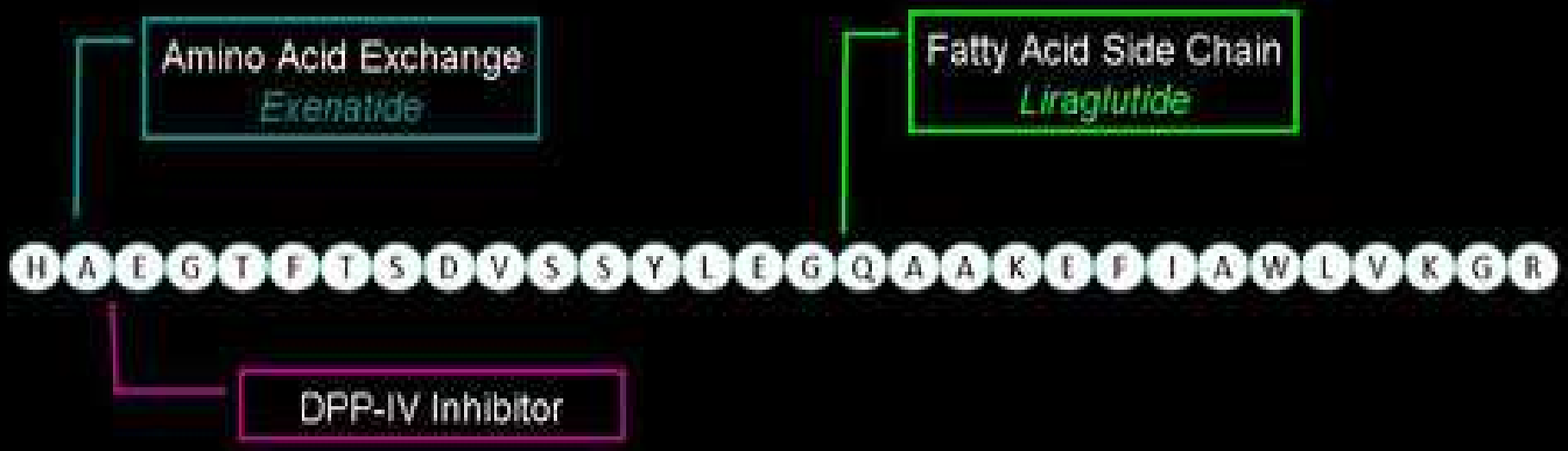

Amylin
GLP-1
Oxyntomodulin
PYY3-36
Leptin
Courtesy Hans-Rudolf Berthoud
Badman MK, et al. Science 2006;307:1909-1913

Péptidos del tubo digestivo que regulan el apetito



Murphy KG, Bloom SR. *Nature*. 2006;444:854-859.

GLP-1



- Péptido de 30 aa producido a partir del pre-proglucagon en el NTS y cel.L Intestinales.
- GLP-1 se produce e incluso acitva neuronas del NTS que se proyectan a regiones claves del hipotálamo.
- GLP-1 disminuye la ingesta en ratas. El antagonista GLP-1R Exendina aumenta el apetito.
- La administración de GLP-1 activa neuronas en el núcleo arcuato, PVN. NTS, y área postrema.
- Inhibe el apetito

Redrawn from Gallwitz B. Rev Diabet Stud. 2005;2:61-69.

Mecanismos potenciales para GLP.1 que median en la disminución de la ingesta y del peso corporal

- **Enlentecimiento del vaciado gástrico**
- **Saciedad**
  - ***Directo*** ***(Vía NTS y/o hipotálamo)***
  - ***Indirecto*** **(Vía Aferentes vagales)**

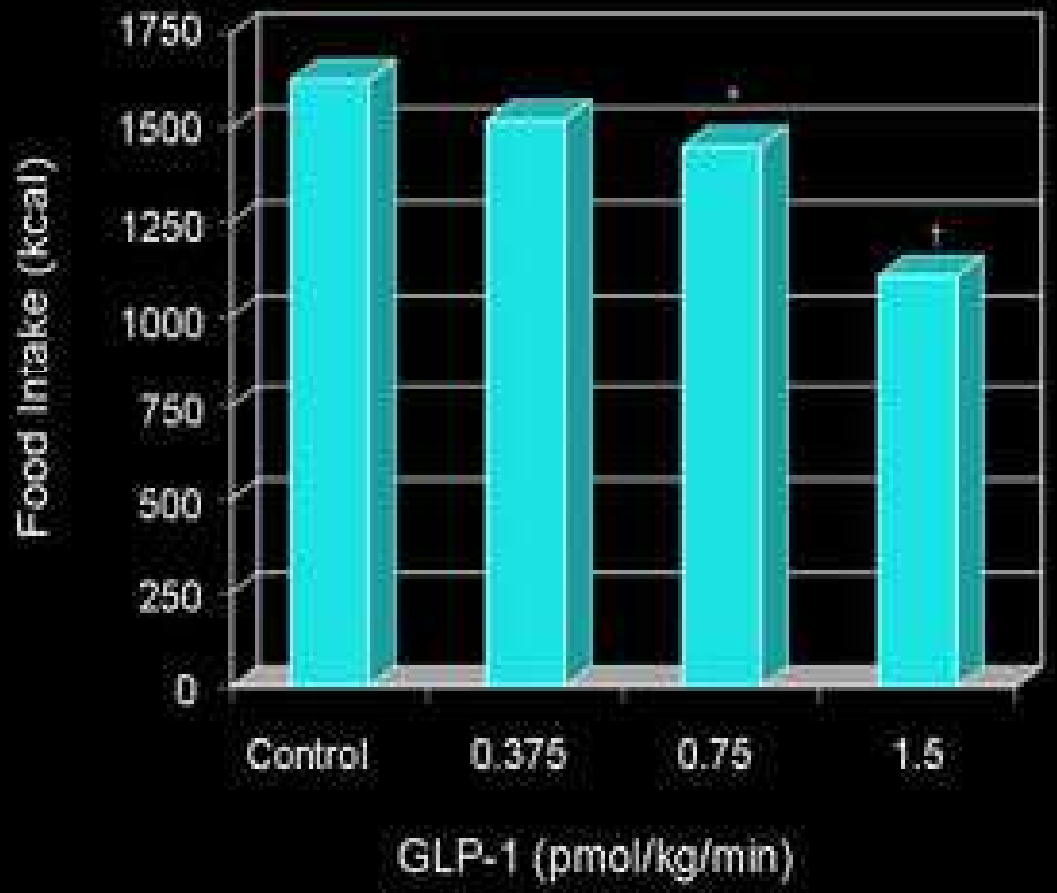
Drucker D.J. Cell Metab. 2006;3:153-155

Otras acciones del GLP-1

- Segregado por las células L-intestinales con la ingesta
- En humanos y en animales
  - Incrementa la liberación de insulina estimulada por glucosa
  - Disminuye la secreción de glucagon
  - Disminuye el vaciado gástrico
  - Reduce el apetito
- En animales in vitro
  - Aumenta la transcripción del gen de insulina
  - Aumenta la masa y diferenciación de las células β

Drucker DJ. *Curr Pharm Des.* 2001;7:1399-1412.
Drucker DJ. *Mol Endocrinol.* 2003;17:161-171.

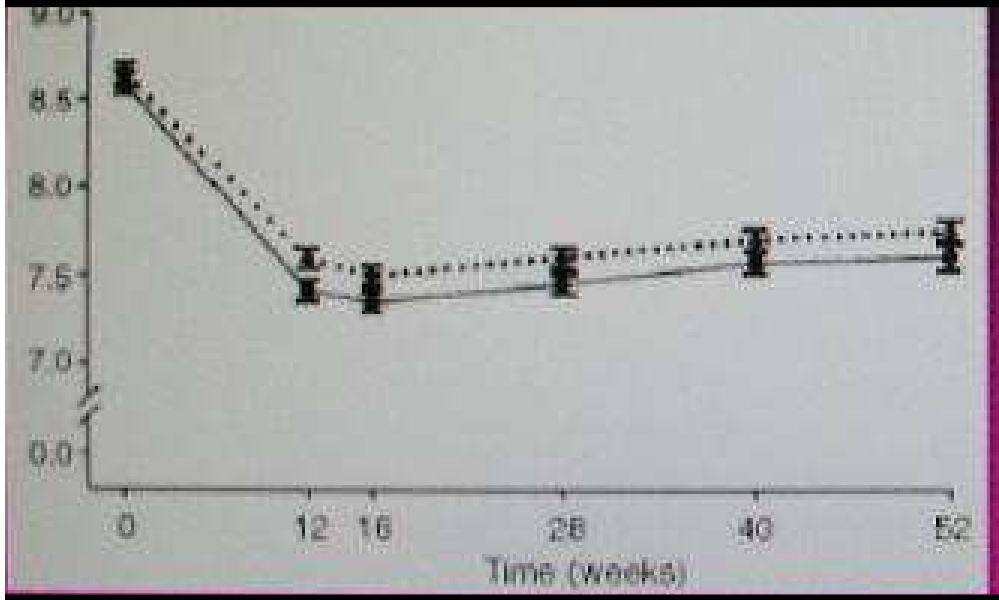
GLP-1 Reduce la ingesta alimentaria



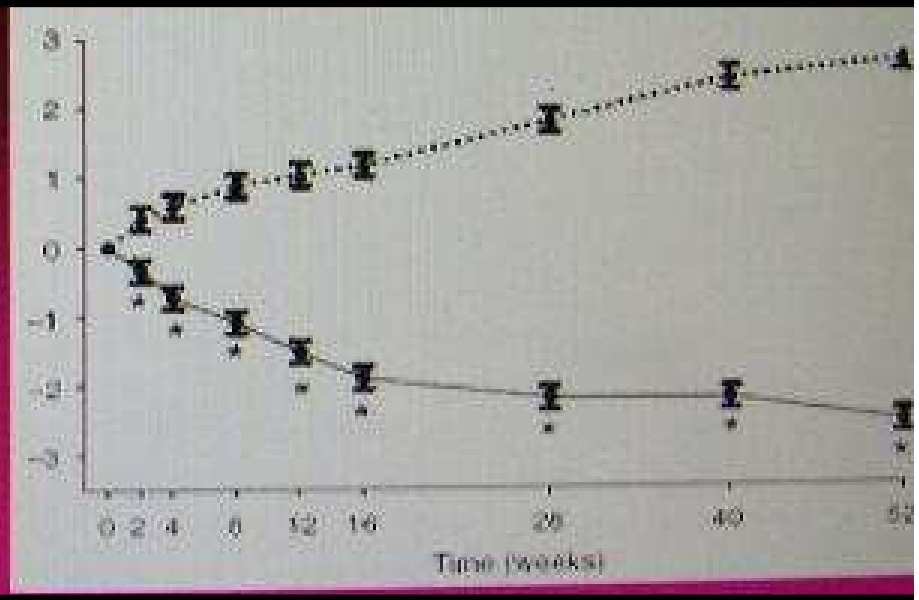
*P< 05, †P< 001; vs control.
Gutzwiller J-P, et al. Gut 1999;44:81-86.

Efecto de un GLP-1 de acción prolongada sobre glucosa y balance energético

HbA1c



Peso corporal



Nawck M. et al Diabetologia 2007

Glicentina y Oxyntomodulina

Glicentina

- -Hormona intestinal producida por las células α y L
- -Liberada durante la digestión
- -Insulino-trópica, disminuye la acidez y el vaciado gástrico
- -No hay todavía data disponible en humanos

Oxyntomodulina

- -37 aa, igual al glucagon más su extensión C terminal
- -Segregado por las células L , luego de la ingesta, se une al receptor GLP-1
- -Reduce la ingesta alimenticia en humanos
- -Puede aumentar el gasto energético ¿vía el eje tiroideo?

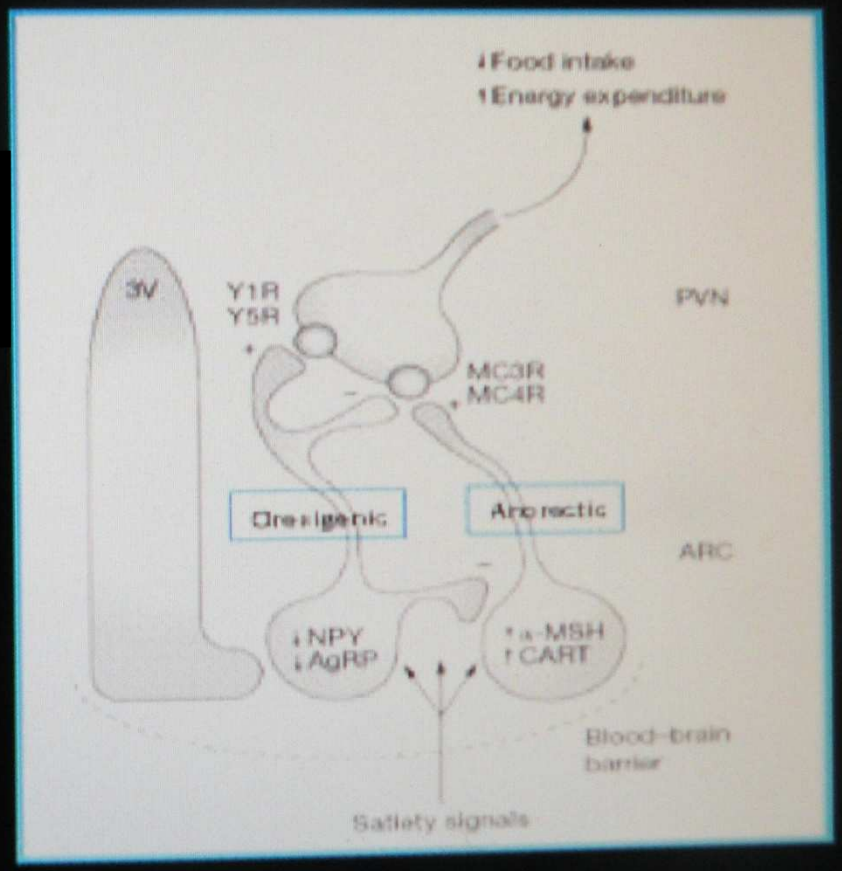
Acciones centrales de PYY_{3-36} y Oxyntomodulina

- **OXM y PYY3-36 se liberan postprandialmente**

-Acción primaria: señales de saciedad en el núcleo arcuato.

-Inhibición coordinada de neuronas orexígenas y activación de anorexígenas

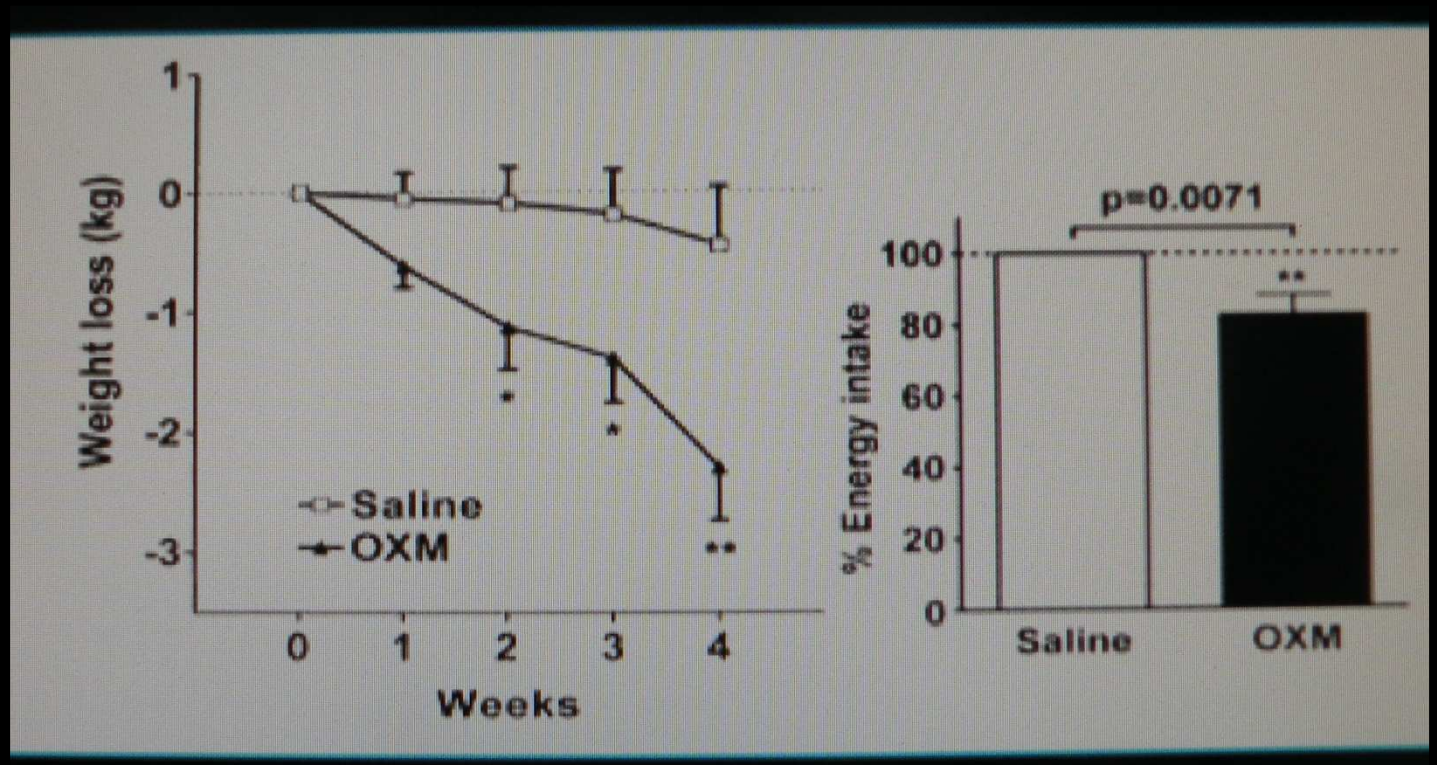
- -**Reducción del gasto energético y del peso corporal.**



Wynne K and Bloom SR. Nature Clin Practice. 2(11):612-620, 2006

13.06.2009 15:16

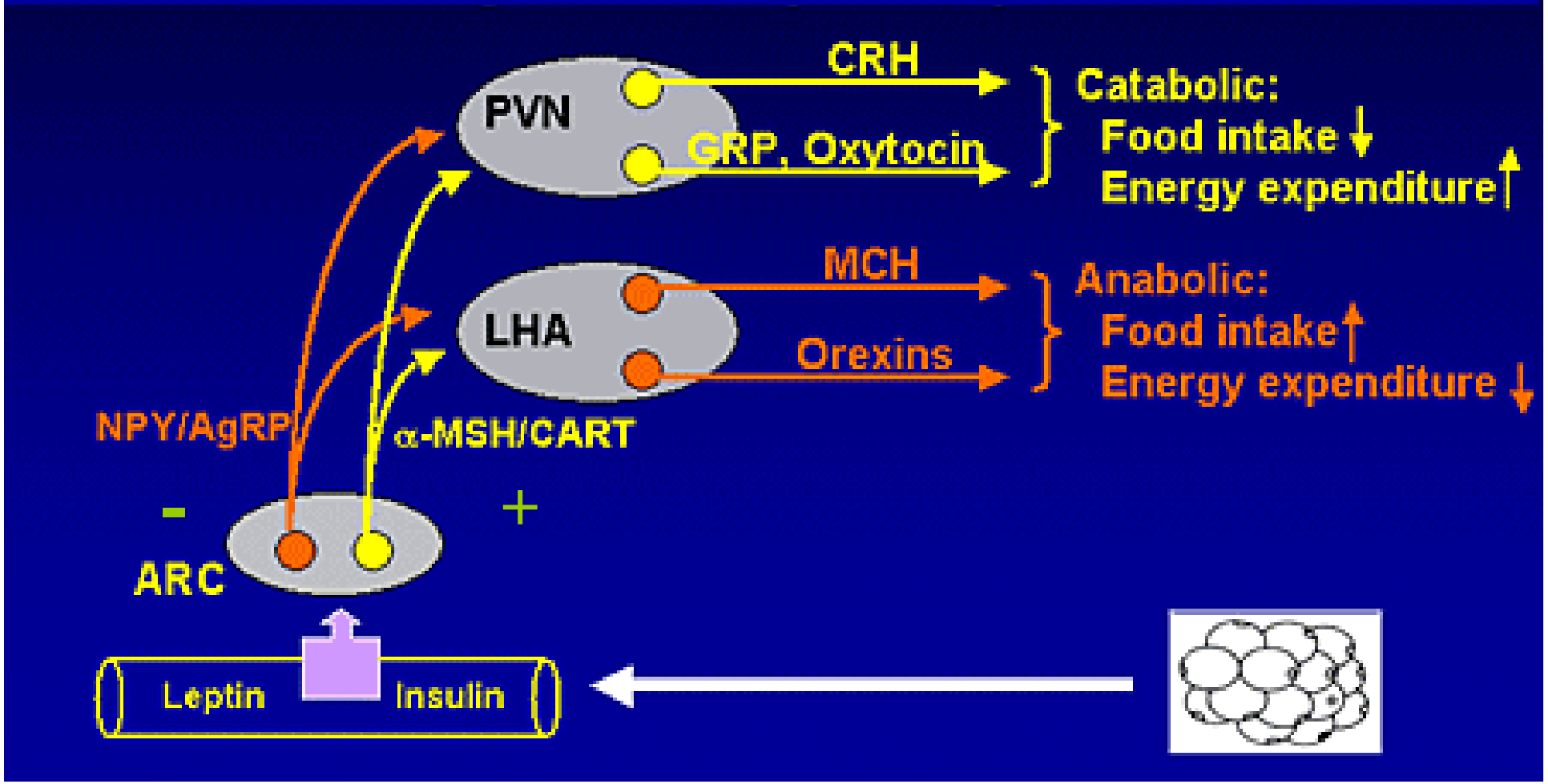
Impacto de la Oxintomodulina en la ingesta alimentaria y en el peso corporal



Cohen et al. JCEM 88(10):4696–4703, 2003
Wynne et al Diabetes 54, August 2005
Wynne et al Int J Obesity 2006 30, 1729–1736

13.06.2009 15:16

Las hormonas leptina e insulina ingresan al núcleo arcuato hipotalámico para estimular las neuronas α-MSH/CART mientras que inhiben NPY/AgRP.
Por lo tanto a nivel central activan los sistemas catabólicos e inhiben los anabólicos.



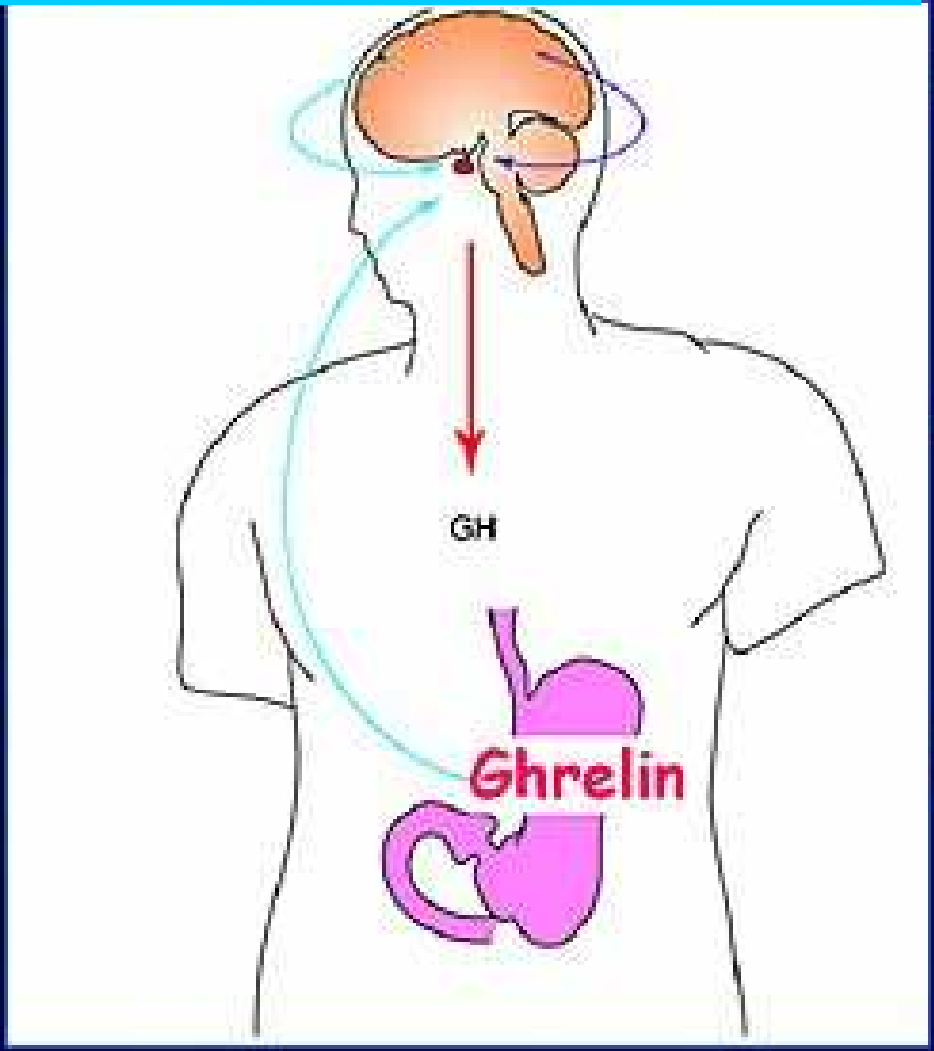
Ghrelina: es un ligando endógeno del receptor secretagogo de GH

Se expresa en estómago

- **Estimula la secreción de GH**
- **Incrementa la adiposidad disminuyendo la oxidación de las grasas y aumentando la ingesta**

Los niveles de Ghrelina están disminuídos en obesos

- **Ghrelina disminuye luego de una cirugía de bypass gástrico**

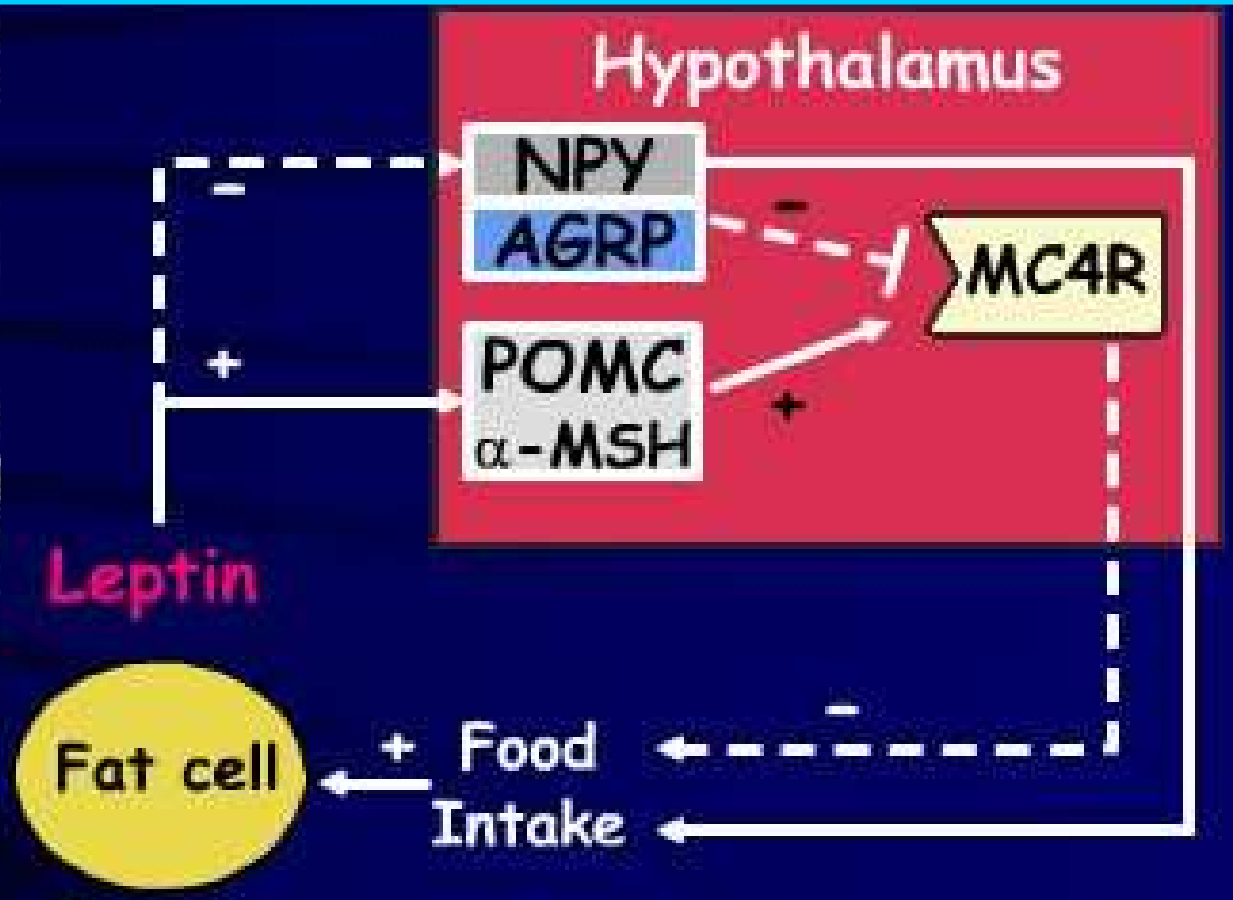


Adapted from Cummings et al. NEJM 346:1623-1630, 2002

Receptor MC4R e ingreso alimentario

Leptin ⇑ POMC and ⇓ AGRP → ⇑ MC4R signaling and ⇓ food intake

MC4R signaling is ⇑ by α-MSH and ⇓ by AGRP

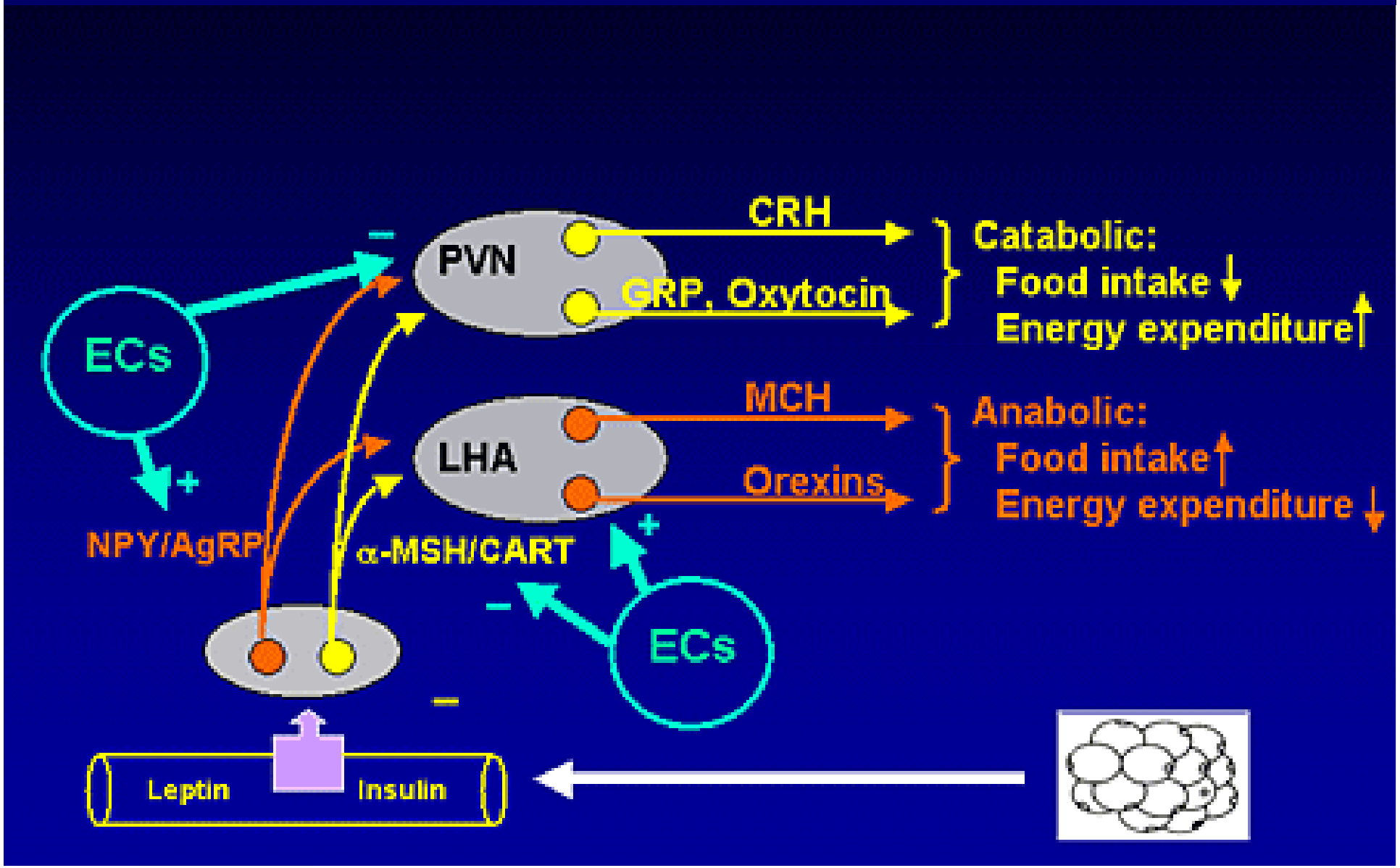


Leptin ⇓ NPY, which is synthesized in the same neurons as AGRP

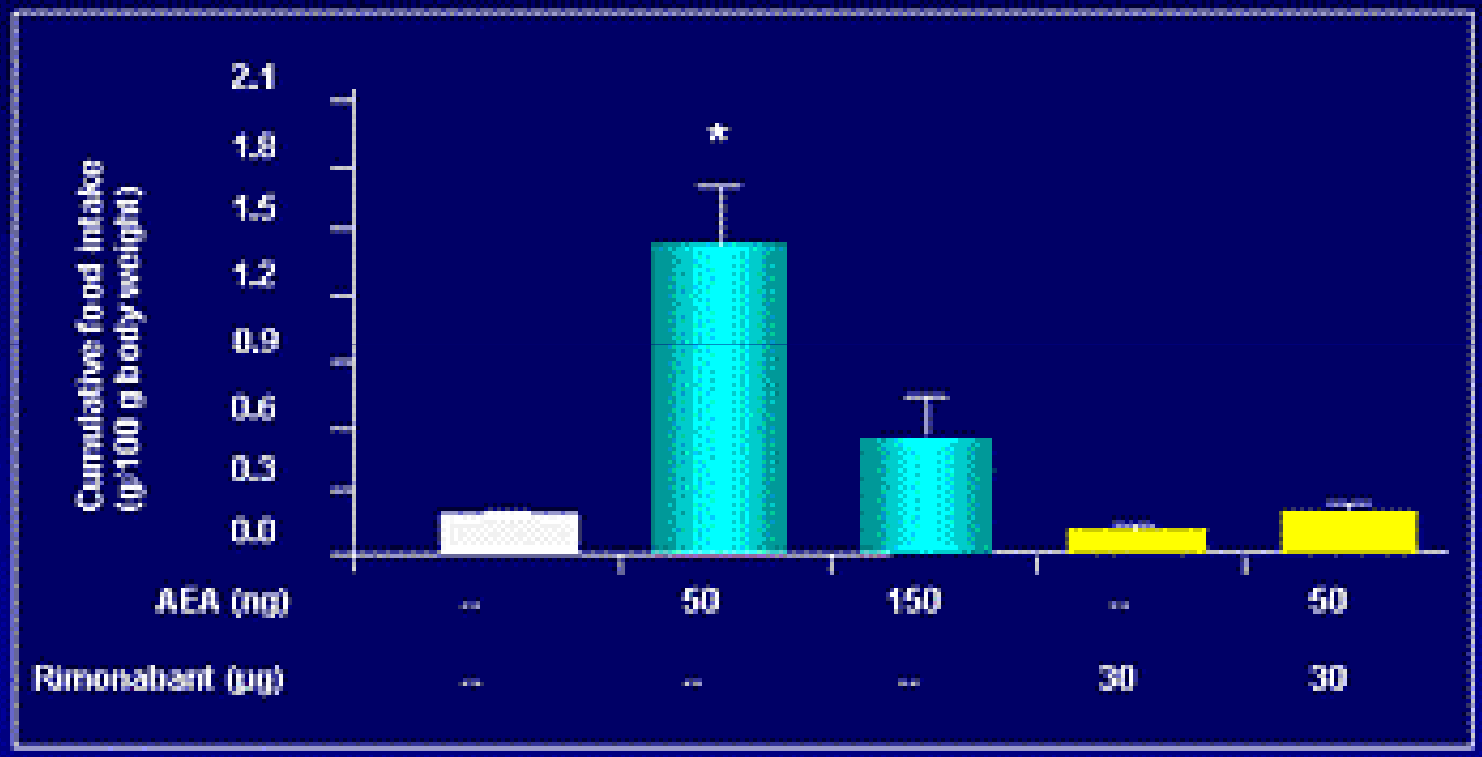
Stimulatory interactions in solid lines; inhibitory in dashed lines

Adapted from SL Wardlaw JCEM 86:1442-1446, 2001

Los Endocanabinoides estimulan los circuitos anabólicos e Inhiben los circuitos catabólicos en el hipotálamo



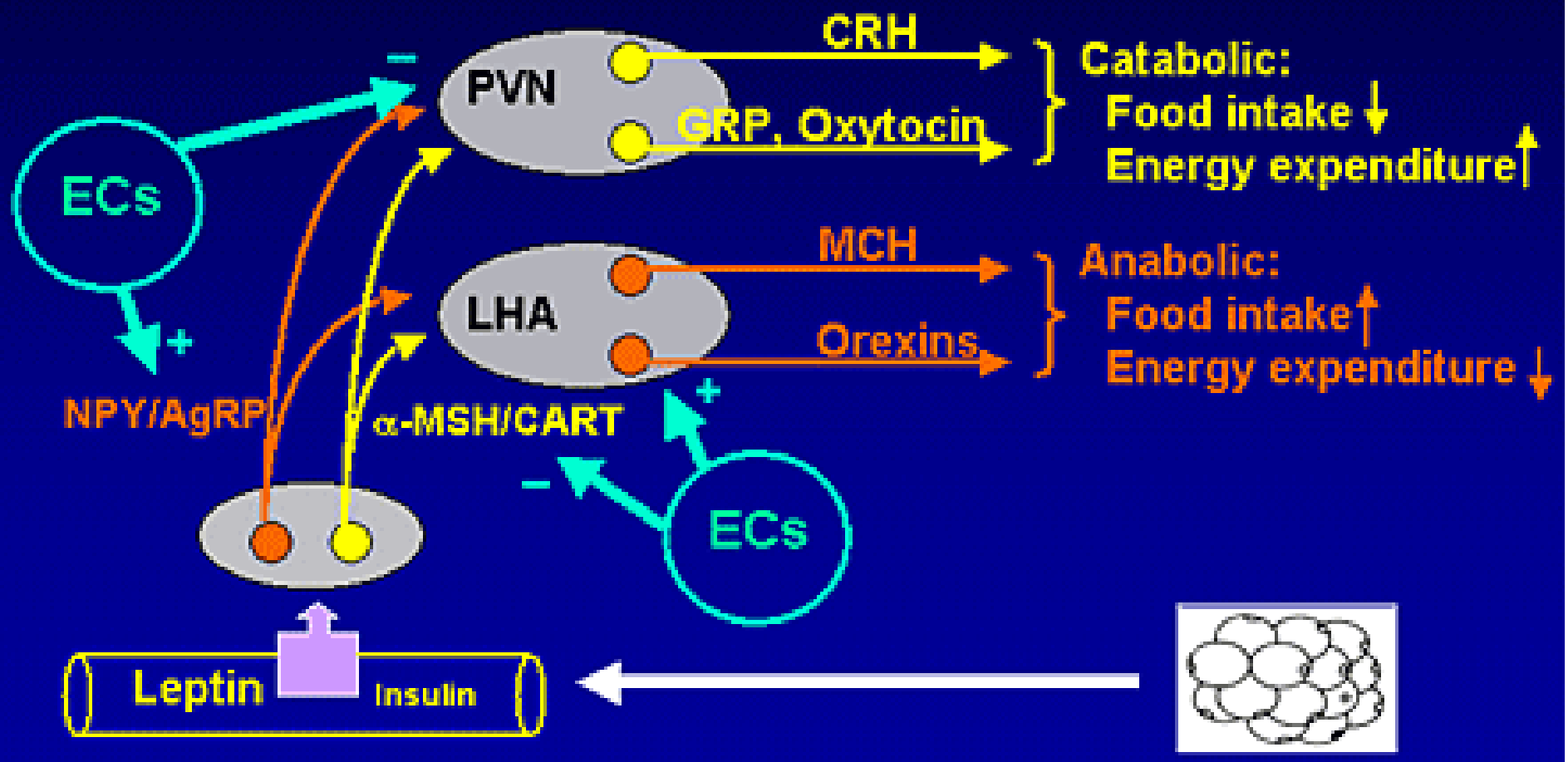
Endocannabinoids Increase Food Intake Through CB_1-Receptor Activation



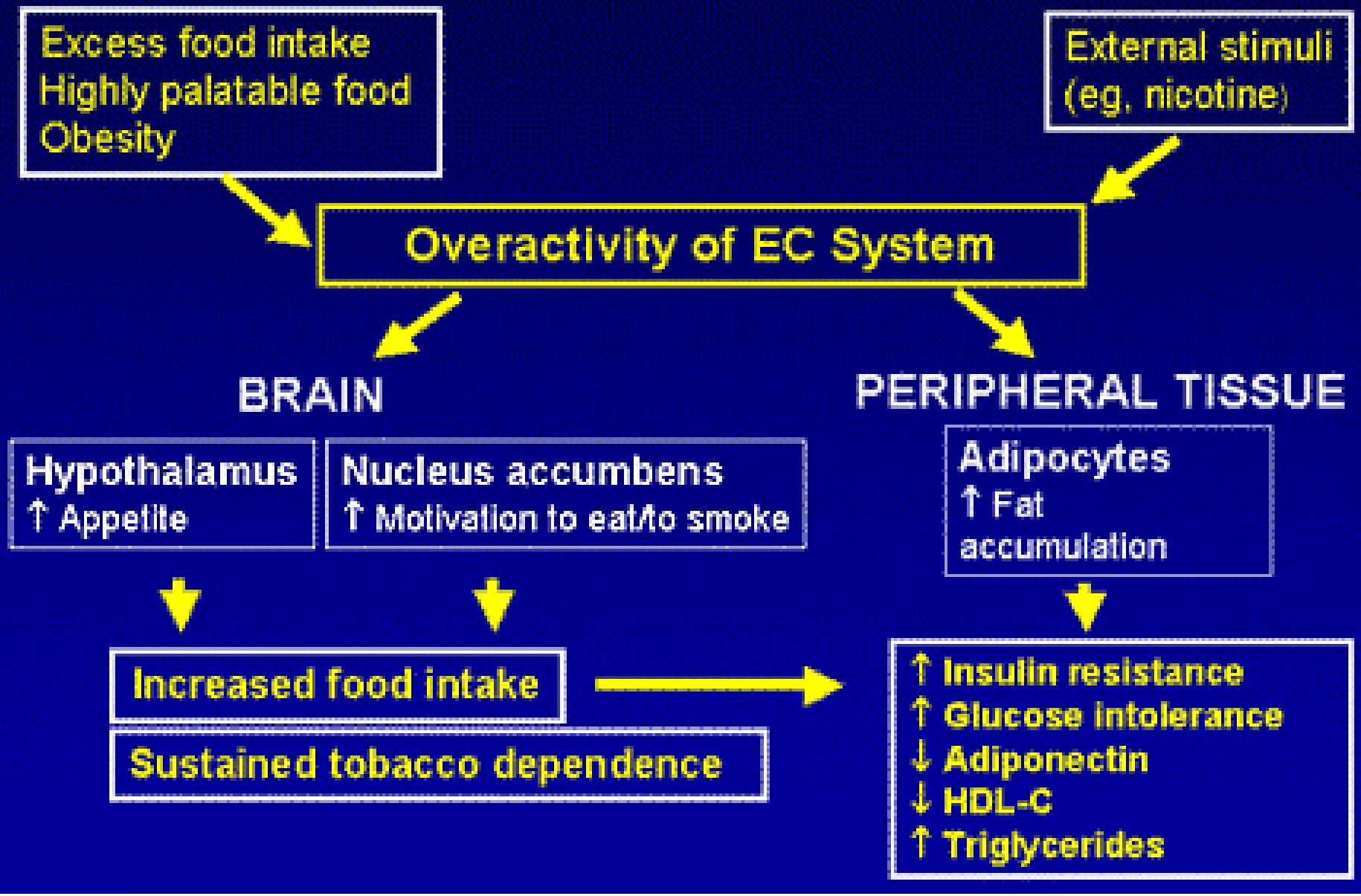
Anandamide administration into the ventromedial hypothalamus induces hyperphagia in presatiated rats

Jamshidi N, et al. *Br J Pharmacol.* 2001;134:1151-1154.

Leptin tonically inhibits endocannabinoids in the hypothalamus.

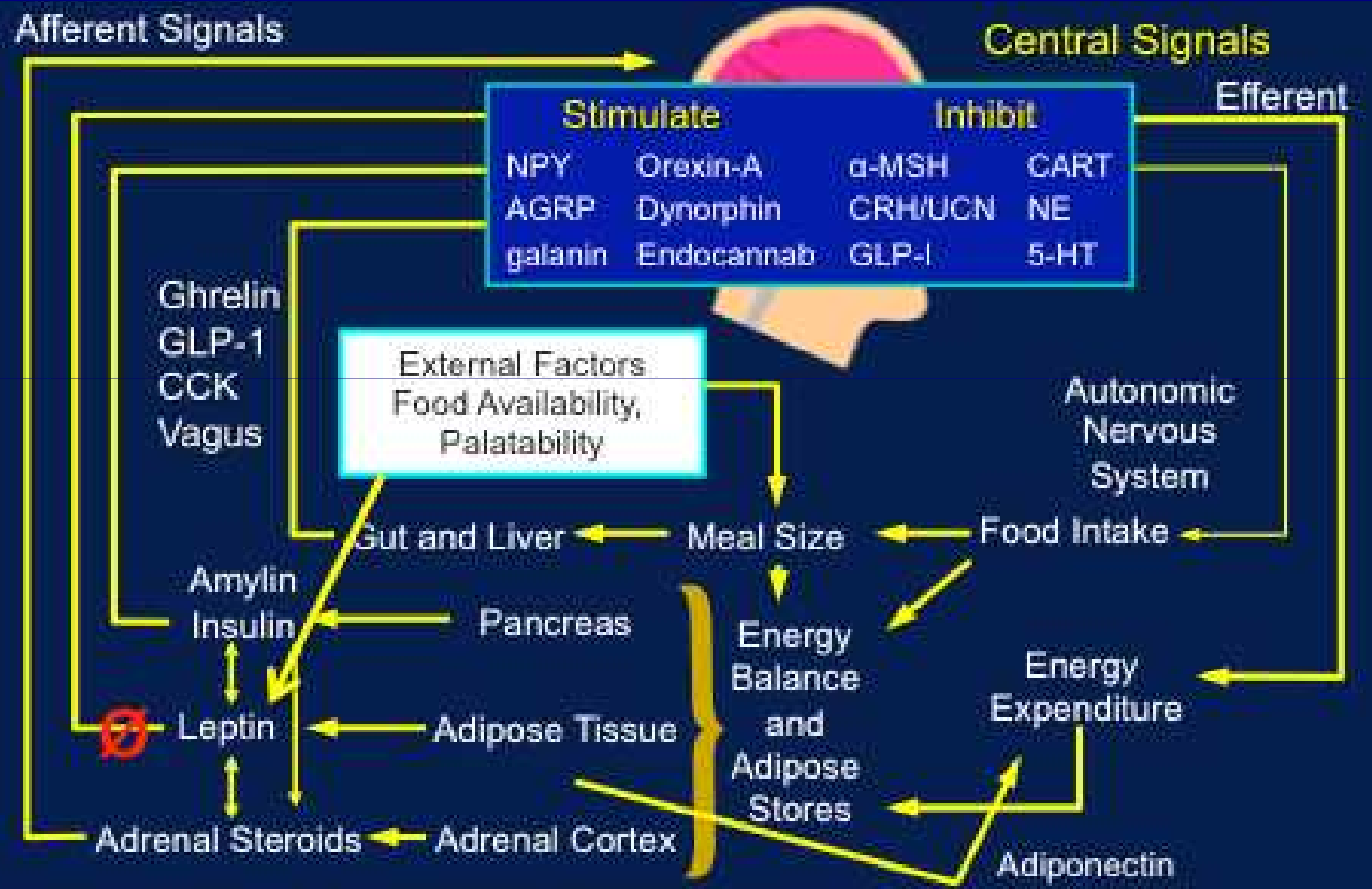


Effects of Endocannabinoid System Overactivity



¿Cuál es la Causa de la Epidemia de Obesidad?

La comida "Basura" provoca Leptino-resistencia



Adapted from Campfield LA, et al. *Science*. 1998;280:1383-1387; Porte D, et al. *Diabetologia*. 1998;41:863-881.

Cell Metabolism
Article

Cell PRESS

Endoplasmic Reticulum Stress Plays a Central Role in Development of Leptin Resistance

- **La alimentación engordante causa Leptino-resistencia**
- **El incremento de peso provoca Leptino-resistencia**
- **La Leptino- resistencia interfiere con la saciedad y altera el metabolismo del tejido muscular favoreciendo el incremento de peso**
- **Los malos hábitos generan también una "Mala Fsiología"**

Ozcan L, et al. *Cell Metab.* 2009;9(1):35-51.

Cell Metabolism
Article

Endoplasmic Reticulum Stress Plays a Central Role in Development of Leptin Resistance

Lale Ozcan,[1,4] Ayse Seda Ergin,[1,4] Allen Lu,[1] Jaeson Chung,[1] Sumit Sarkar,[1] Duyu Niu,[2] Martin G. Myers, Jr.,[3] and Umut Ozcan[1,*]
[1]Division of Endocrinology
[2]Division of Neurology
Children's Hospital Boston, Harvard Medical School, Boston, MA, 02115, USA
[3]Division of Metabolism, Endocrinology, and Diabetes, Department of Medicine, University of Michigan Medical School, Ann Arbor, MI, 48109, USA
[4]These authors contributed equally to this work.
[*]Correspondence: umut.ozcan@childrens.harvard.edu
DOI: 10.1016/j.cmet.2008.12.004

- "Taking all of these phenomenons into account, we think that it is possible that overconsumption of nutrients could itself be a reason for development of leptin resistance"

- "This line of thinking favors the fact that increased adiposity and consequent hyperleptinemia decreases the leptin action and creates the leptin resistance"

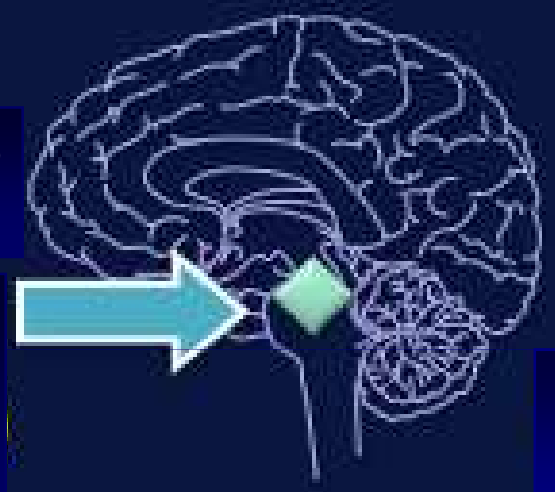
Ozcan L, et al. *Cell Metab.* 2009;9(1):35-51.

Otras Areas del Cerebro están Involucradas además del Hipotálamo

Los Circuitos de Recompensa también Influencian en la Conducta Alimentaria

Sistema mesolímbico Dopaminérgico

Adicción
Placer (opioides)
Deseo (dopamina)



Ingesta por palatibilidad

Motivación

- **Dopamina (bupropion: tratamiento para dejar de fumar)**
- **Opioides (Naltrexona: utilizada para tratar la dependencia opioidea y alchólica)**

Neurobiología del apetito apetito como adicción

- **Amígdala, insula, corteza orbito-prefrontal y striatum son elementos Centrales en el control de la conducta alimentaria.**

  - ✓ **Aprendizaje en relación a la recompensa alimentaria**
  - ✓ **Prestar atención y esfuerzo para lograr dicha recompensa**
  - ✓ **Cuál es el valor que se le otorga ese estímulo en el medio ambiente**
  - ✓ **Integrar esa información en relación a la reserva energética y a la disponibilidad alimentaria**

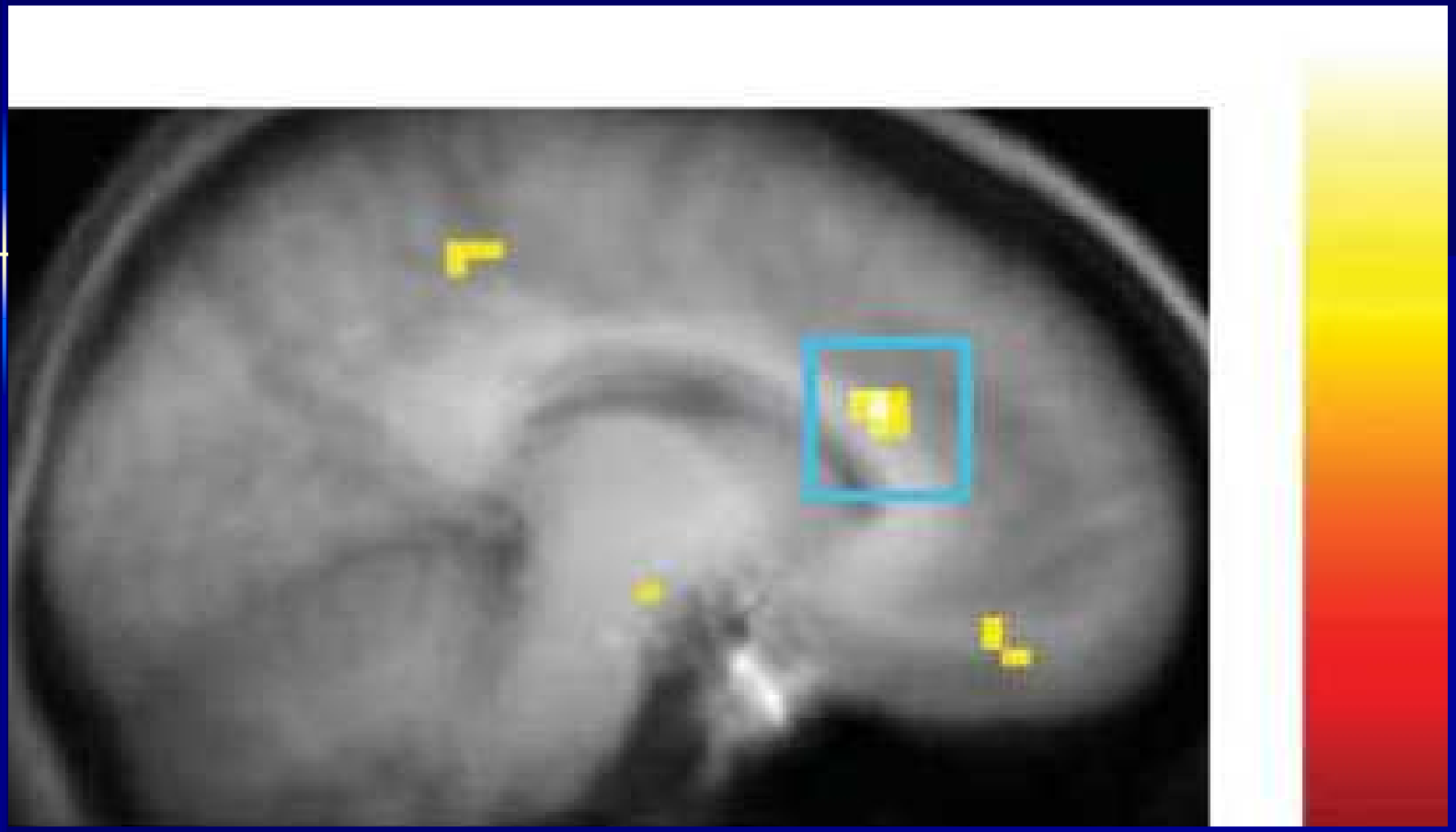


Figure 2. Activation in a region of the anterior cingulate cortex (Montreal Neurological Institute coordinates x, y, z: −9, 24, 27; z=4.64; false discovery rate–corrected P.001) during milkshake cues vs tasteless solution cues as a function of Yale Food Addiction Scale scores, with the graph of parameter estimates (PE) from that peak.

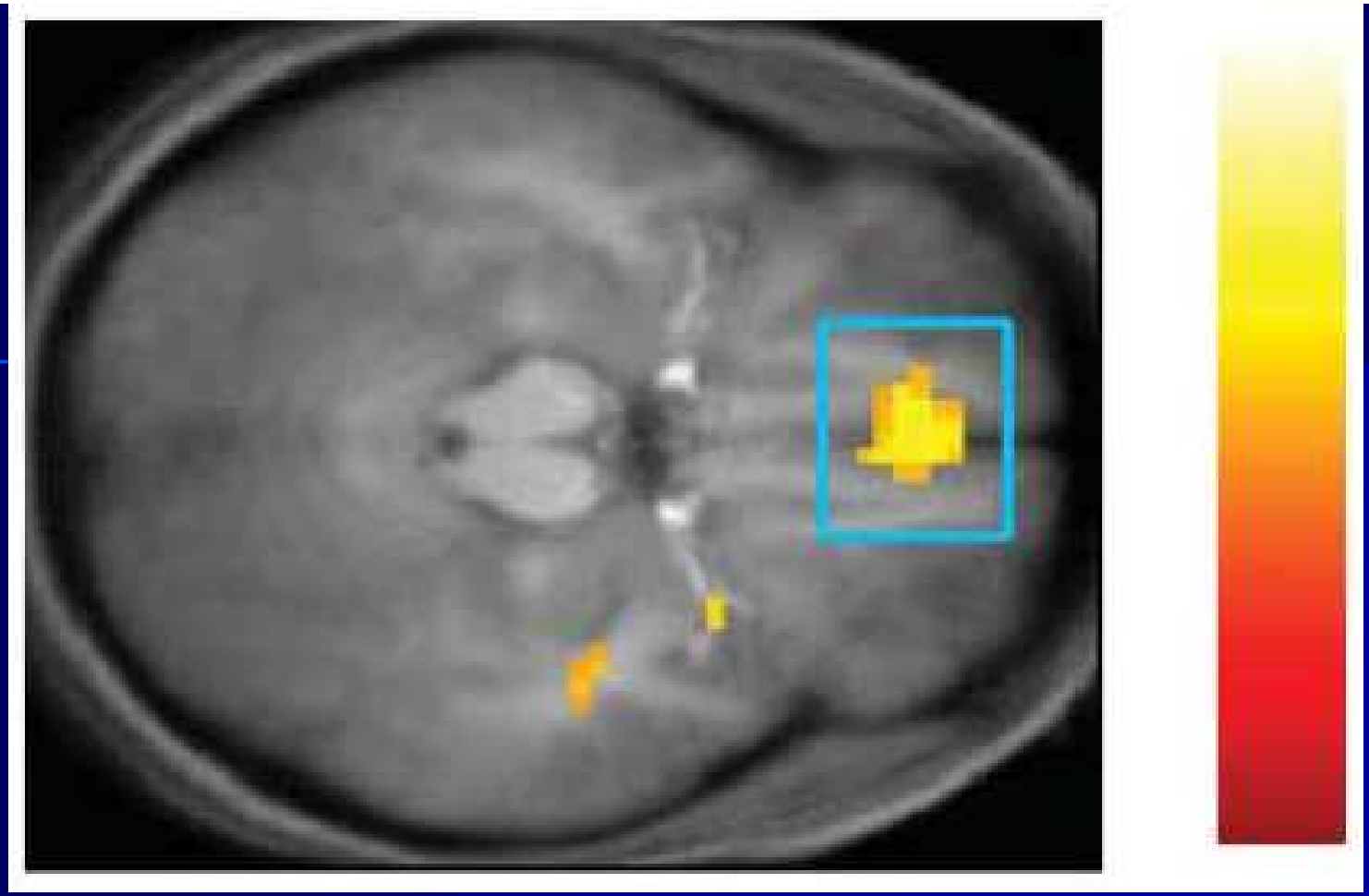


Figure 3. Activation in a region of the medial orbitofrontal cortex (Montreal Neurological Institute coordinates x, y, z: 3, 42, −15; *z*=3.47; f alse discovery rate–corrected *P*=.004) during milkshake cues vs tasteless solution cues as a function of Yale Food Addiction Scale scores, with the graph of parameter estimates (PE) from that peak

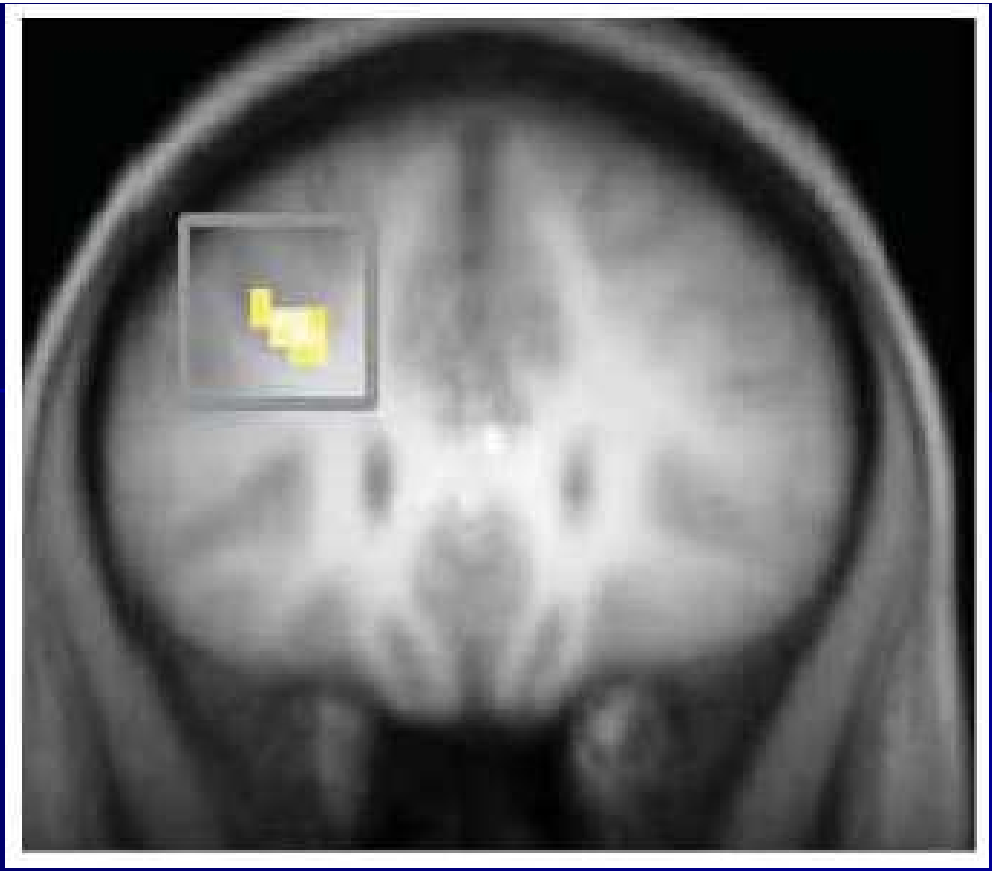


Figure 4. Activation in a region of the dorsolateral prefrontal cortex (DLPFC) (Montreal Neurological Institute coordinates x, y, z: −27, 27, 36; z=3.72; falsediscovery rate–corrected P=.007) during anticipatory food reward (milkshake cue vs tasteless solution cue) in the high food addiction (FA) group vs the low FAgroup, with the bar graphs of parameter estimates (PE) from that peak.

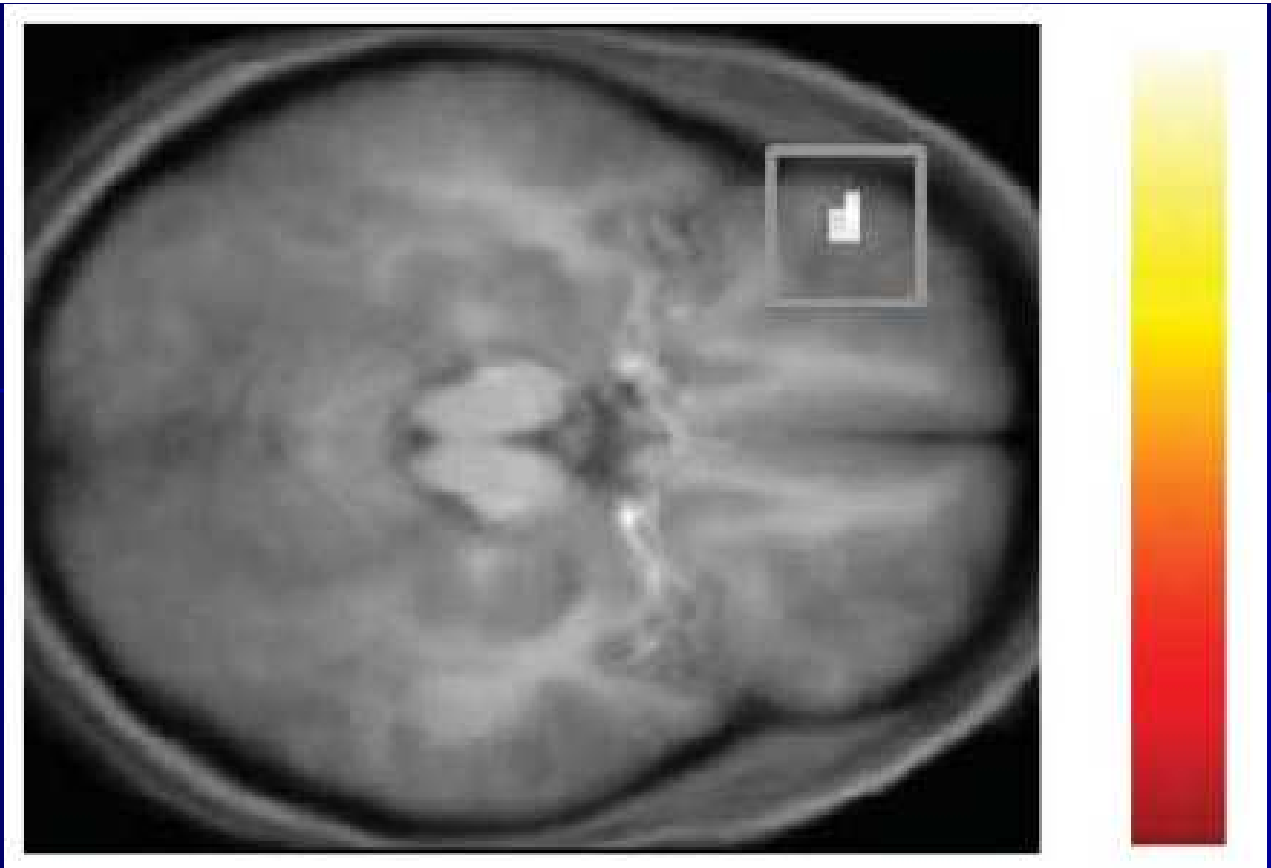


Figure 6. Activation in a region of the lateral orbitofrontal cortex (Montreal Neurological Institute coordinates x, y, z: −42, 42, −12; z=−3.45; false discoveryrate–corrected P=.009) during consummatory reward (milkshake receipt vs tasteless solution receipt) in the high food addiction (FA) group vs the low FA group, with the bar graphs of parameter estimates (PE) from that peak.

- La extirpación de la amigdala anula la atracción por las características del alimento ej. Aroma
- Dopamina proveniente del cerebro mesolímbico produce efecto hedónico
- Ghrelina refuerza mientras que insulina y leptina inhiben el deseo

- **Algunos individuos reaccionan con más impulsividad ante ciertos alimentos (Caroline Davis)**
- **Los opioides promueven los alimentos de alta densidad energética estimulan el deseo y lentifican la saciedad**
- **La amigdala recibe múltiples estímulos tales como textura, aromas, sabores, temperatura y controles de las hormonas peptídicas intestinales.(su lesión quita estimulo de los alimentos muy calóricos y las ganas de fumar)**

- La lesión del área prefrontal o su atrofia produce hiperfagia a veces con preferencia por alimentos más elaborados (síndrome del gourmand)
- La hiperactividad (epilepsia) provoca un símil anorexia nerviosa que cede con la terapia anticonvulsivante
- El área prefrontal derecha elige mejor los alimentos cuanto mayor es su desarrollo. Los obesos desarrollan más el hemisferio izquierdo,
- También influye en la percepción de la imagen corporal.
- La disfunción del area prefrontal derecha por atrofia provoca incremento de la alimentación, sobretodo fast food

Modelo cerebral de la obesidad humana

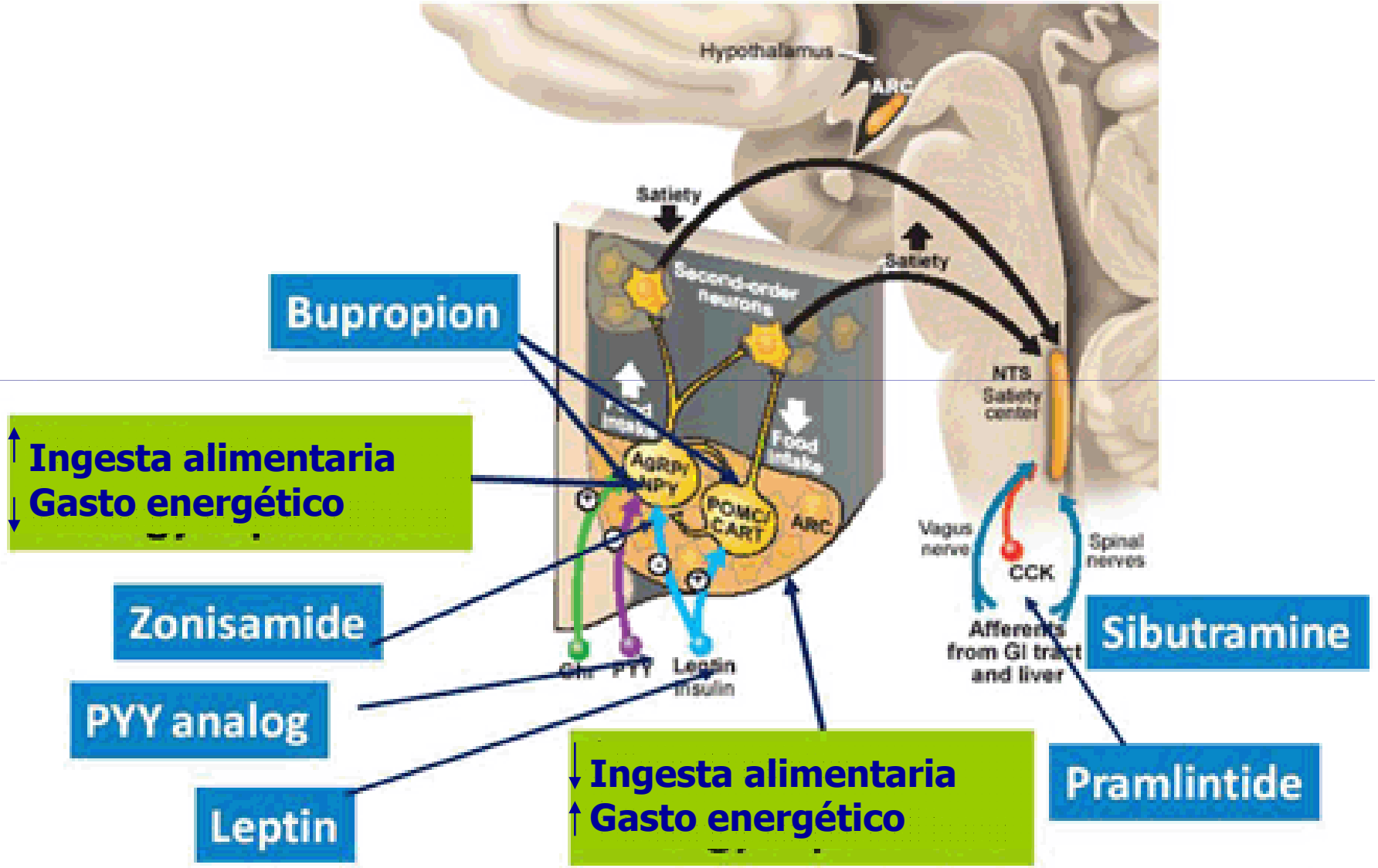
- La alimentación en los humanos se puede dividir en refleja o reflexiva
- La refleja depende de los circuitos neurohipotalámicos y de los neuropéptidos que controlan el apetito y la saciedad.
- Por encima se ubica la reflexiva que involucra conductas relacionadas con criterios sociales y culturales.

  Cultura del alimento sano, de la figura esbelta, etc.

Mecanismo hipotético de "Alimentación Progresiva" para generar un continuo Incremento de peso

Wang J, et al. *Diabetes*. 2001;50(12):2786-2791; DiMarzo V, personal communication.

El futuro: Tratamientos combinados



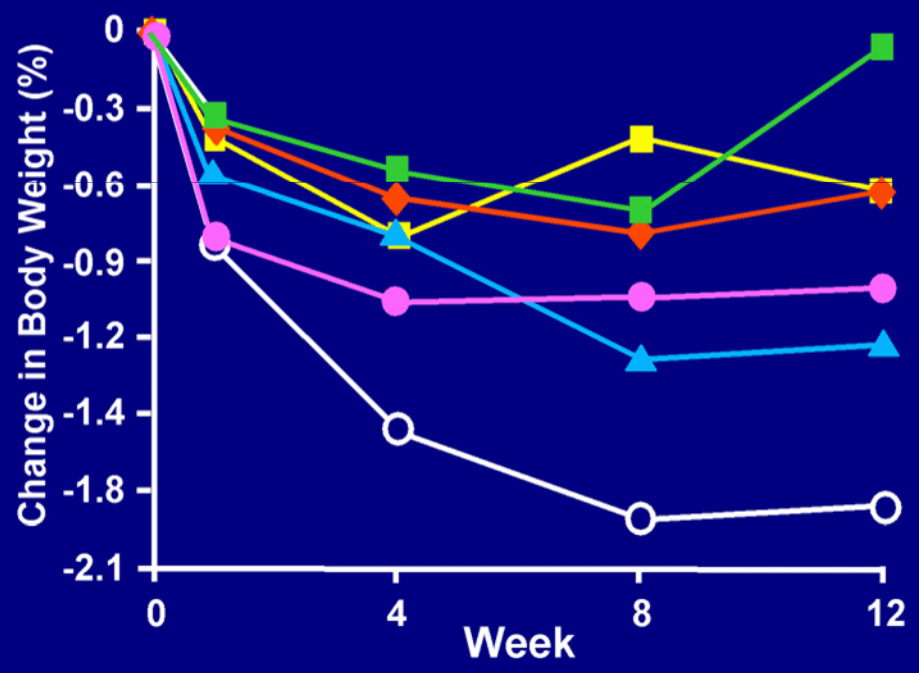
Marx J . *Science*. 2003;299:846-849. Illustration by Katharine Sutliff.

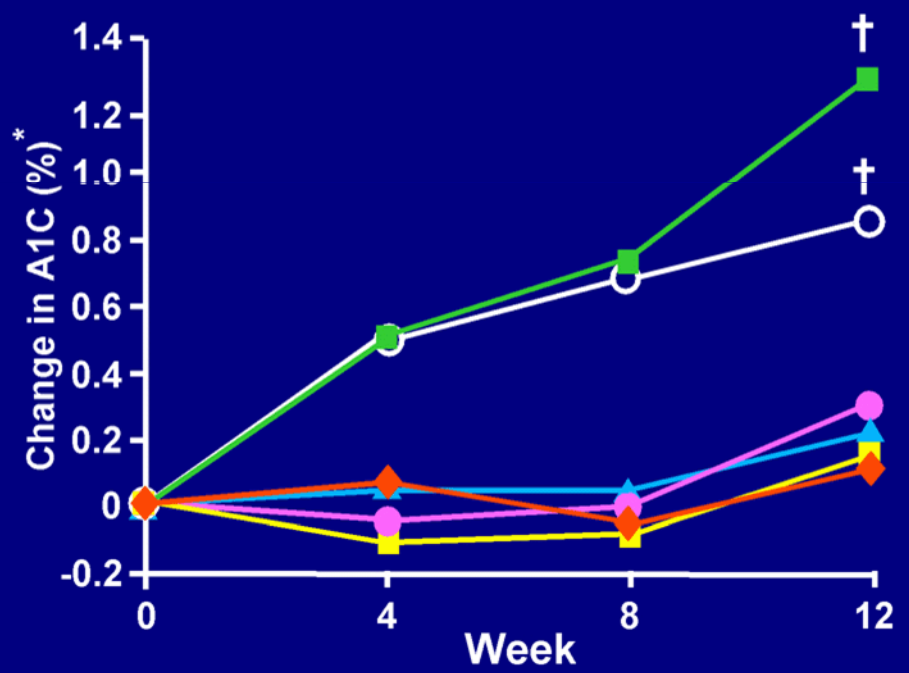
¡Gracias por haberme escuchado!

Liraglutide Effects on Glycemic Control and Body Weight

Liraglutide (qd) ■ 0.045 mg ○ 0.225 mg ▲ 0.45 mg ■ 0.60 mg ● 0.75 mg

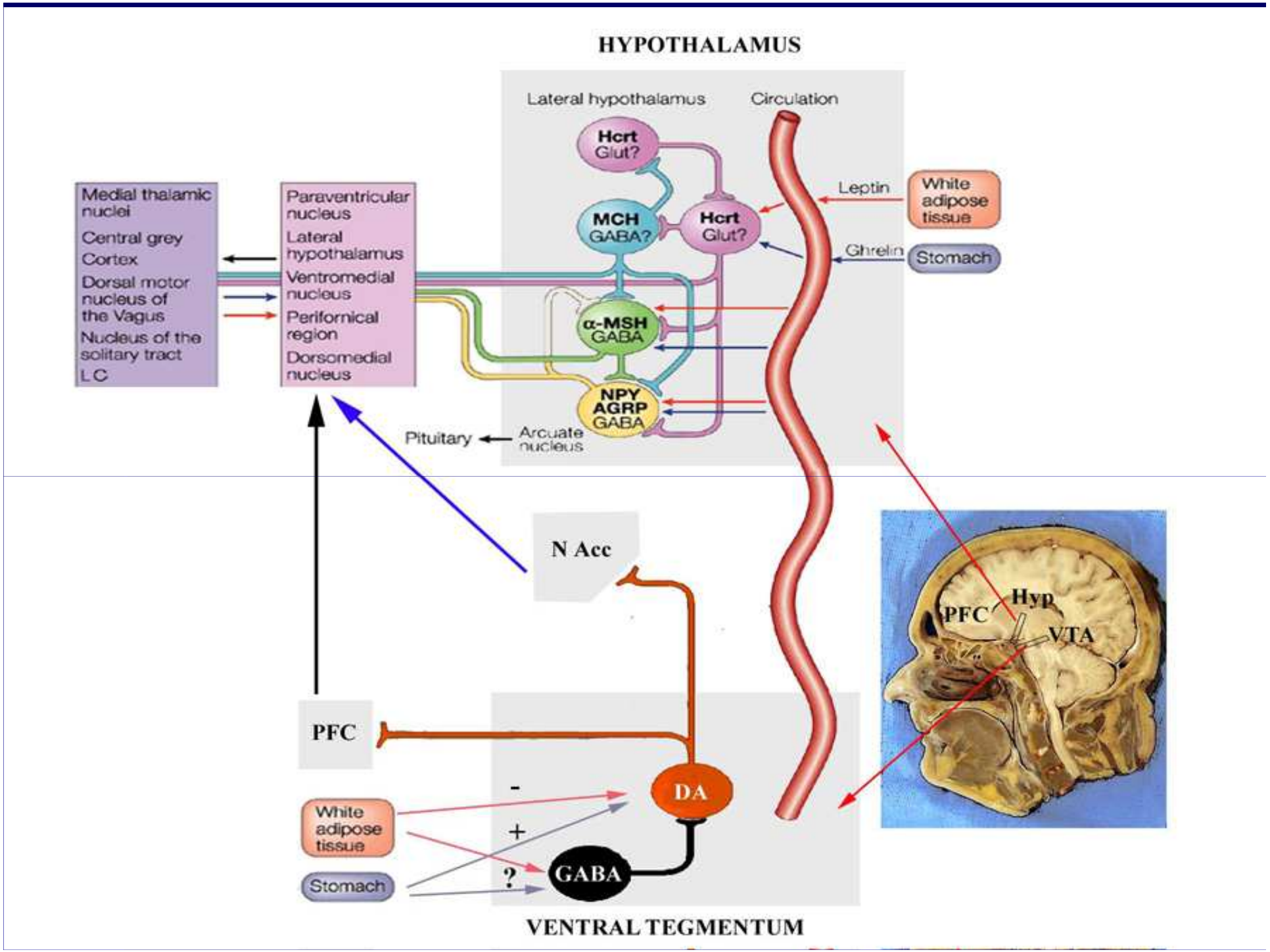
Metformin ◆ 1,000 mg bid





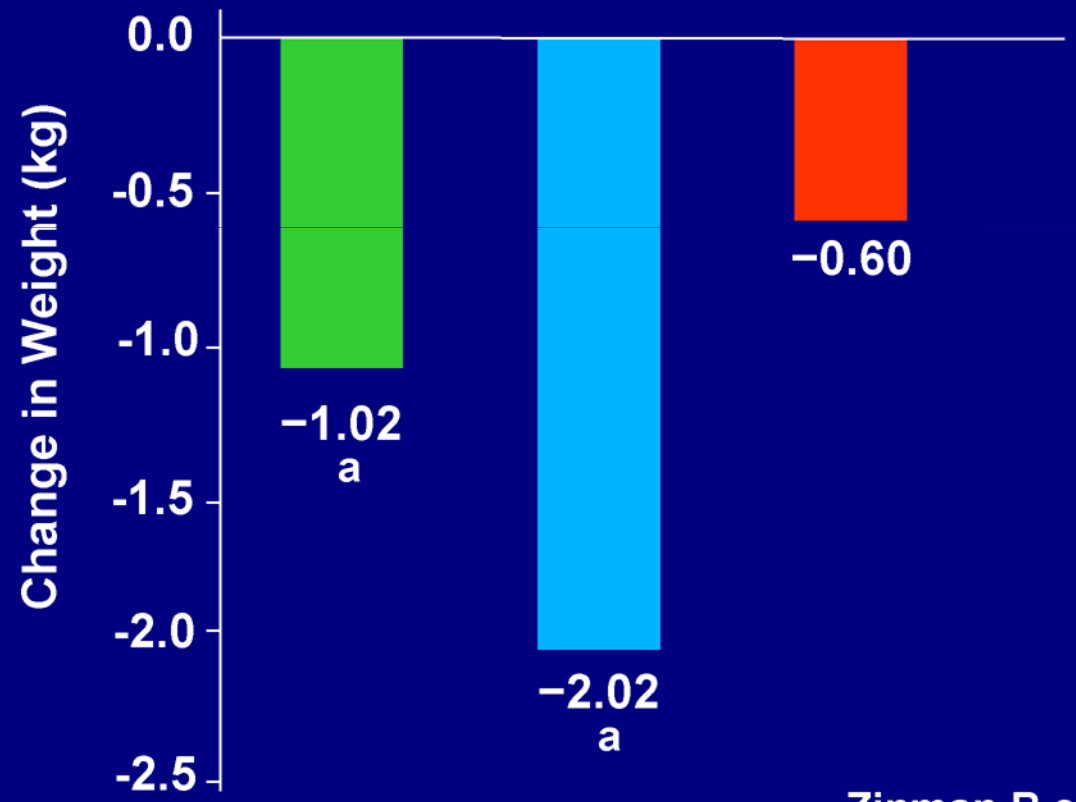
*Mean baseline A1C for all groups: 6.8% to 7.5%.
†Significant difference compared to metformin.

Feinglos MN et al. *Diabet Med*. 2005;22:1016-1023.


HYPOTHALAMUS
Lateral hypothalamus
Circulation
Hcrt
Glut?
MCH
GABA?
Hcrt
Glut?
α-MSH
GABA
NPY
AGRP
GABA
Leptin
White adipose tissue
Ghrelin
Stomach
Medial thalamic nuclei
Central grey
Cortex
Dorsal motor nucleus of the Vagus
Nucleus of the solitary tract
LC
Paraventricular nucleus
Lateral hypothalamus
Ventromedial nucleus
Perifornical region
Dorsomedial nucleus
Pituitary
Arcuate nucleus
N Acc
PFC
Hyp
VTA
PFC
DA
GABA
White adipose tissue
Stomach
-
+
?
VENTRAL TEGMENTUM

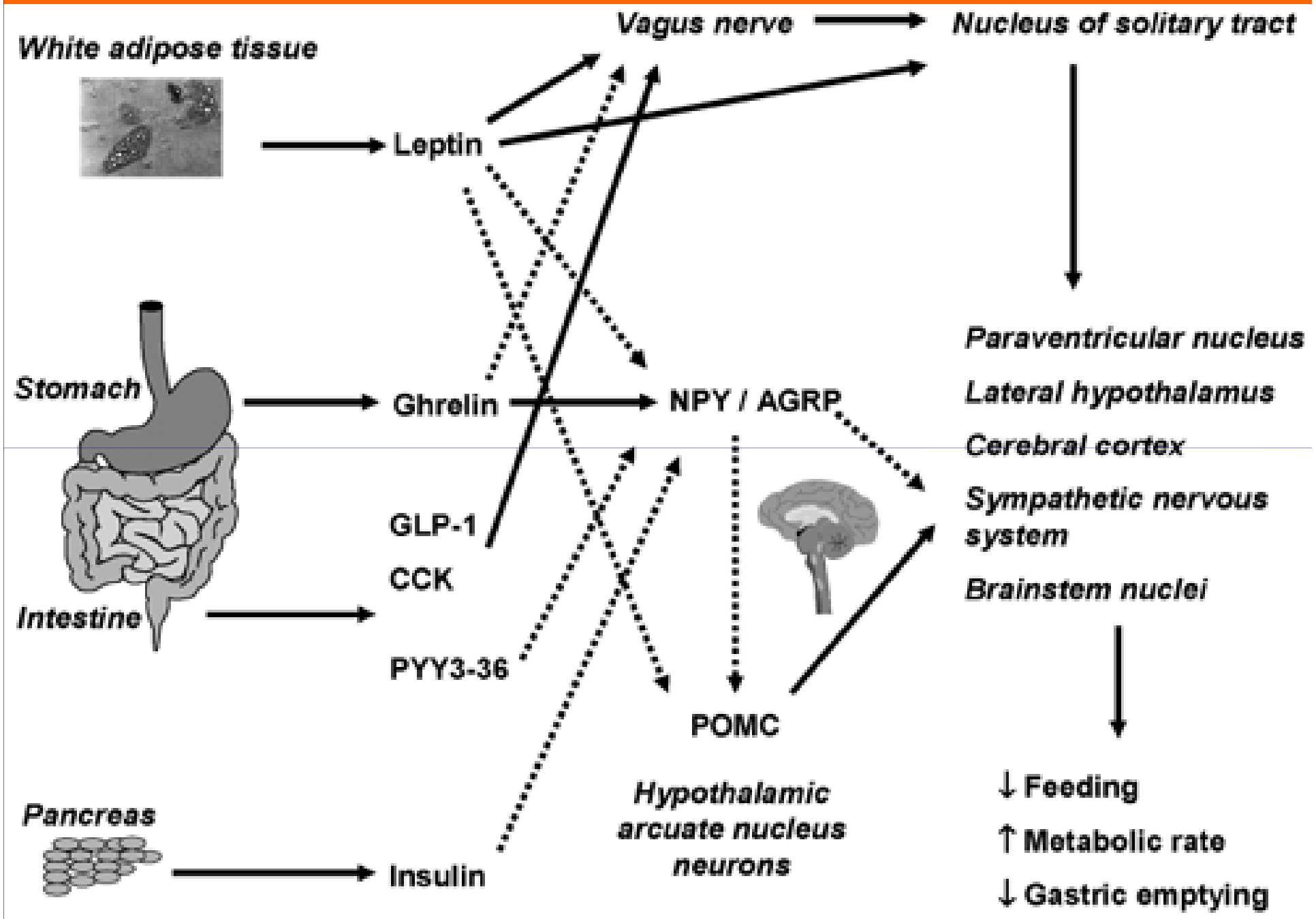
LEAD-4: Effect of Liraglutide in Combination With Metformin and Rosiglitazone on Body Weight in Patients With Type 2 Diabetes

- Liraglutide (1.2 mg/qd) + metformin (1 g/bid) + rosiglitazone (4 mg/bid) (n=178)
- Liraglutide (1.8 mg/qd) + metformin (1 g/bid) + rosiglitazone (4 mg/bid) (n=178)
- Placebo + metformin (1 g/bid) + rosiglitazone (4 mg/bid) (n=177)



Zinman B et al. *Diabetologia*. 2008;51(suppl 1):Poster 898.

[a] $P<0.05$ vs placebo.

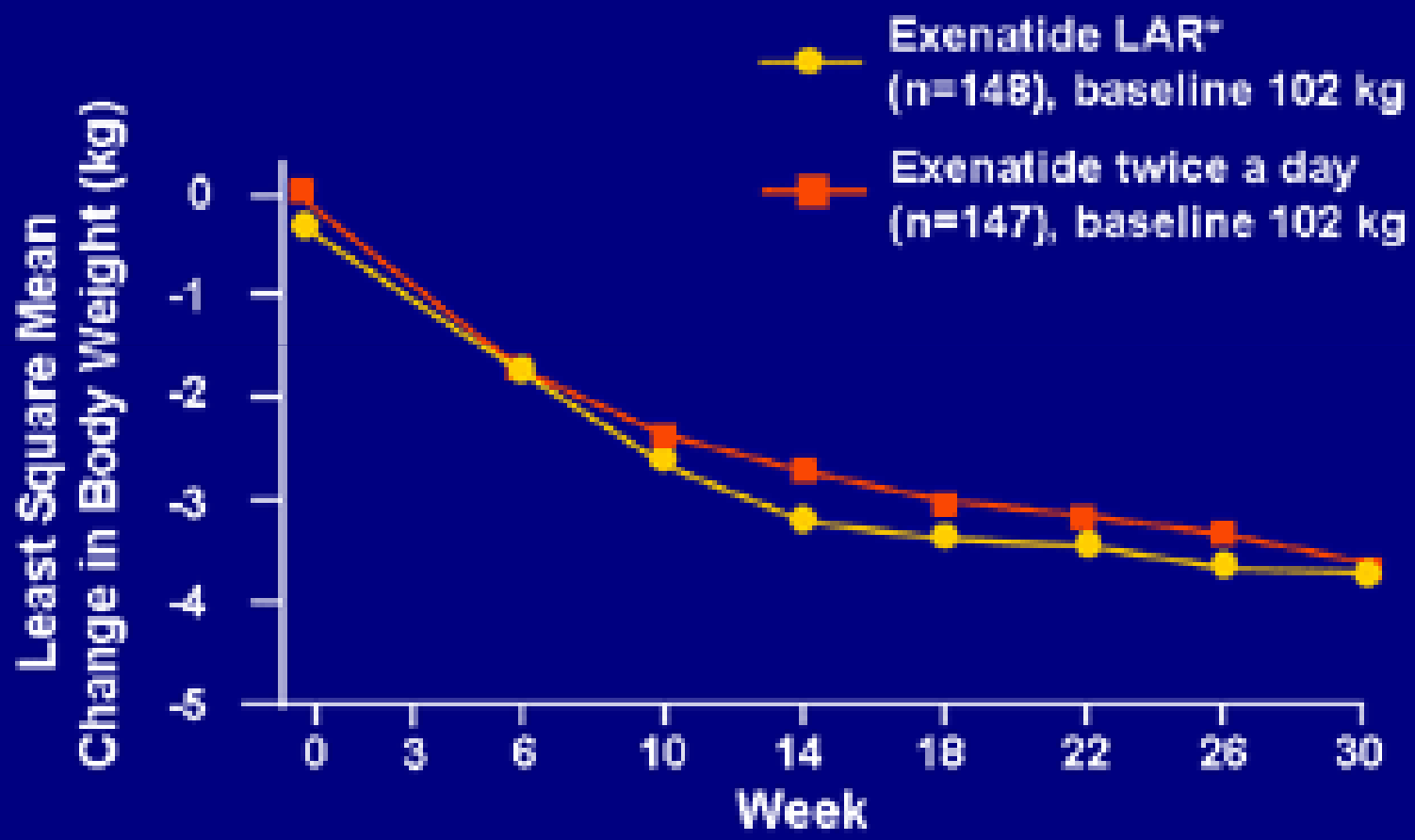

White adipose tissue
Leptin
Vagus nerve
Nucleus of solitary tract
Stomach
Ghrelin
NPY / AGRP
Paraventricular nucleus
Lateral hypothalamus
Cerebral cortex
Sympathetic nervous system
Brainstem nuclei
GLP-1
CCK
Intestine
PYY3-36
POMC
Hypothalamic arcuate nucleus neurons
Pancreas
Insulin
↓ Feeding
↑ Metabolic rate
↓ Gastric emptying

Glucagon-Like Peptide-1

- Secreted from intestinal L-cells with meal ingestion
- In humans and animals
  - enhances glucose-stimulated insulin release
  - decreases glucagon release
  - slows gastric emptying
  - reduces food intake
- In animals and in vitro
  - increases insulin gene transcription
  - increases β-cell mass and β-cell differentiation

Drucker DJ. *Curr Pharm Des.* 2001;7:1399-1412.
Drucker DJ. *Mol Endocrinol.* 2003;17:161-171.

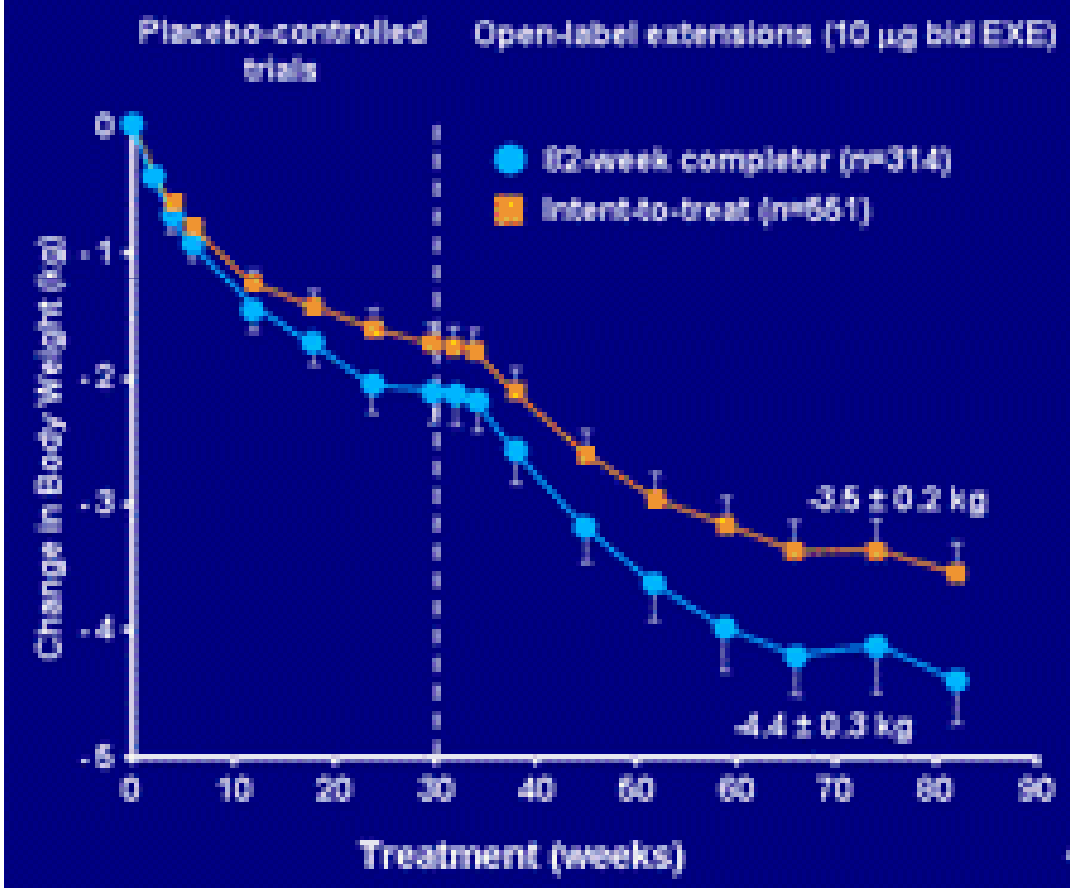
Once-Weekly vs Twice-Daily Exenatide in Type 2 Diabetes: Body Weight

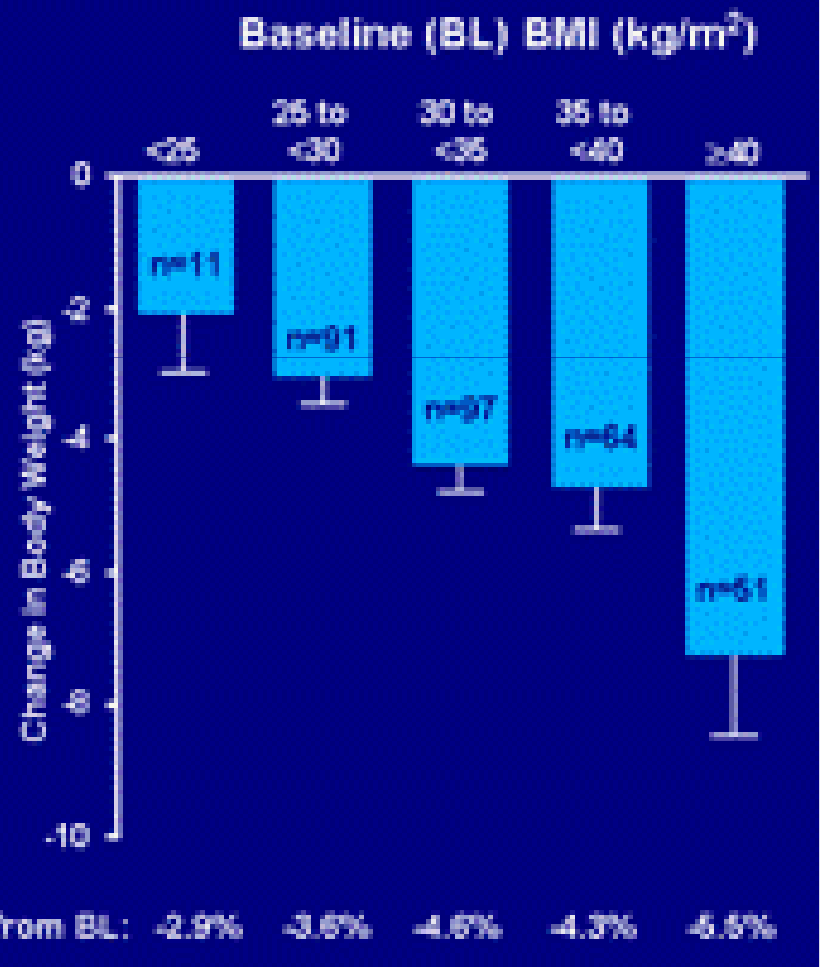


* Exenatide's once-weekly dosage is investigational. LAR=long-acting release.

Drucker DJ et al. [Published online ahead of print September 8, 2008]. Lancet. doi:10.1016/S0140-6736(08)61206-4.

Change in Body Weight Following 82 Weeks of Exenatide Treatment



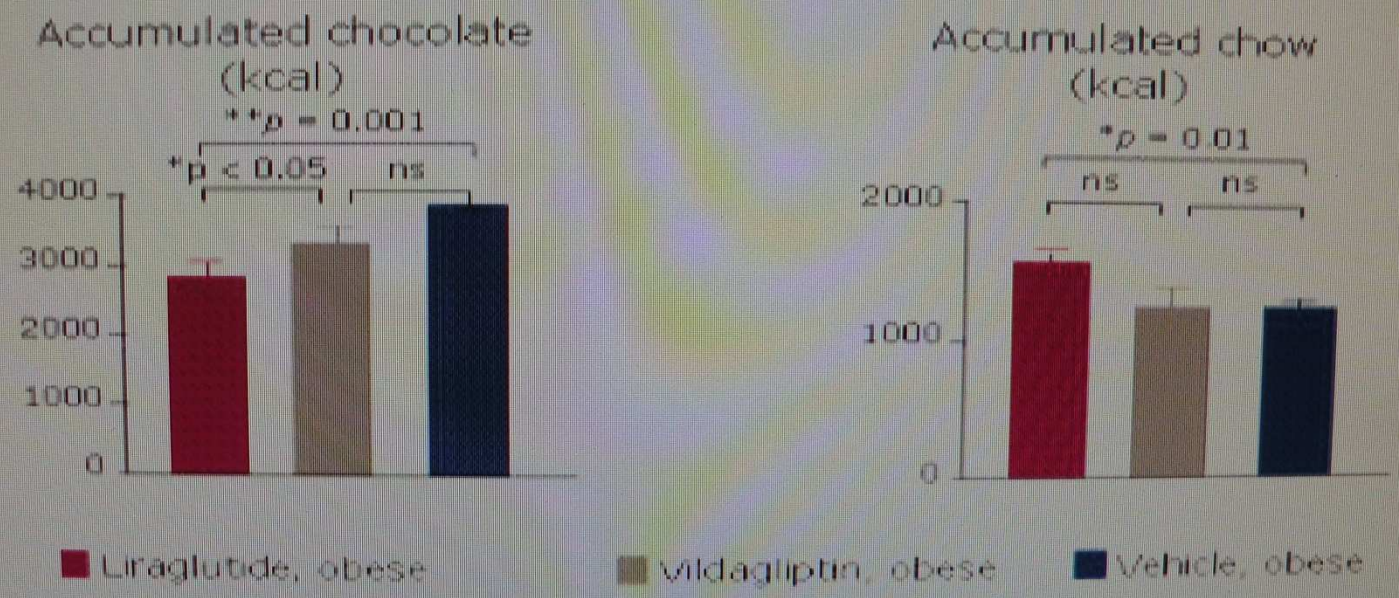


Blonde L et al. *Diabetes Obes Metab.* 2006;8:436-447.

Liraglutide

- -Una dosis diaria es efectiva
- -Posee efectos beneficiosos en la glucemia y peso corporal en pacientes
- diabéticos
- -Estimula la liberación de insulina, suprime la gluconeogénesis y provoca
- náuseas-

Liraglutide altered food preference: decreased chocolate but increased chow intake

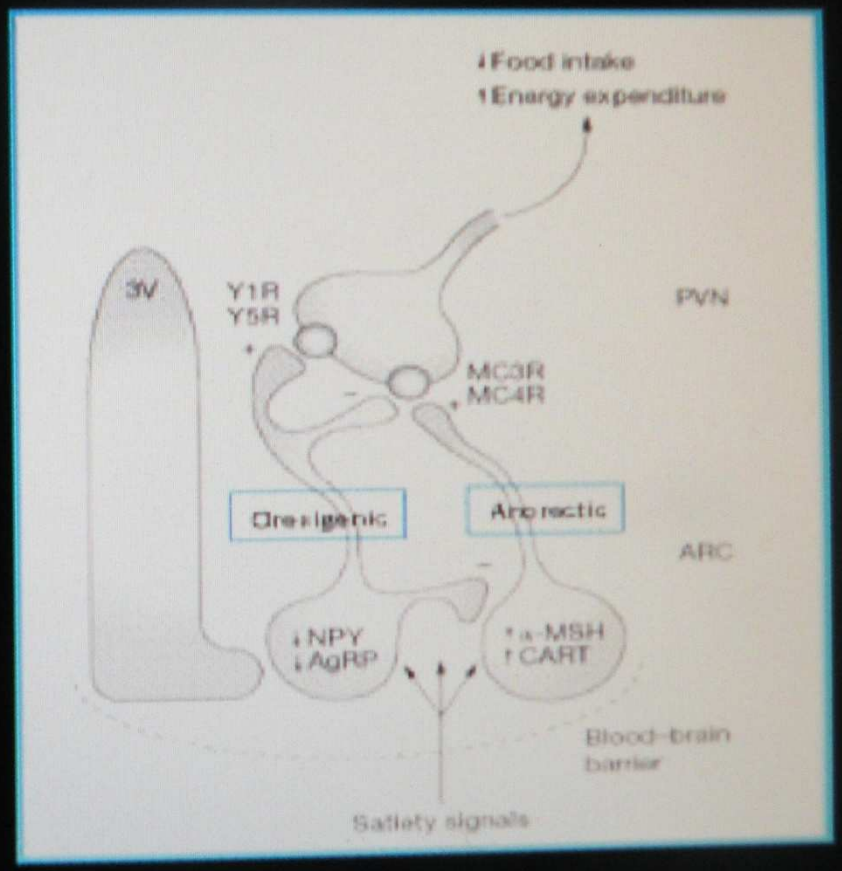


Raun, Voss, Gotfredsen, Golozoubova, Rolin & Bjerre Knudsen, Diabetes 2007;56:8-15

13.06.2009 20:55

Complementary Central Action in Obesity PYY_{3-36} and Oxyntomodulin

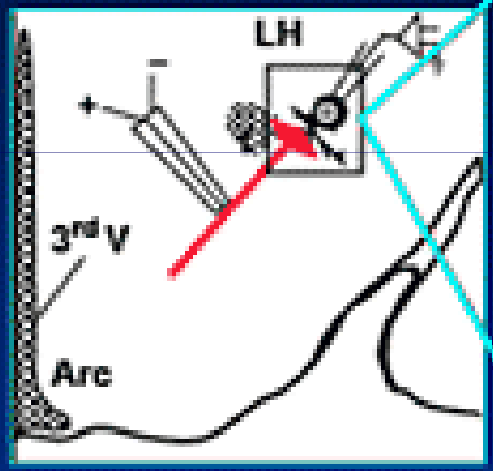
- OXM and PYY_{3-36} released post-prandially
  - Primary action → as satiety signals in hypothalamic arcuate nucleus
  - Coordinated inhibition of *orexigenic* neurons and activation of *anorectic* neurons
- Animal/human studies
  - Reduced energy intake and weight loss

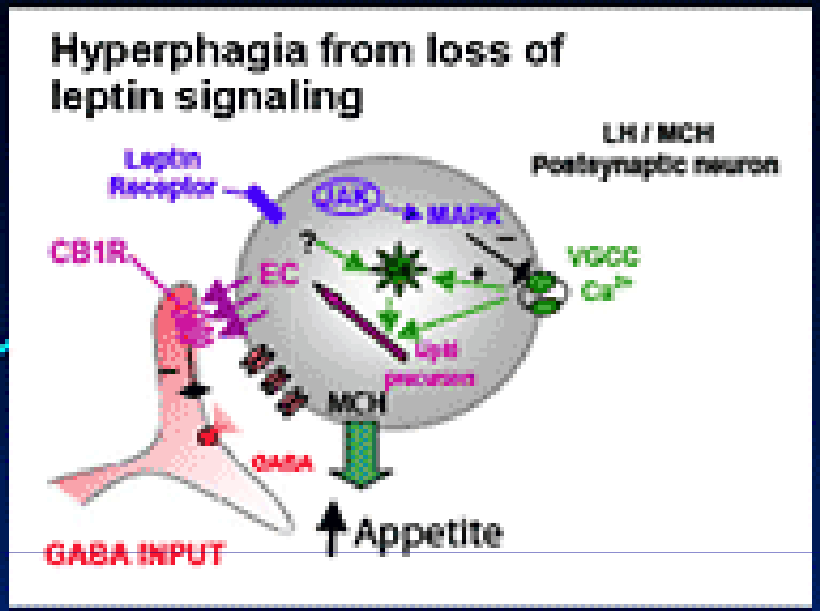


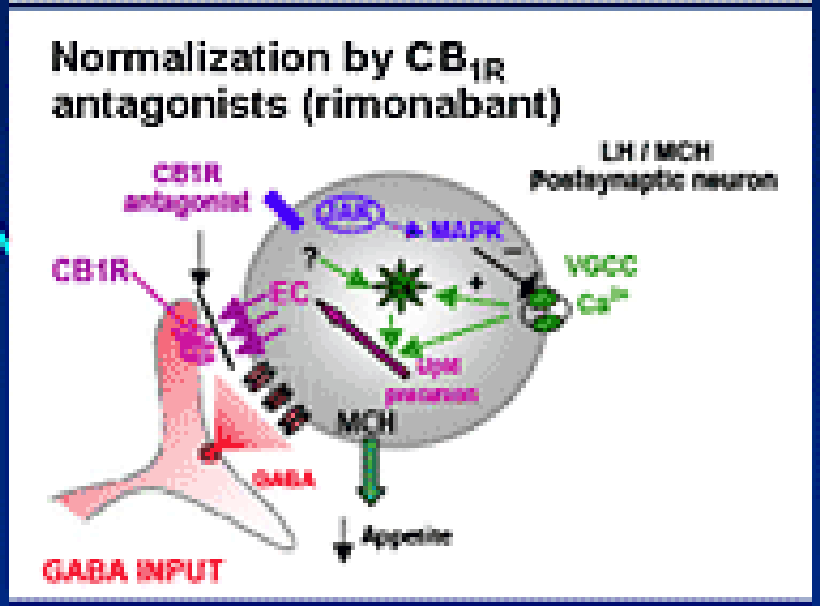
Wynne K and Bloom SR. Nature Clin Practice. 2(11):612-620, 2006

13.06.2009 15:16

Leptin/Endocannabinoid Interaction in the Lateral Hypothalamus

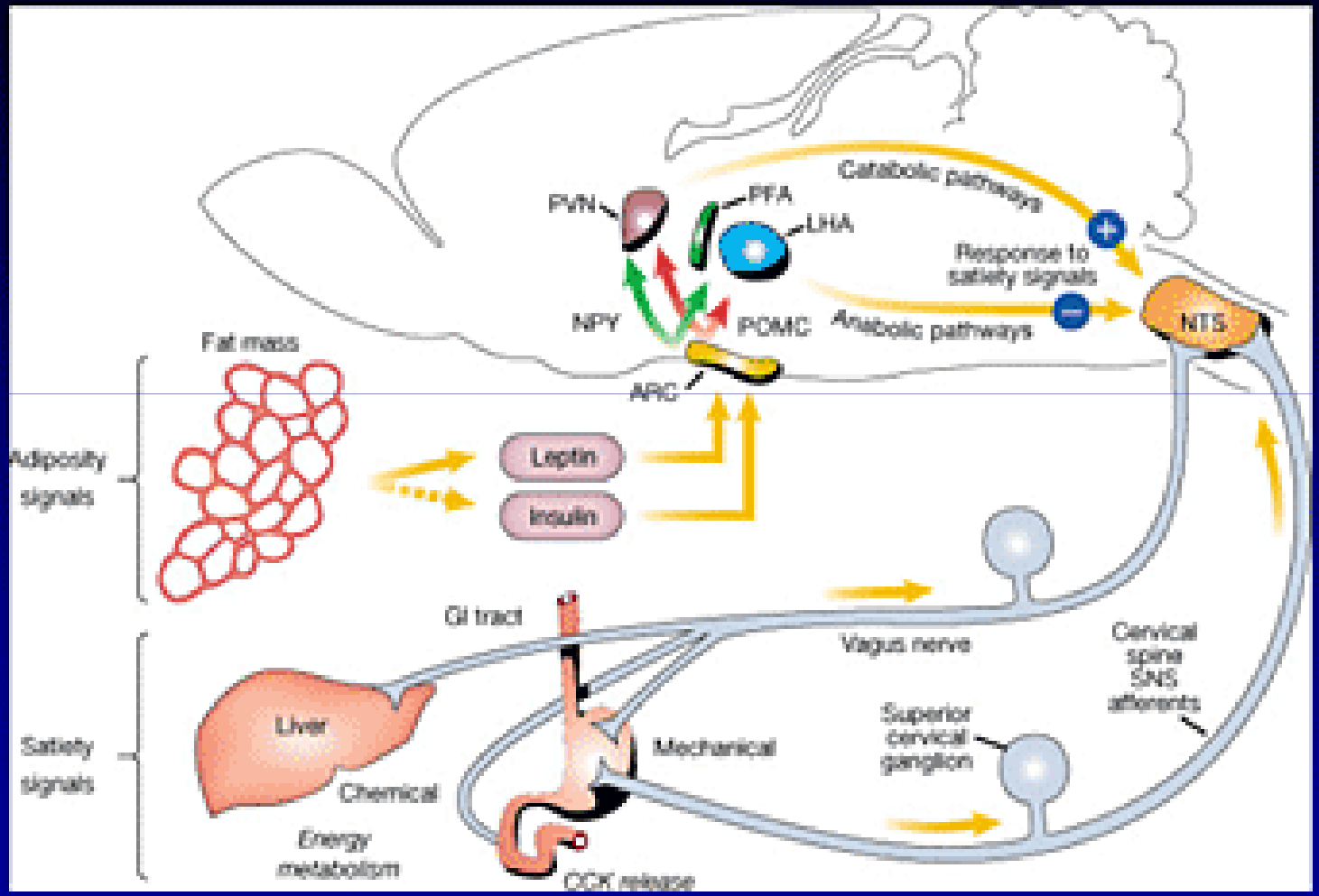






Reproduced from Jo YH, et al. *Neuron*. 2005;48:1055-1066.

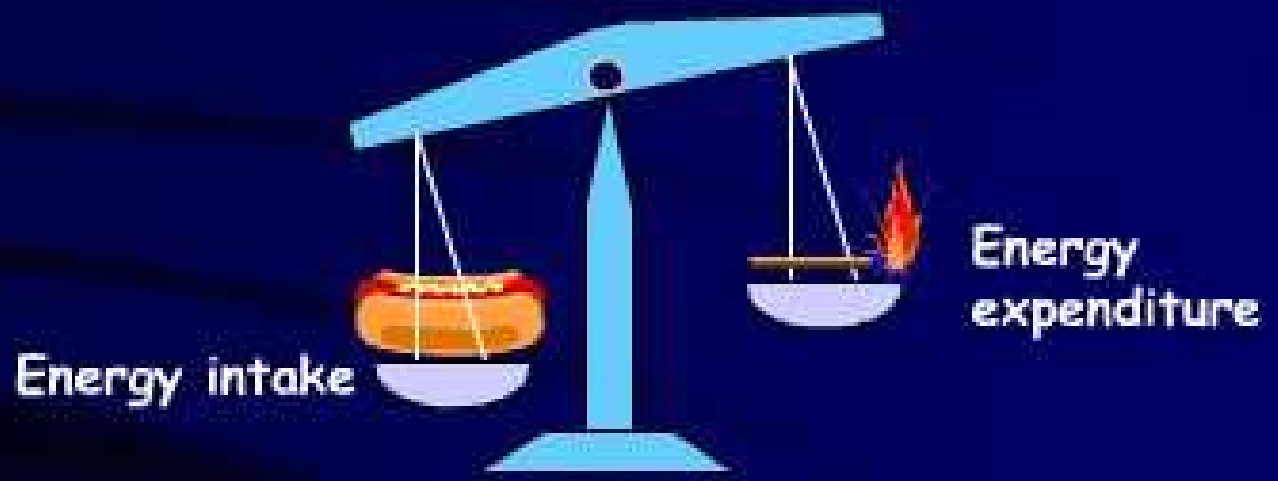
The control system over caloric homeostasis is complex, relying upon several types of signals



Schwartz MW, et al. *Nature*. 2000;404:661-671.

How does the body control its own weight?

1 ton of food = 1 million calories in 1 year

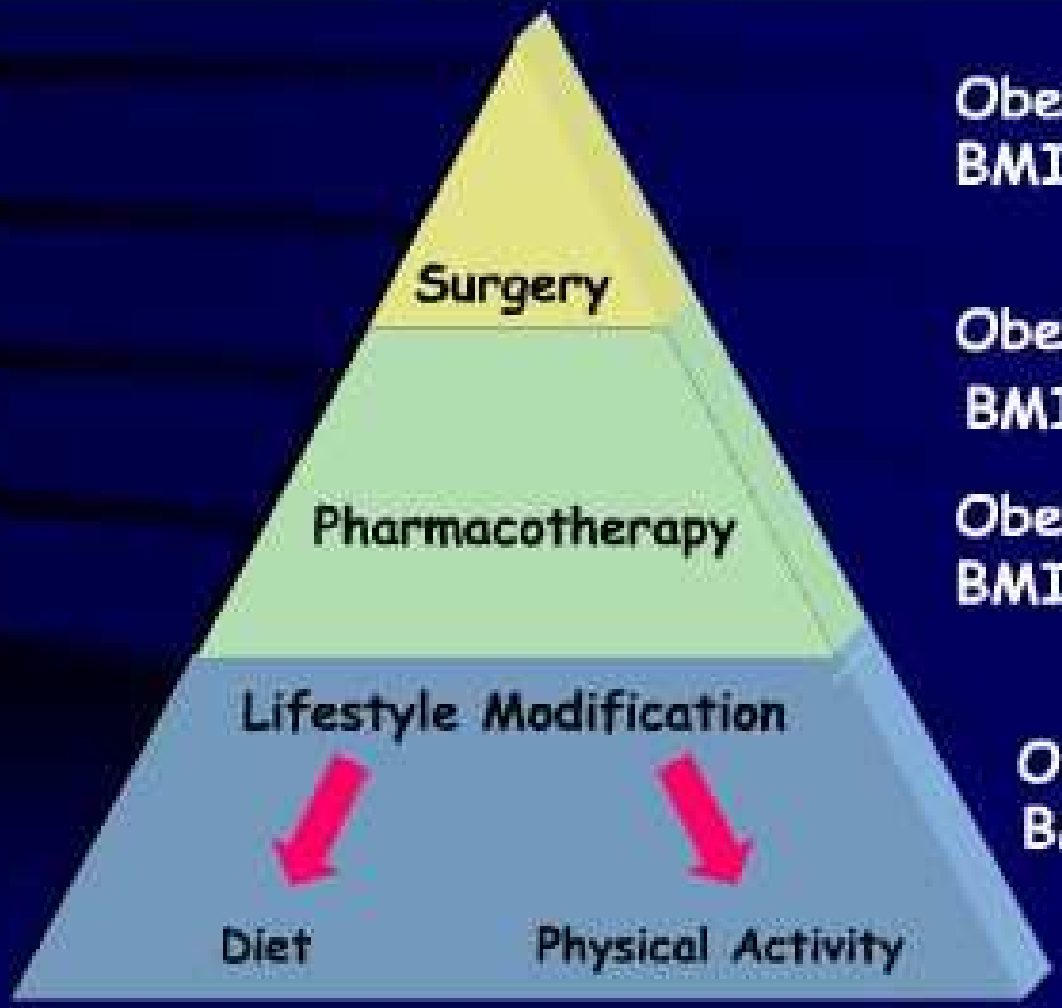


Genetics and Environment

Sweet, high fat foods
Hormones to suppress appetite
Storing fat; energy expenditure

Alcohol; smoking
Excess calories
Physical inactivity

Obesity Treatment Pyramid



Obese Class 3
BMI ≥ 40 kg/m²

Obese Class 2
BMI ≥ 35 kg/m²

Obese Class 1
BMI ≥ 30 kg/m²

Overweight
BMI ≥ 25 kg/m²

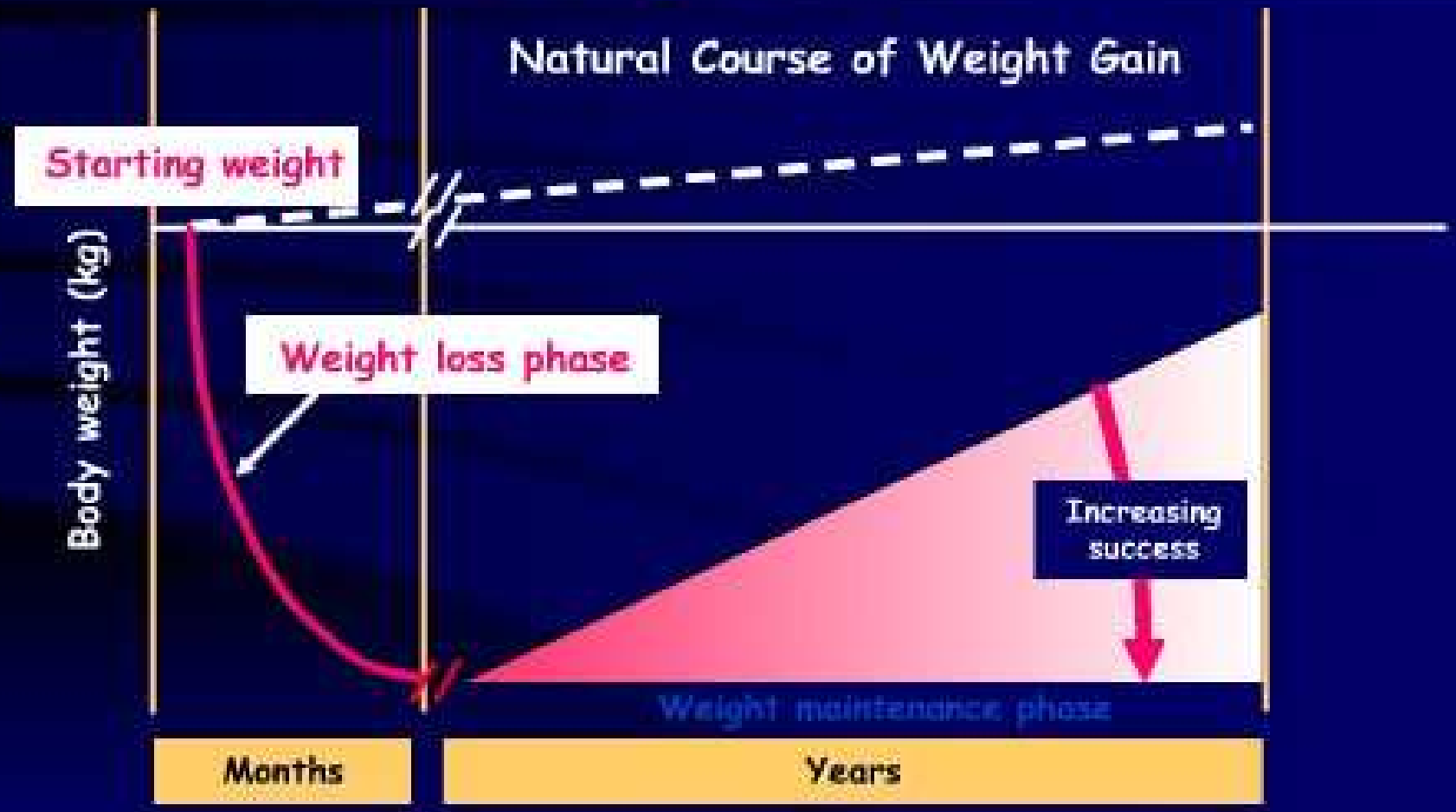
Multi-disciplinary Approach to Obesity Management

Weight Management Care Team

Optimal Weight Loss Goals

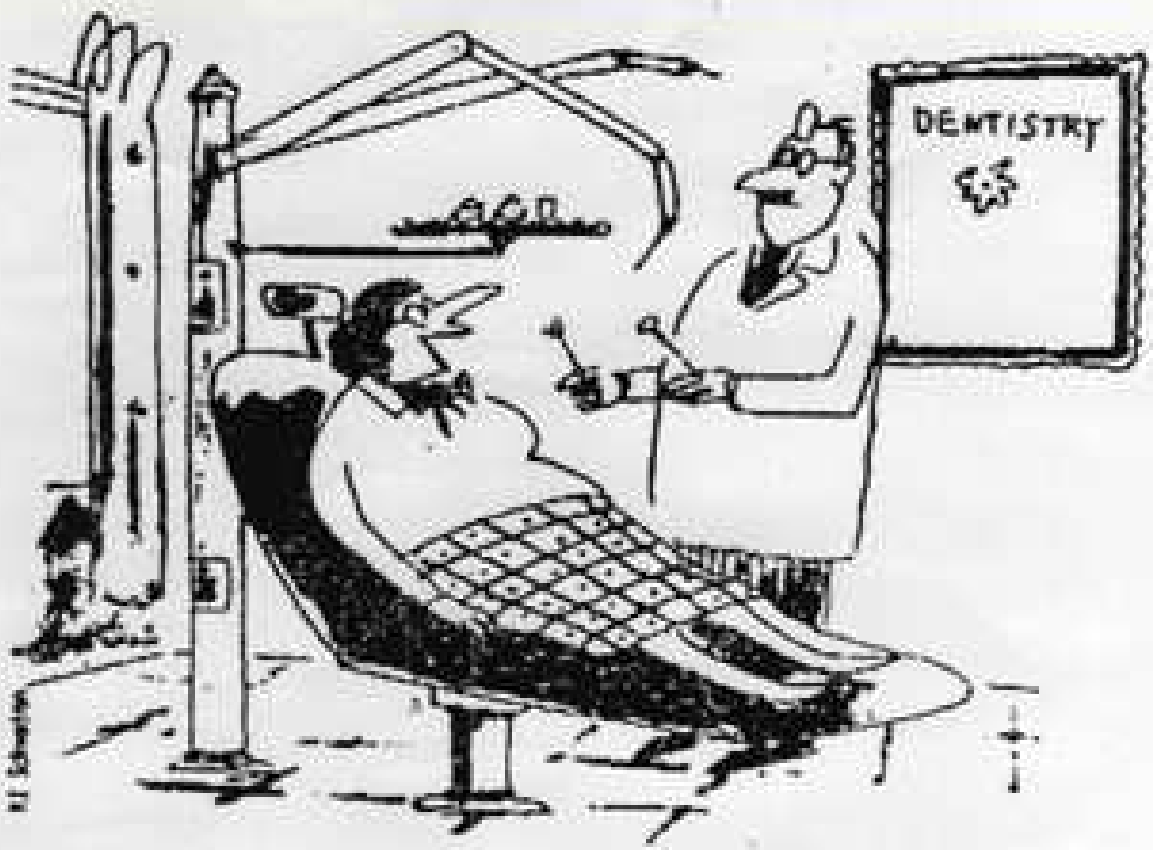
- Optimal rate of weight loss is 1-2 kg, or 2-4 pounds, a month.
- Aim for a deficit of 500 kcal/day to achieve a weight loss of a pound (or 3500 kcal) a week
- A 500 kcal deficit diet would amount to approximately 20-30% decrease in average daily food intake

What is Success in Weight Management?



Age-related Weight Gain Cannot Be Prevented Despite Continued Intervention Efficacy

No quick fixes!

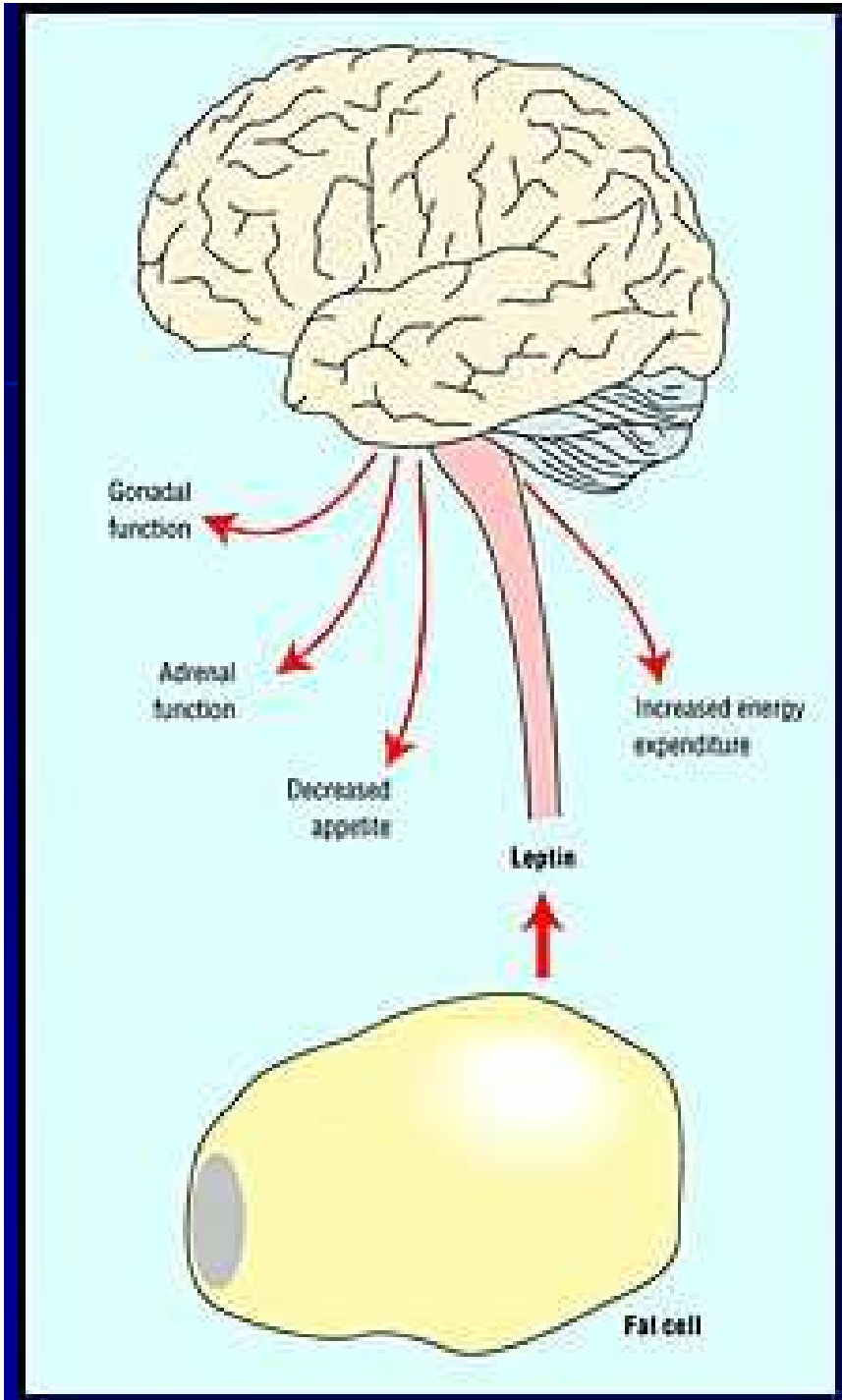


"Just pull my sweet tooth"

Source: 1989 H.L. Schwadron

Novel Anti-obesity Drugs

- Appetite suppressants that target
  - Leptin (recombinant leptin)
  - Neuropeptide Y
  - Melanocortin-4 receptor
  - Cannabinoid receptors (CB1 antagonist-rimonabant)
  - Dopamine (ecopipam)
- Ghrelin antagonist
- PYY3-36
- Ciliary nueroptrophic factor – Axokine
- Selective β_3 adrenergic receptor agonists to increase energy expenditure
- Fat mobilization via lipolysis, inhibitors of fat digestion and absorption
- Nutrient partitioning to favour lean body mass



Is leptin the brain signal?

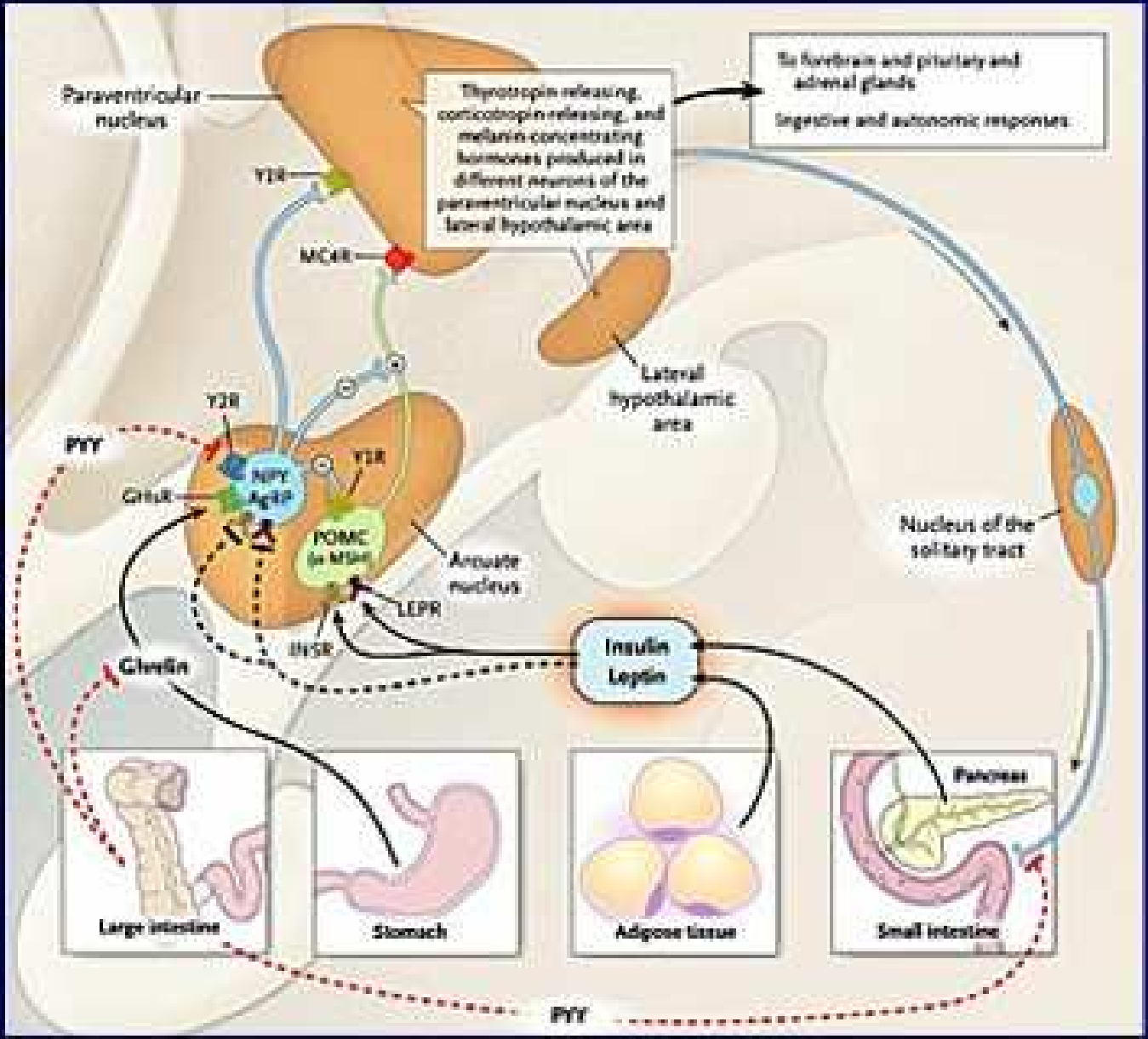
Leptin is a fat-derived lipostat signaling hormone

Recombinant Leptin Therapy

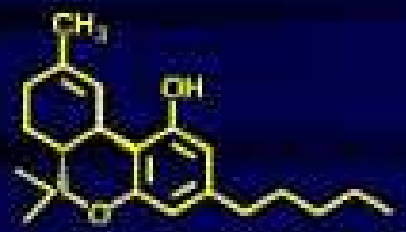
- Randomized, double-blind, placebo-controlled trial in 54 lean and 73 obese adults (BMI 30-36) for 4-24 weeks
  - Dose-dependent weight loss in obese subjects
  - 0.7 to 7.1 kg
- Antileptin antibodies present in 38% and 71% at 4 and 24 weeks
- Injection site reactions common
- Majority of obese subjects are leptin resistant!

Adapted from Heymsfield et al, JAMA 282:1568-1575, 1999

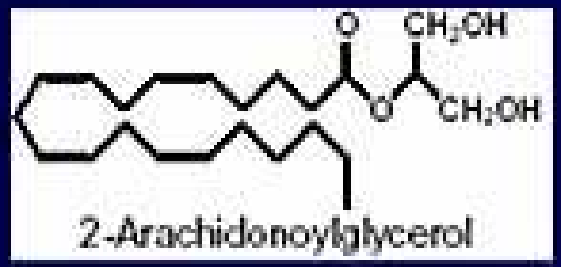
Regulation of Appetite



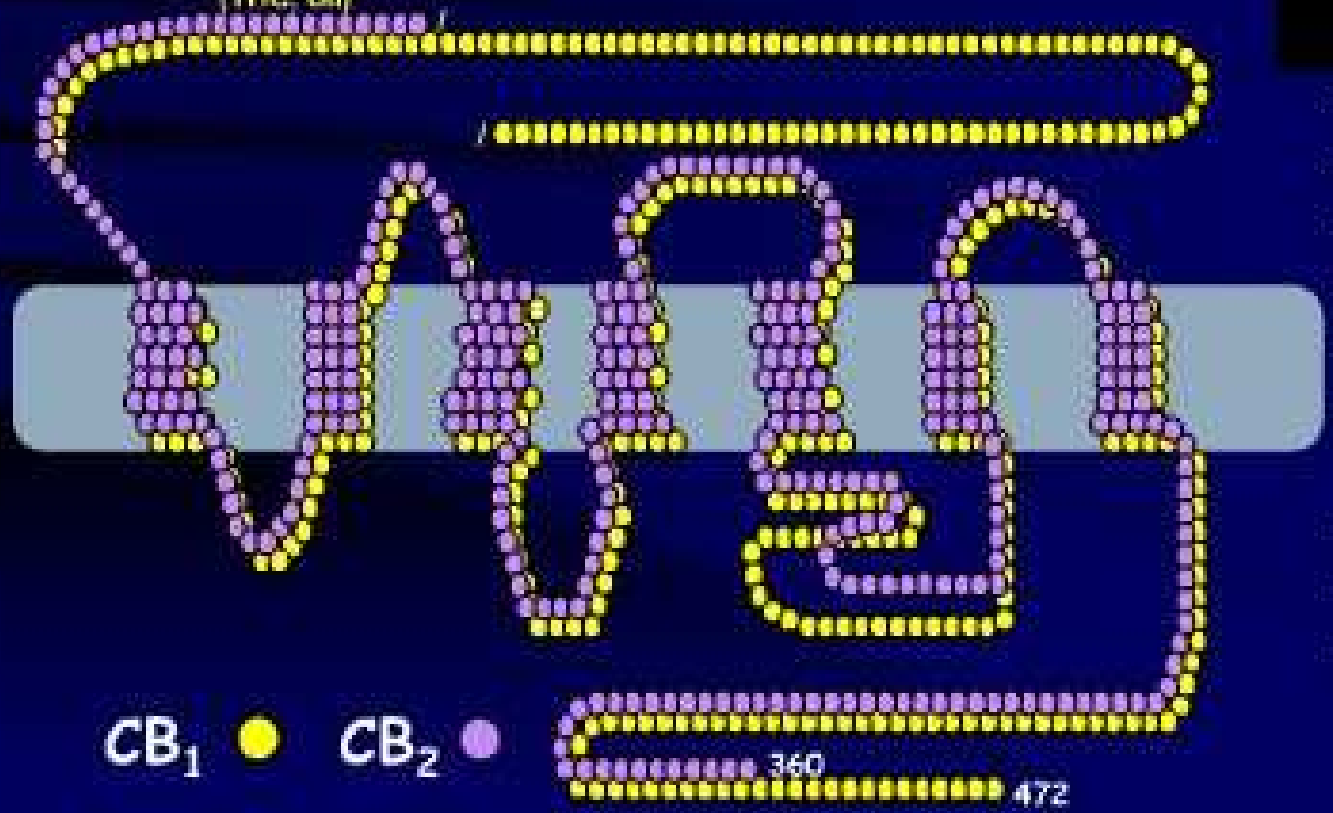
Cannabinoid Receptors



(-)-Δ9-tetrahydrocannabinol
(THC, pill)



2-Arachidonoylglycerol



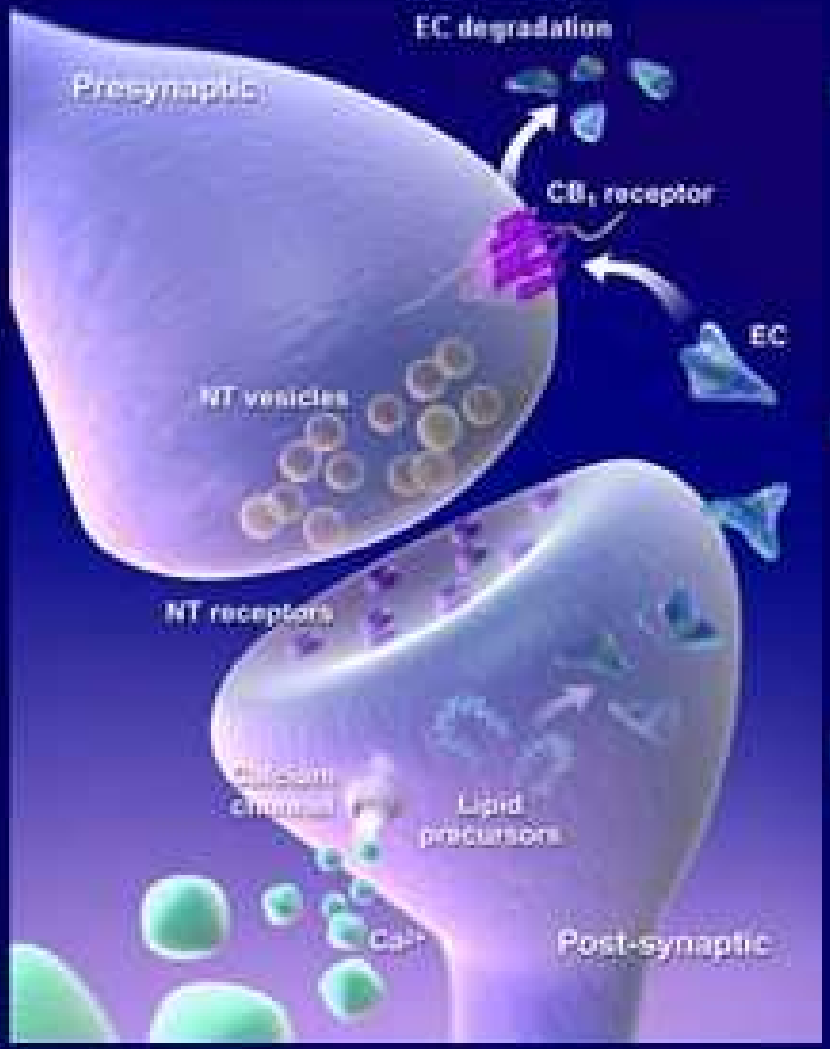
CB_1 CB_2

- Hippocampus
- Basal Ganglia
- Cortex
- Cerebellum
- Hypothalamus
- Limbic structures
- Brainstem
- GI tract
- Immune cells & tissues

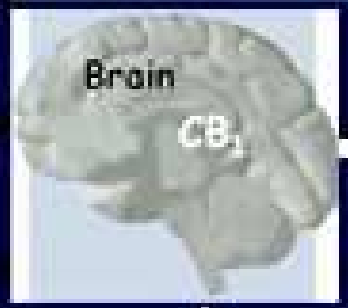
The Endocannabinoid System is a Modulatory System

- Endocannabinoids:
  - Synthesized on demand from lipid precursors in postsynaptic cell
  - Activate CB_1 receptors presynaptically, then degraded immediately
  - Act as retrograde messengers
  - Inhibit neurotransmitter release
- CB_1 receptors:
  - Play a key role in food intake, energy balance and lipid and glucose metabolism

V Di Marzo 2005
V Di Marzo 1998
R Wilson 2002



Rimonabant (CB_1 Blocker)



Central effects

↓ food intake (palatable & non-palatable food)
Control of nicotine dependence

↓ Body weight

↑ FA oxidation

↑ FFA clearance

Rimonabant

Metabolic peripheral effects

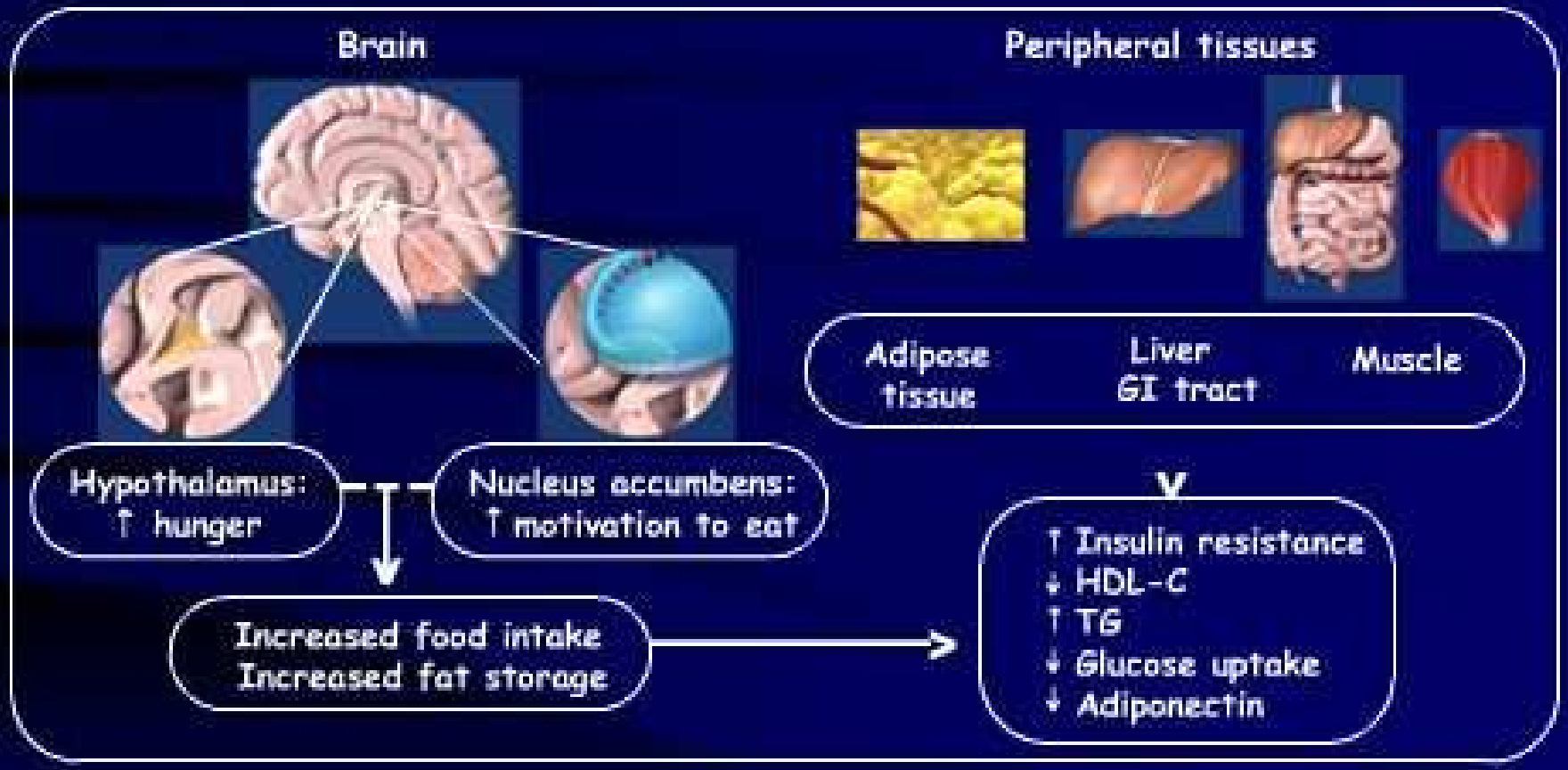
Adipocyte

CB_1

↑ Adiponectin

↓ Hyperinsulinemia
↑ Insulin sensitivity
↓ TG
↑ HDL-C

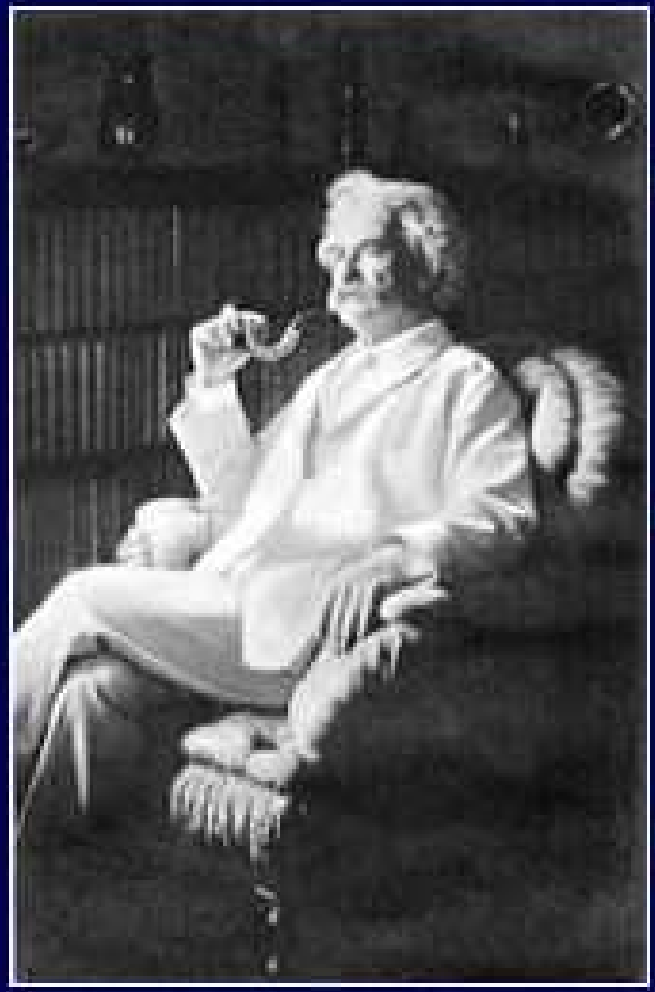
Central and Peripheral Targets of ECS and Effects of Overactivity

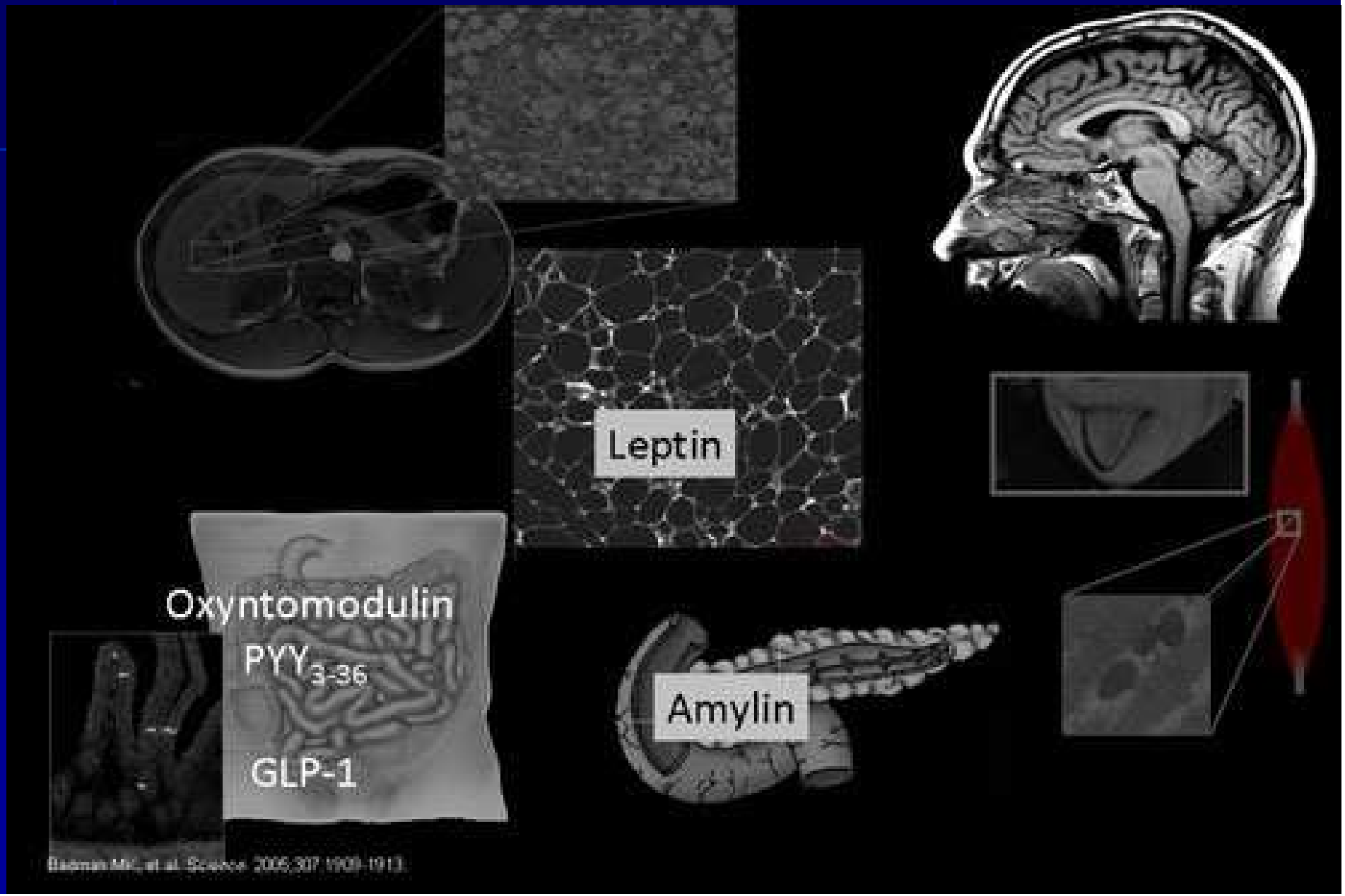


M Bensaid M 2003; U Pagotto 2005; D Osei-Hyiaman 2005; V DiMarzo 2005; YL Liu 2005

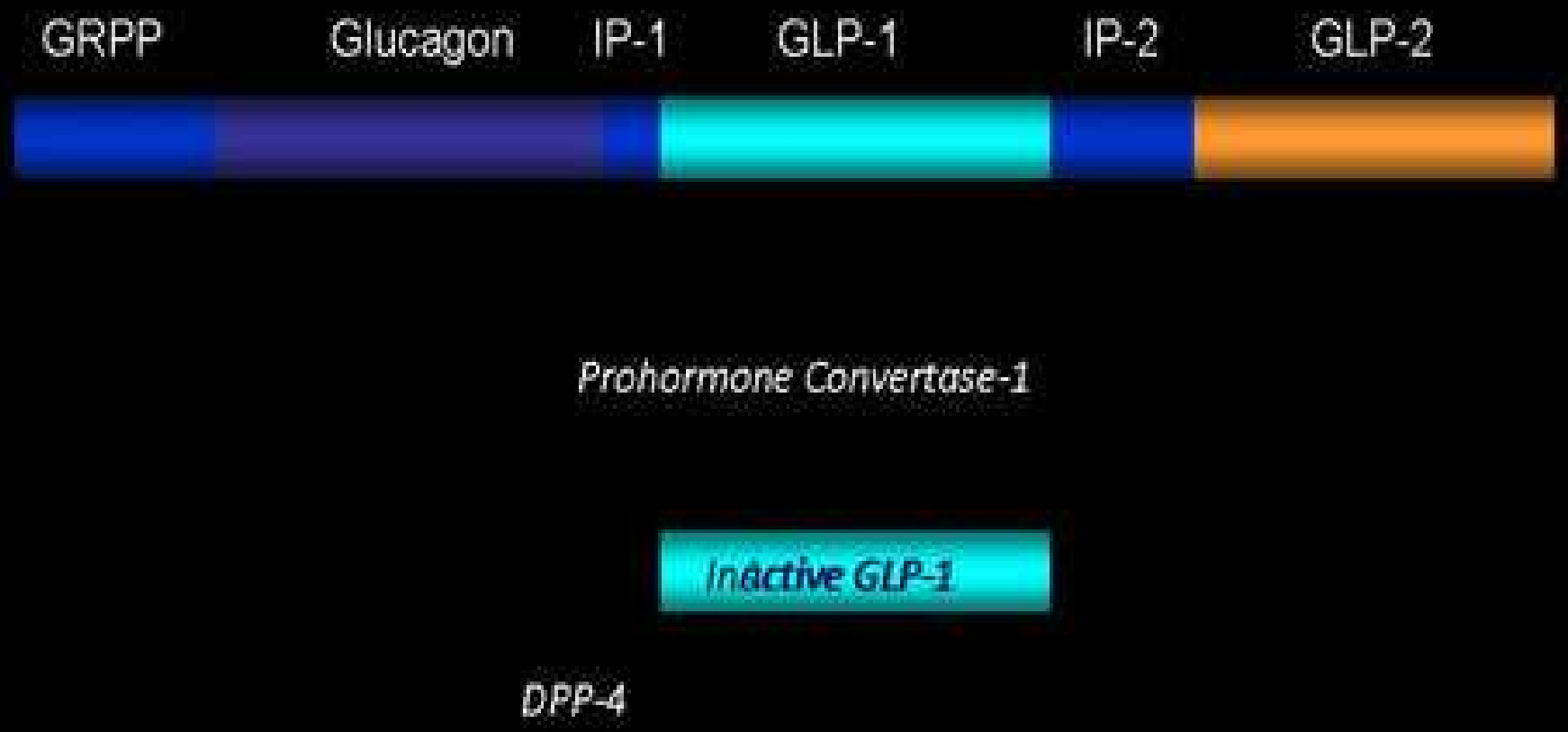
The only way to keep healthy is to eat what you don't want, drink what you don't like and do what you would rather not do

Mark Twain (1835 – 1910)



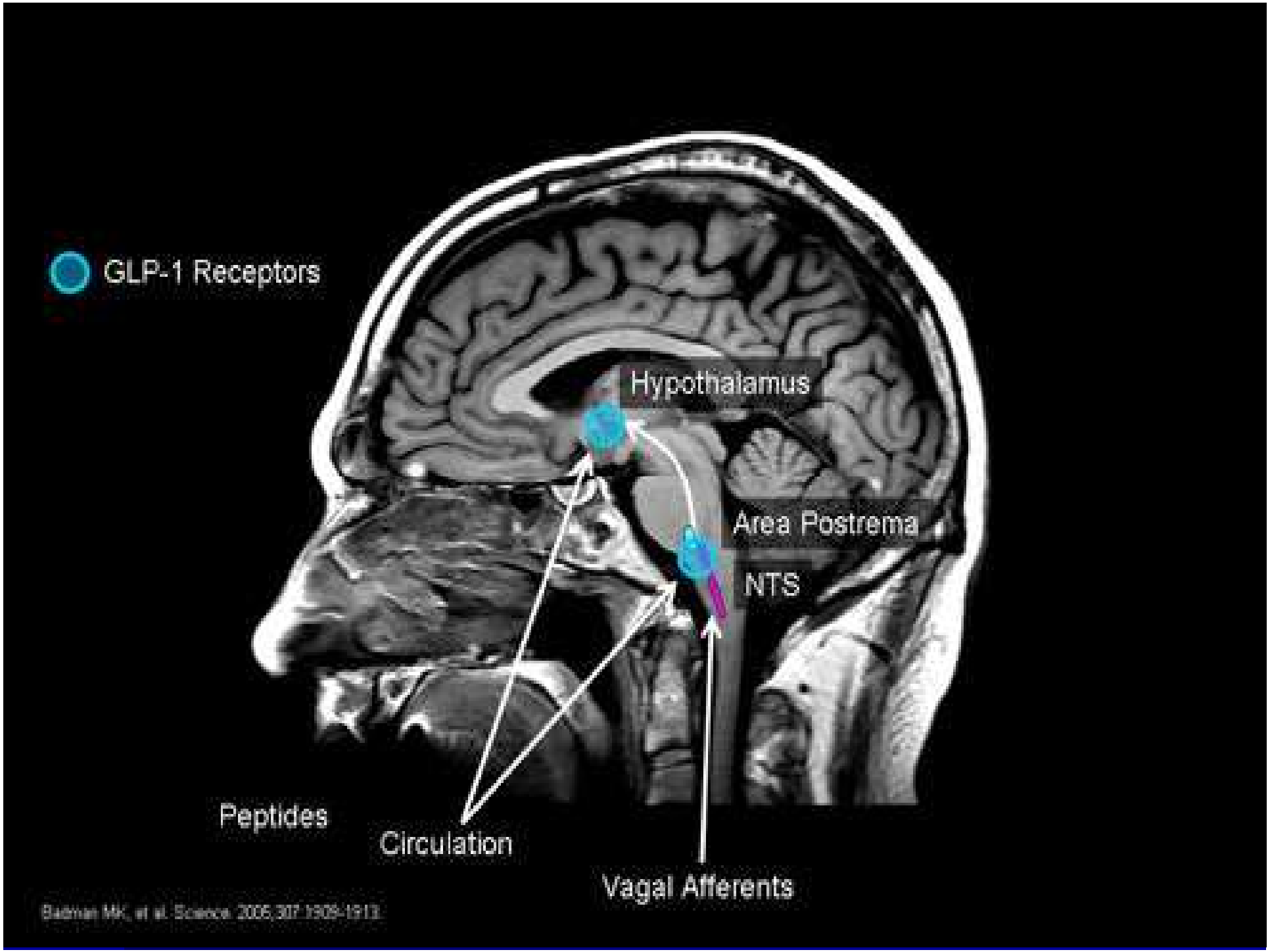

Leptin
Oxyntomodulin
PYY3-36
GLP-1
Amylin
Badman MK, et al. Science 2006;307:1909-1913.

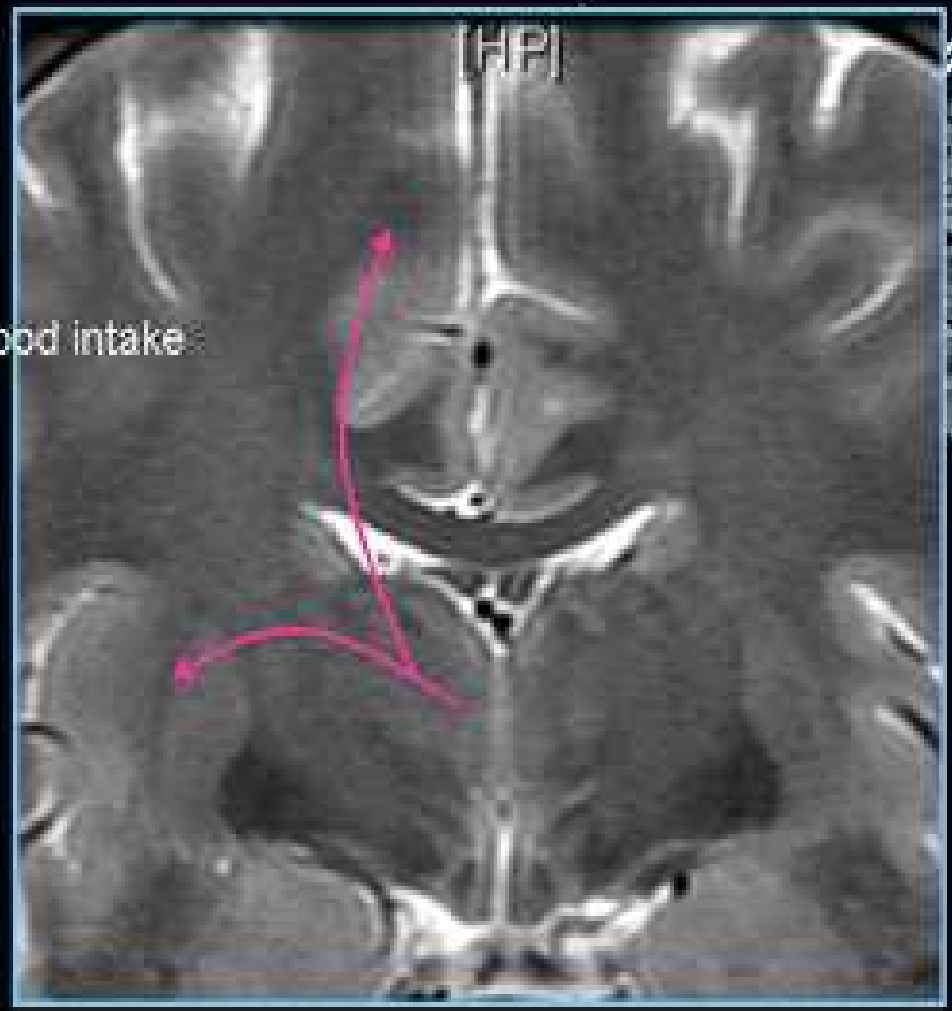
GLP-1 Processing



GLP-1 and -2= Glucagon-like peptide-1 and -2; GRPP=Glicentin-related pancreatic peptide; IP-1 and -2 = Intervening peptides 1 and 2

Redrawn from Moller DE. *Nature*. 2001;414:821-827


GLP-1 Receptors
Hypothalamus
Area Postrema
NTS
Peptides
Circulation
Vagal Afferents
Baldwin MK, et al. Science. 2005;307:1909-1913.



↓ Food intake

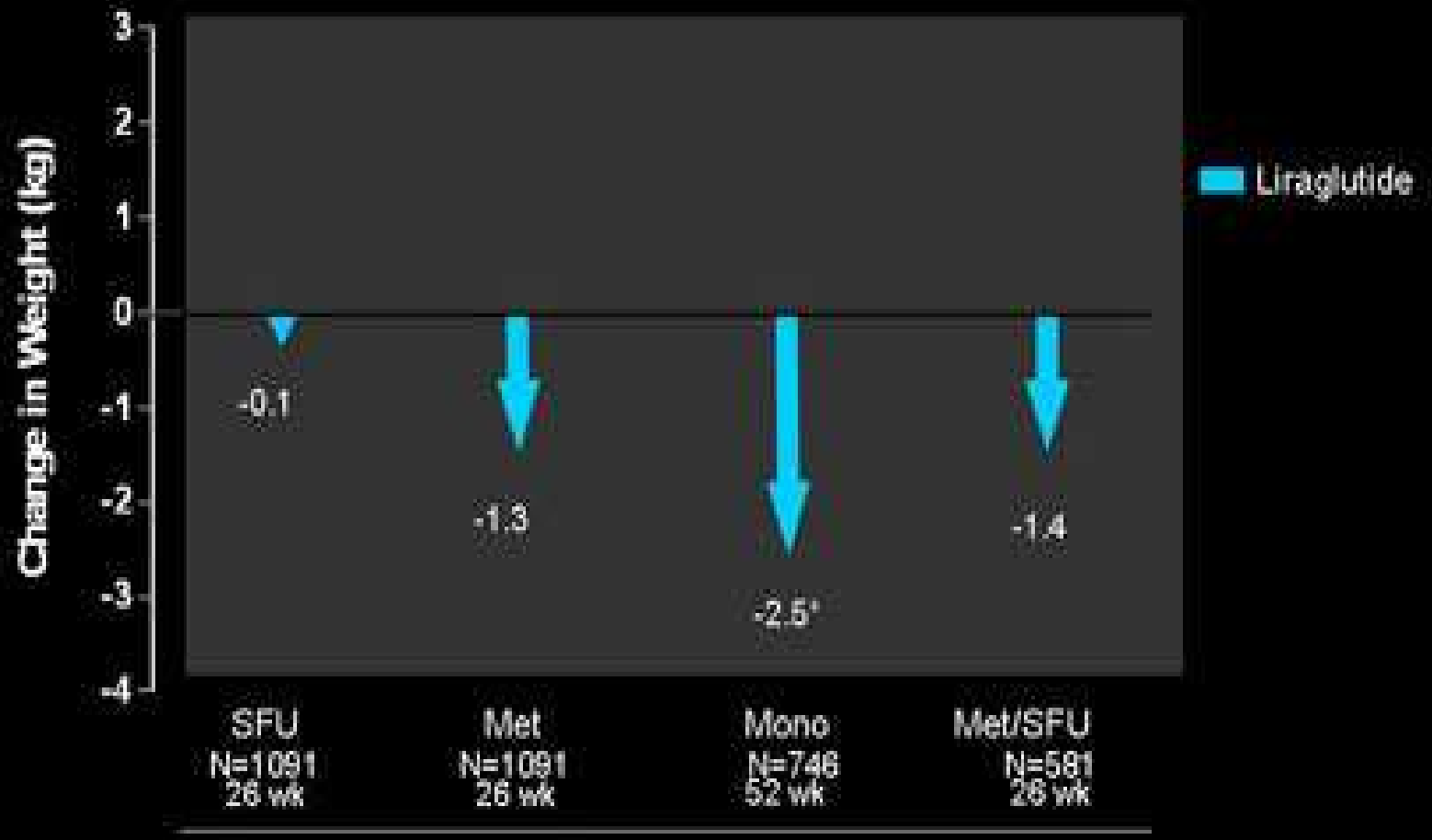
↓ 'bum'

Ghrelin receptor

GLP-1R

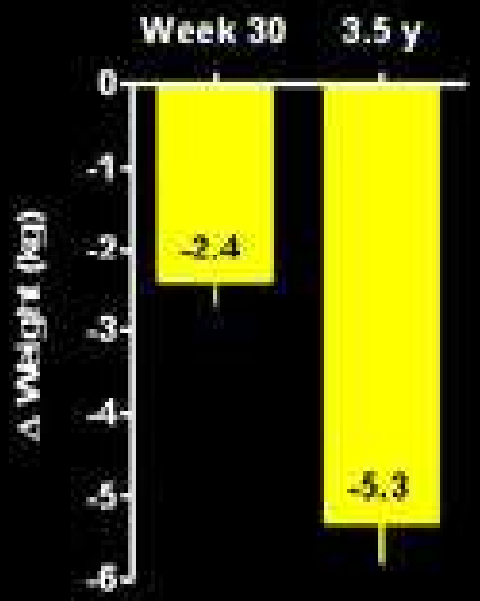
Ma X, et al. J Neurosci. 2007 Jul 4;27(27):7125-9.

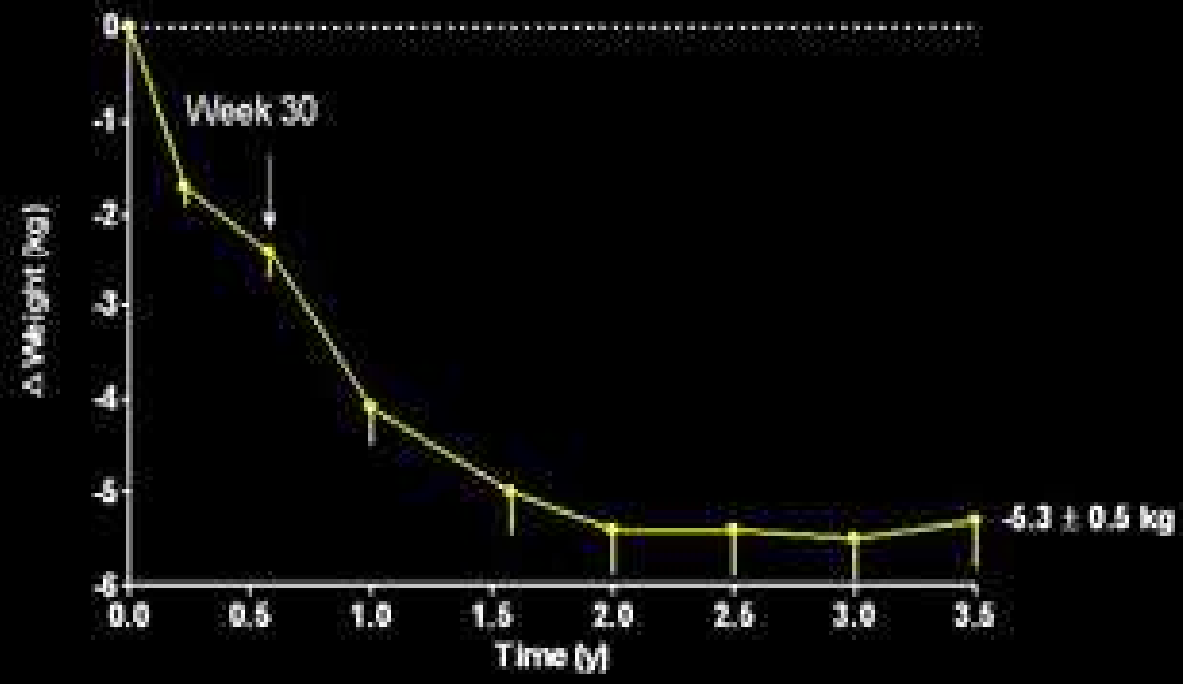
Placebo-Corrected Change in Weight



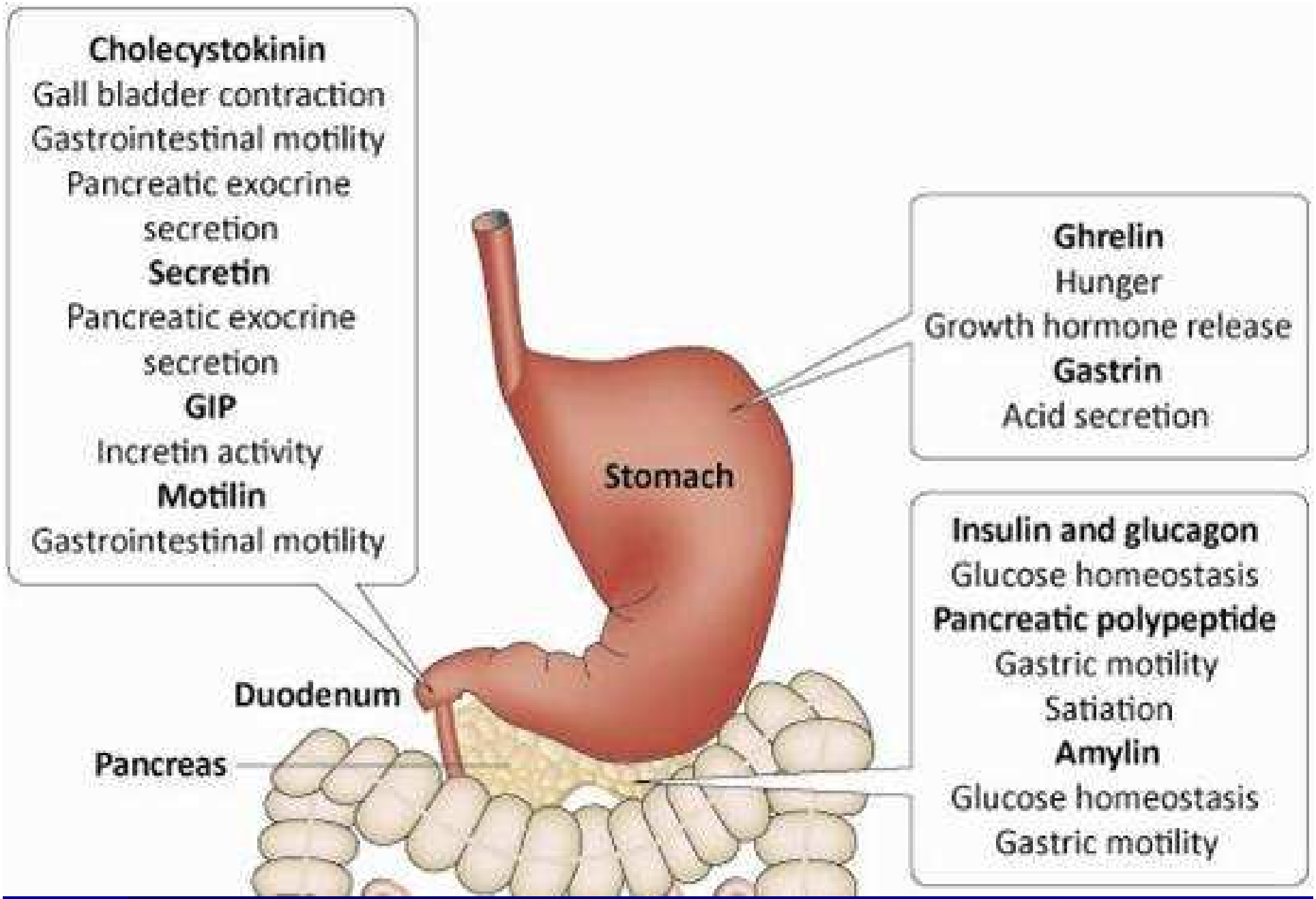
Data summarized from results reported in abstracts from the 68th sessions of the American Diabetes Association, 2008.
Liraglutide and exenatide have not been studied in head to head trials.
*Changes in weight for trials with no placebo arm are shown as change from baseline.

Weight Reductions With 3.5 Years of Exenatide



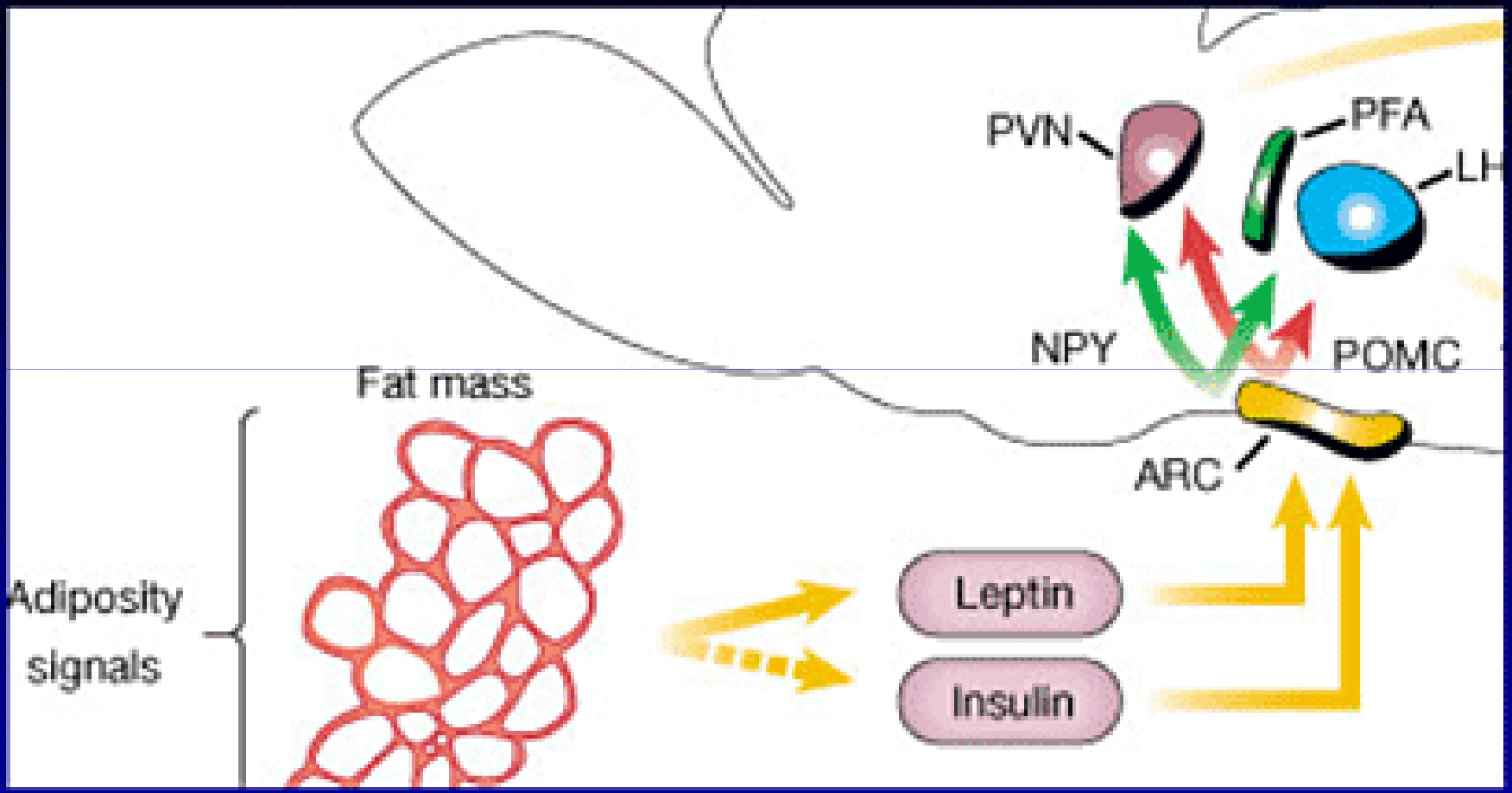


3.5-year completer cohort (n=151). Baseline weight 99.9 kg. Mean ± SE.
Kendall D, et al. Diabetes 2007;56(suppl 1):A148; Data on file, Amylin Pharmaceuticals, Inc.

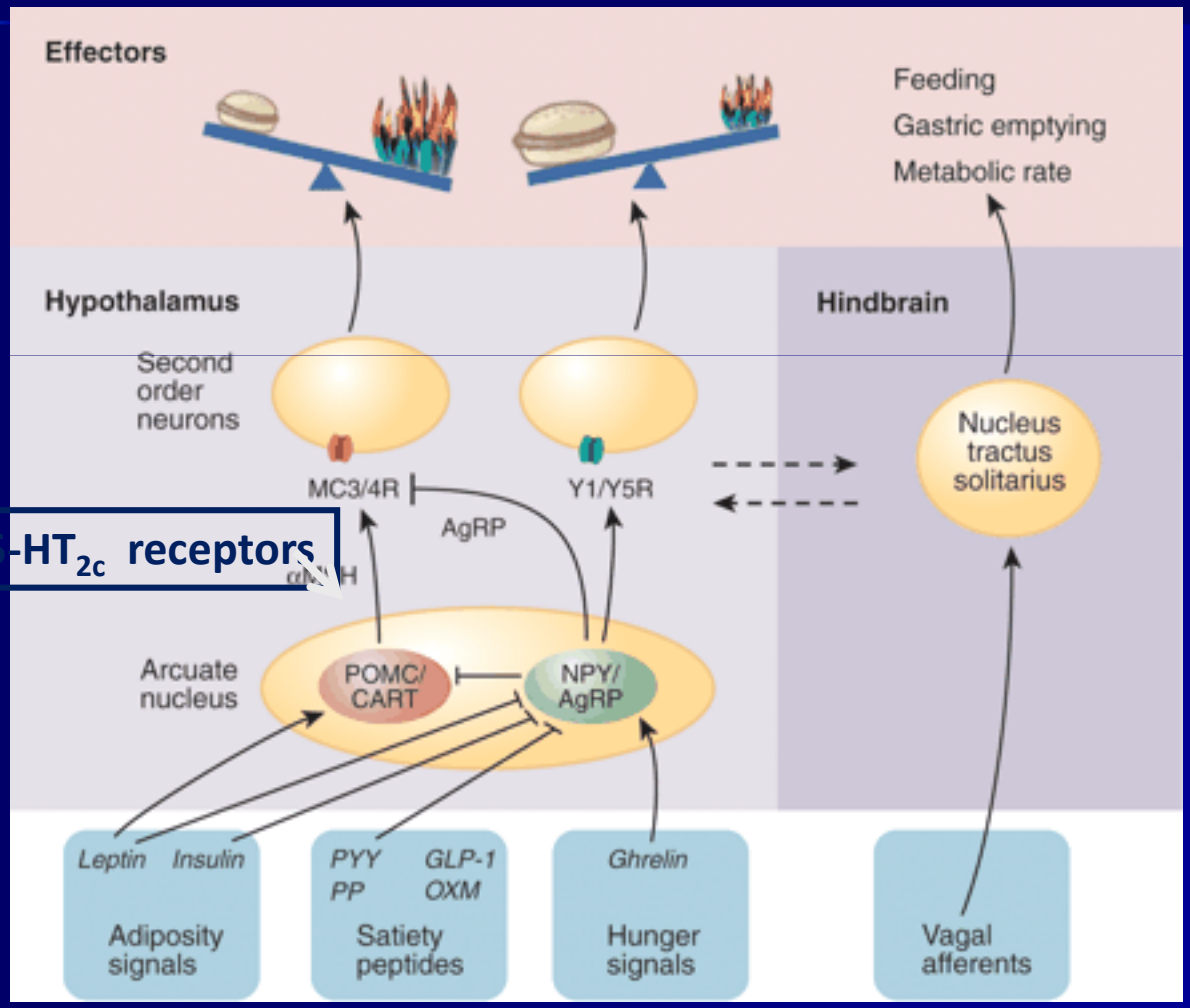


Murphy KG, Bloom SR. *Nature*. 2006;444:854-859.

Adiposity Signals: Leptin

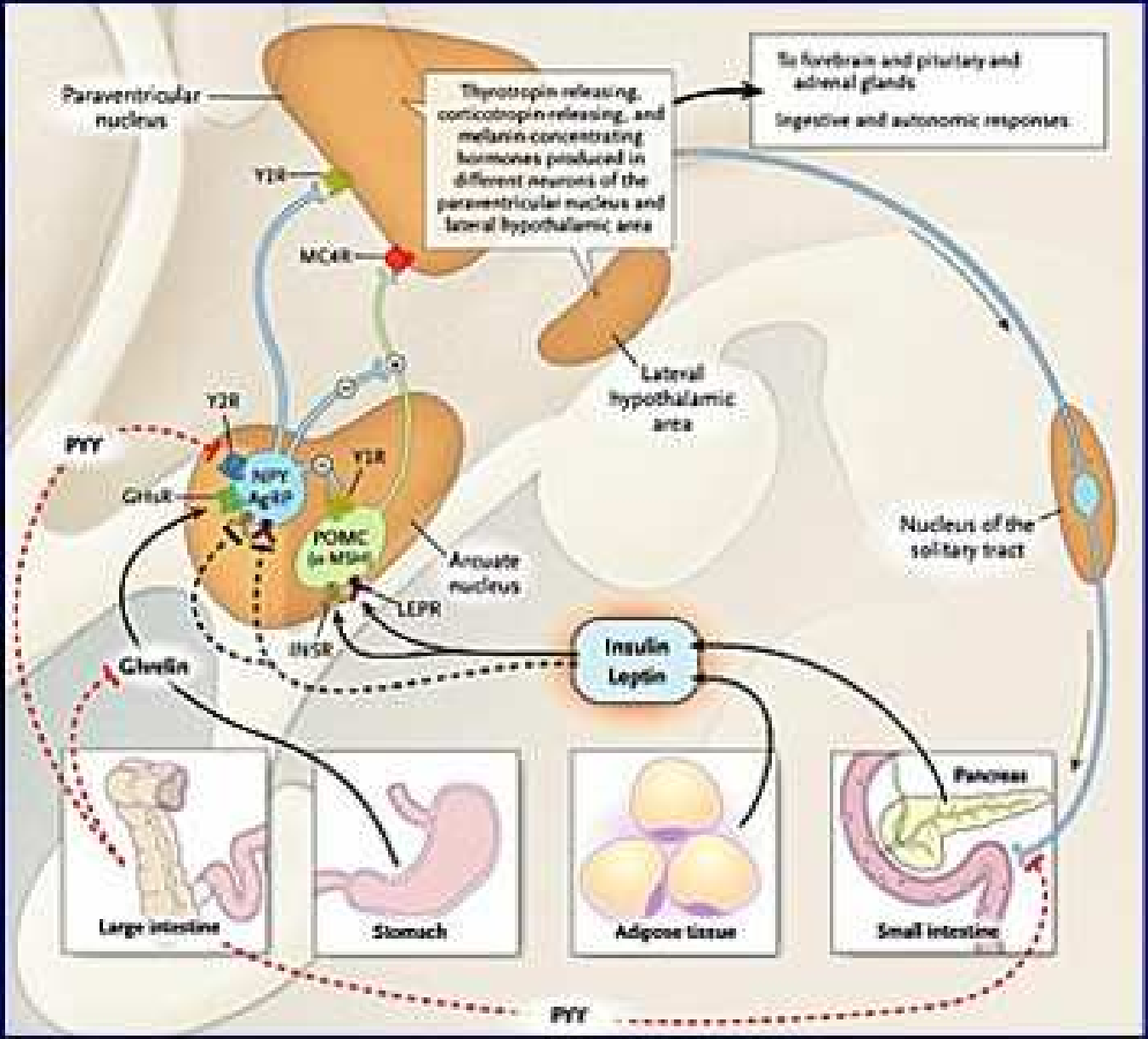


Neuroregulation of Energy Balance

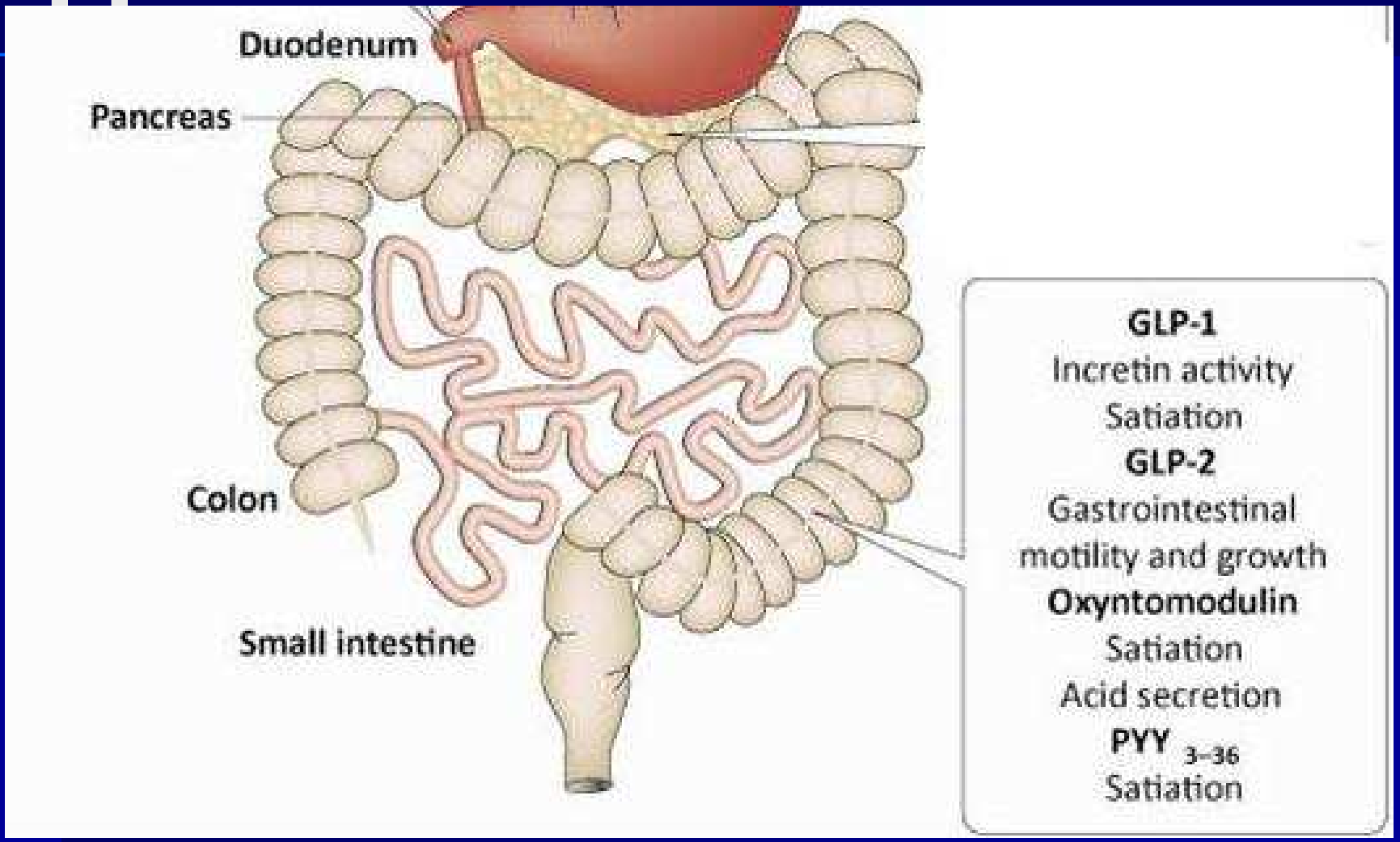


5-HT_{2c} receptors

Regulation of Appetite

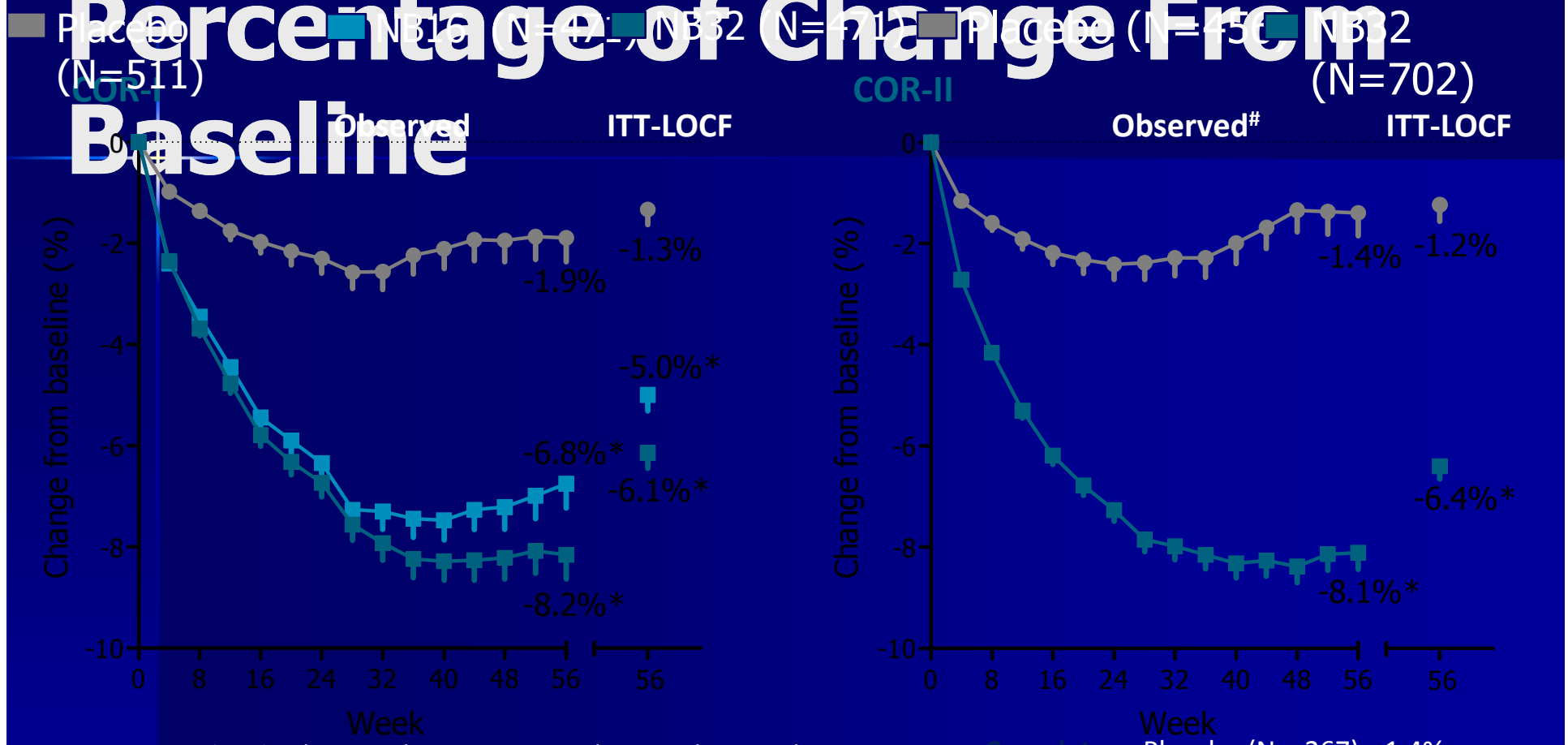


Gut Peptides That Regulate Appetite



Murphy KG, Bloom SR. *Nature*. 2006;444:854-859.

COR-I, II: Body Weight, Percentage of Change From Baseline



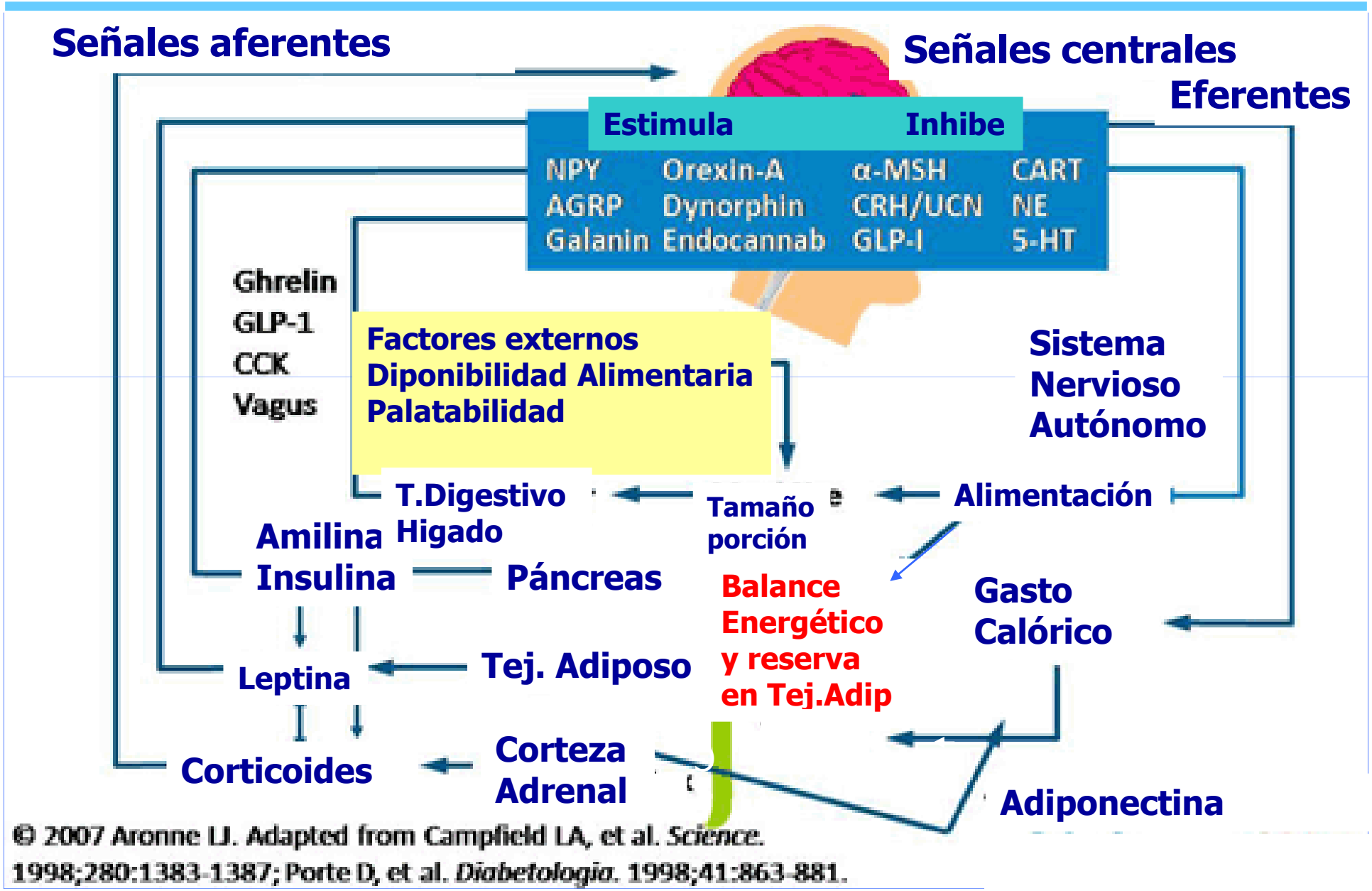
Completers: Placebo (N = 290): -1.8% , NB16 (N = 284): -6.7%*
NB32 (N = 296): -8.1%*

Completers: Placebo (N = 267): -1.4%
NB32 (N = 434): -8.2%*

NB = naltrexone/bupropion. #COR-II: NB observed data are NB32/NB48 pooled (N = 825); no differences were observed for patients rerandomized to NB32 vs NB48. LS mean ± SE; *$P < .001$ vs placebo at all timepoints. COR-II: week 56 ITT-LOCF data from patients rerandomized to NB32 are double weighted to account for the prespecified exclusion of patients rerandomized to NB48. ITT-LOCF: patients with a baseline and ≥ 1 postbaseline weight measurement while on study drug.

Press release. October 27, 2009. Available at: http://ir.orexigen.com/phoenix.zhtml?c=207034&p=irol-newsArticle&ID=1346886&highlight Accessed April 29, 2010.

Modelo simplificado de los mecanismos de regulación del peso corporal

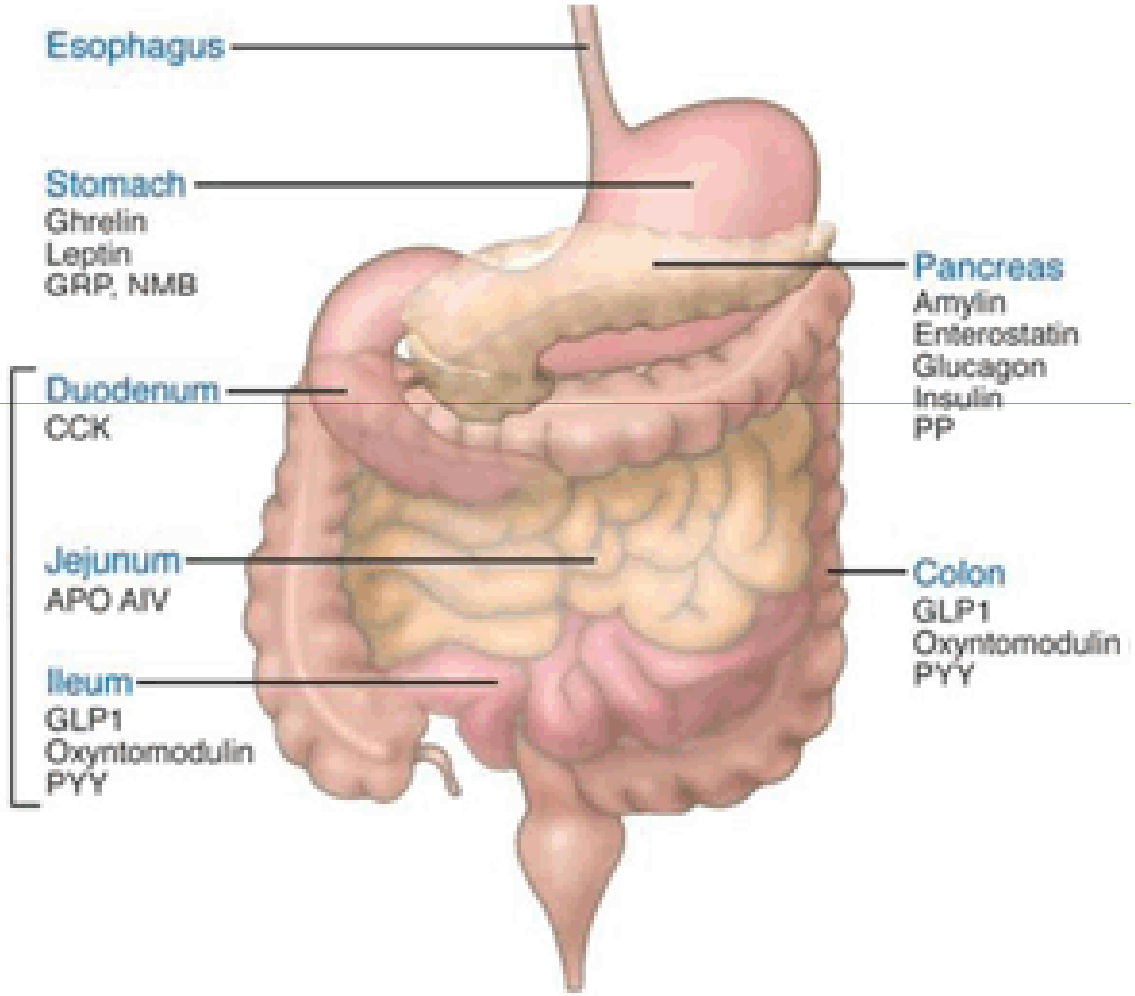


© 2007 Aronne LJ. Adapted from Campfield LA, et al. *Science*. 1998;280:1383-1387; Porte D, et al. *Diabetologia*. 1998;41:863-881.

Circuitos metabólicos periféricos del balance energético

Las señales para comer o no comer que se dirigen al hipotálamo provienen de:

- **Tubo digestivo**
- **Páncreas**
- **Tejido Adiposo**



Foccosi D. http://www6.ufrgs.br/lavet/imunovet/molecular_immunology/gastrointestinal.html