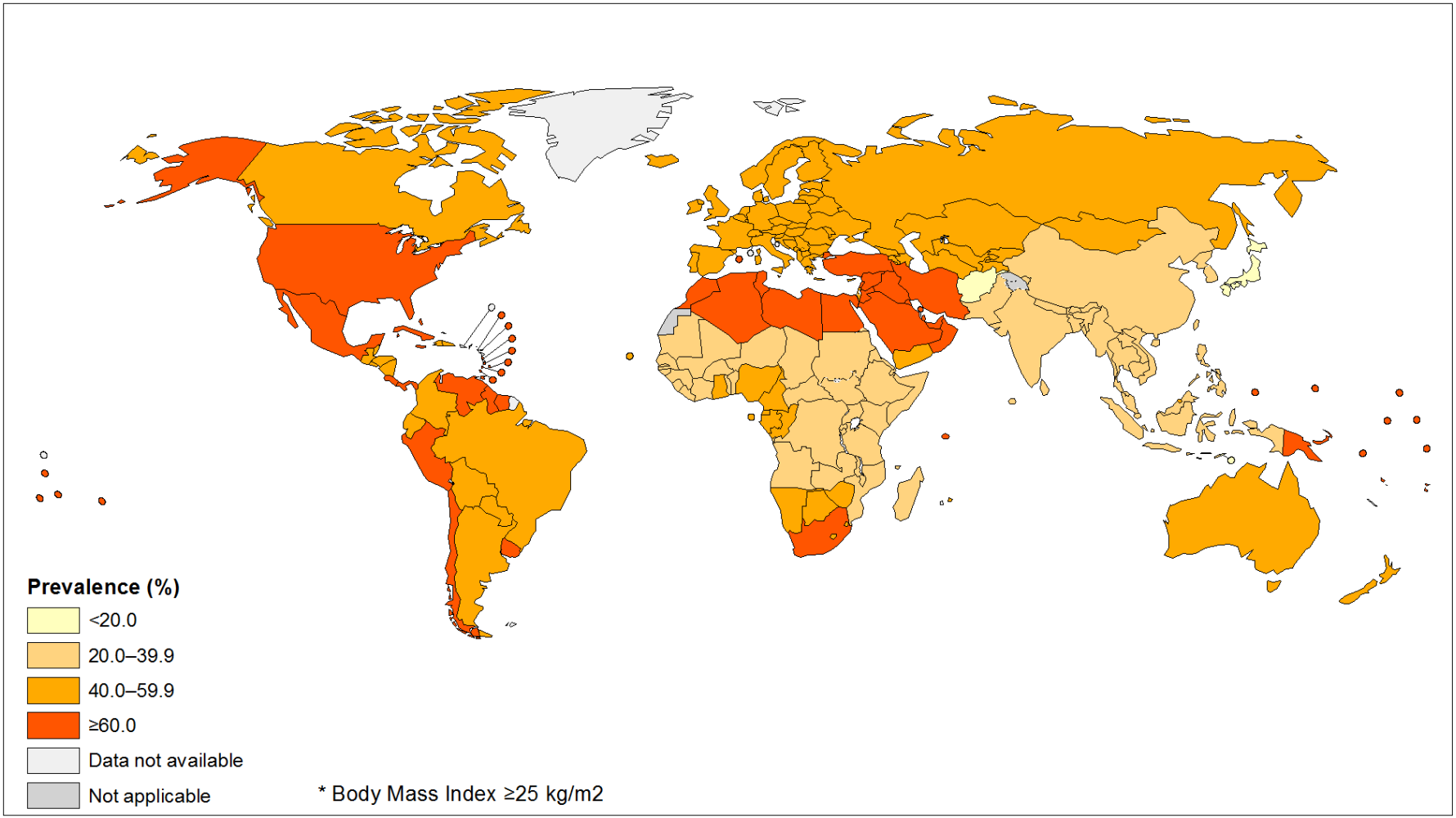
UNIVERSIDADE DE SÃO PAULO
FACULDADE DE MEDICINA DE RIBEIRÃO PRETO

CONTROLE NEUROENDÓCRINO DA INGESTÃO ALIMENTAR

Lucila Leico Kagohara Elias

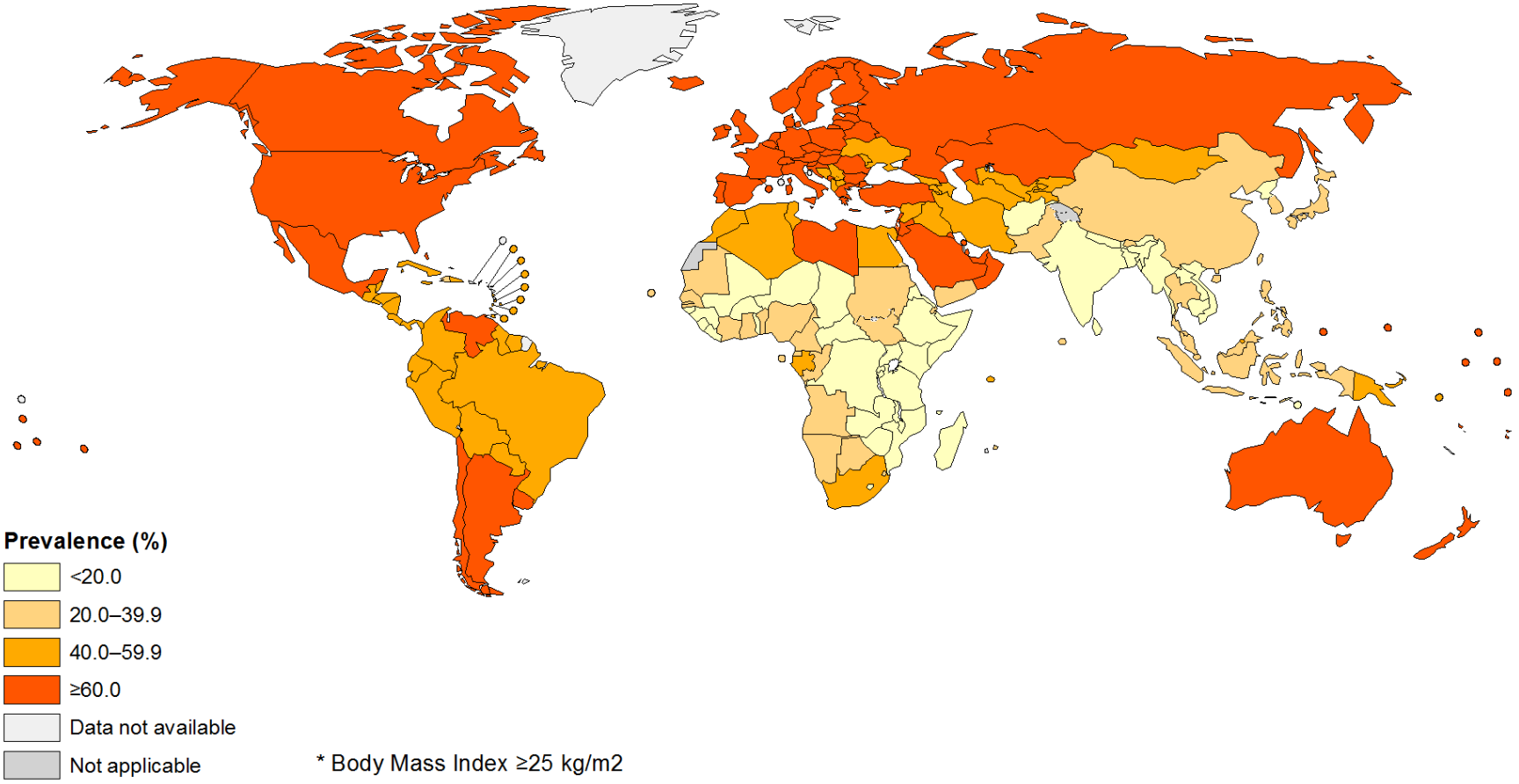
Prevalence of overweight*, ages 18+, 2014 (age standardized estimate)
Female



Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

World Health Organization

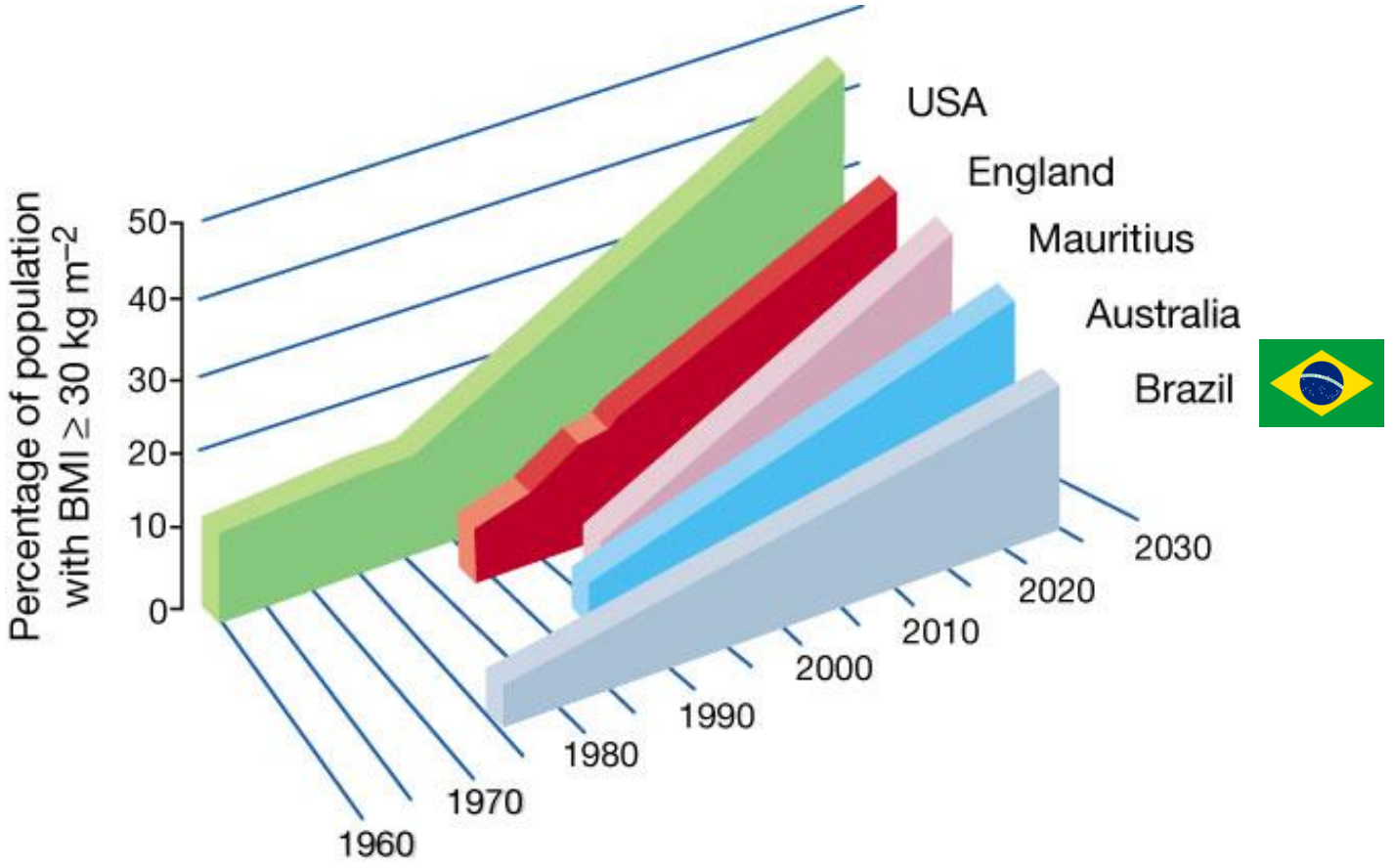
Prevalence of overweight*, ages 18+, 2014 (age standardized estimate)
Male



Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

World Health Organization

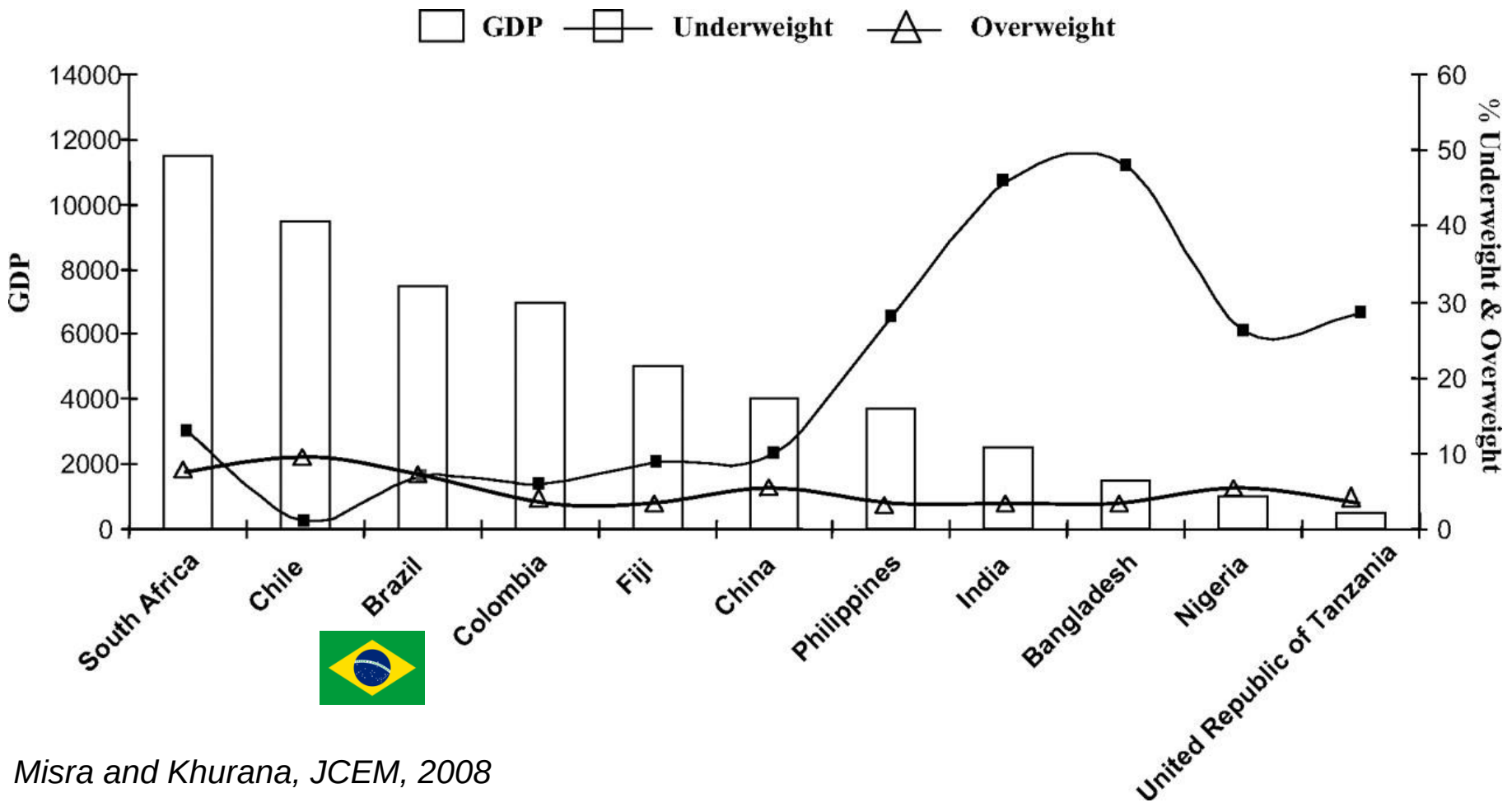
Historic, current and projected obesity prevalence rates



Peter G. Kopelman
Nature, 2010

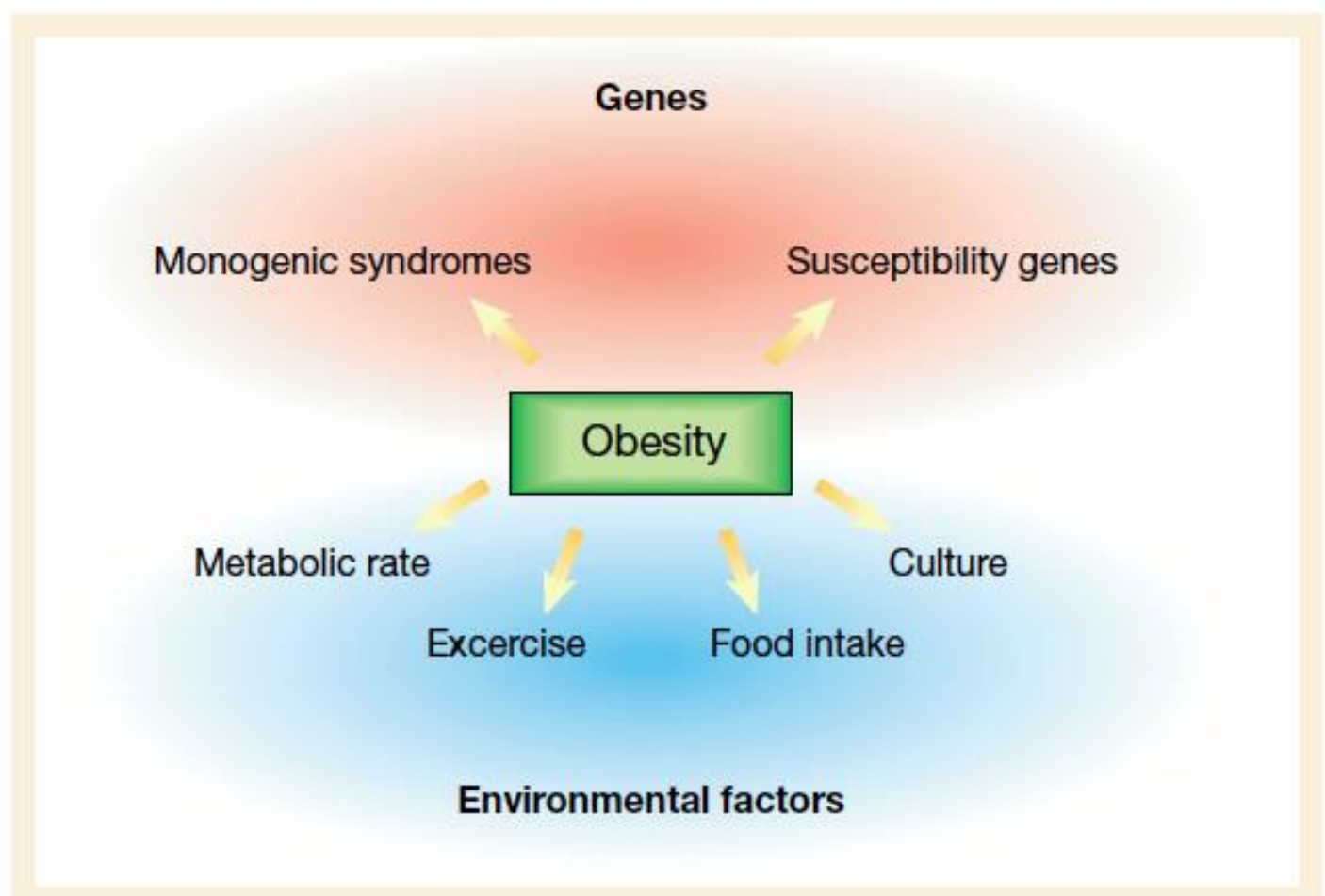
Obesity and the Metabolic Syndrome in Developing Countries

Relationship between GDP and underweight and overweight children younger than 5 yr of age



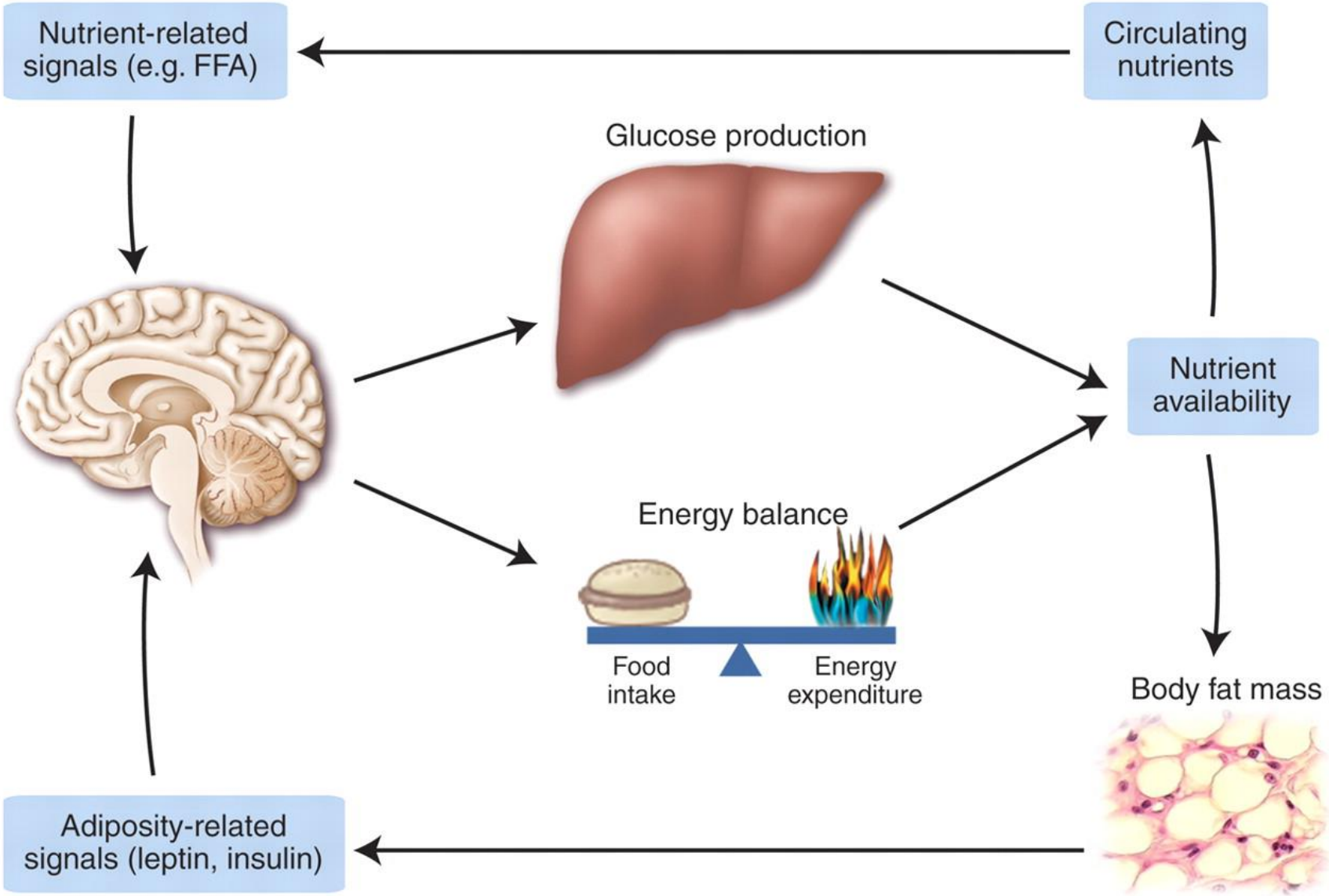
Misra and Khurana, JCEM, 2008

Factors influencing the development of obesity



Obesity as a medical problem. Peter G. Kopelman, Nature 200

CONTROL OF ENERGY HOMEOSTASIS



Diabetes, Obesity, and the Brain Michael W. Schwartz and Daniel Porte, Jr. Science, 2005

COMPONENTES DA INGESTÃO ALIMENTAR

- ***Fome homeostática:*** fome que resulta na ingestão alimentar, desencadeada por uma sinalização em resposta ao estado nutricional/energético/déficit metabólico (Sinalização enviada para o SNC, a partir do tecido adiposo, sangue, estômago, intestino delgado e grosso, pâncreas e fígado)

- ***Componente hedonístico:*** Ingestão alimentar induzida pela variedade dos alimentos, sabor, textura, odor.

- ***Componente emocional:*** Social, estresse, ansiedade, motivação.

COMPORTAMENTO ALIMENTAR

- **Comportamento motivado:** desencadeado por um déficit de um dos componentes do meio interno.

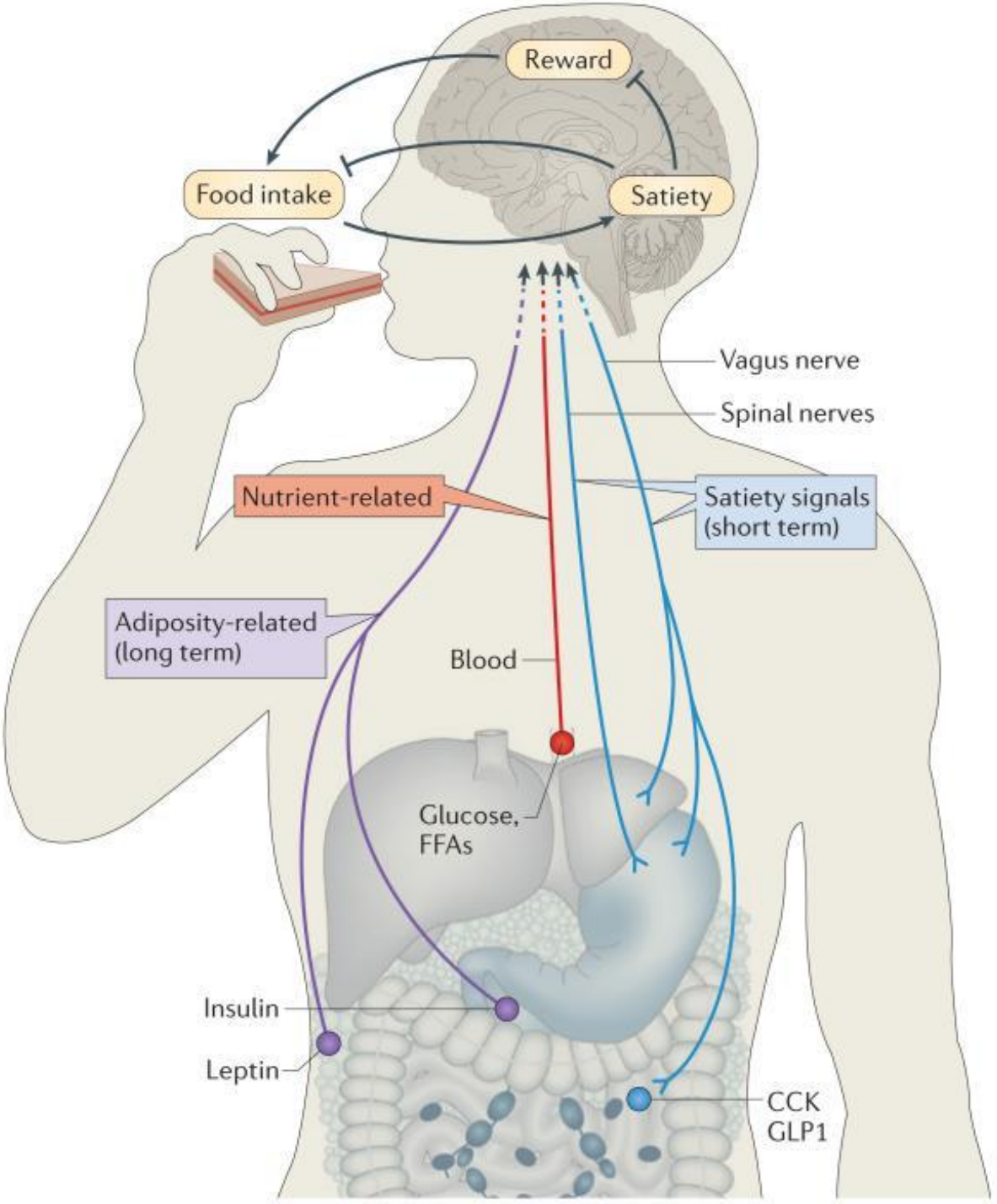
- **Comportamento instintivo:** resposta locomotora ou comportamento exploratório pela procura por alimento

- **Resposta consumatória:** ato de comer

- **Saciedade:** sensação de plenitude e contribui para o término da refeição.

CNS regulation of energy homeostasis

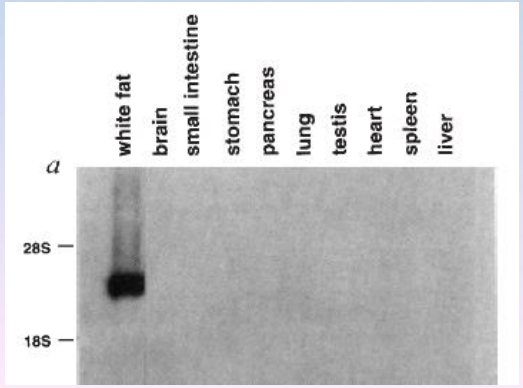
Morton, et al., 2014



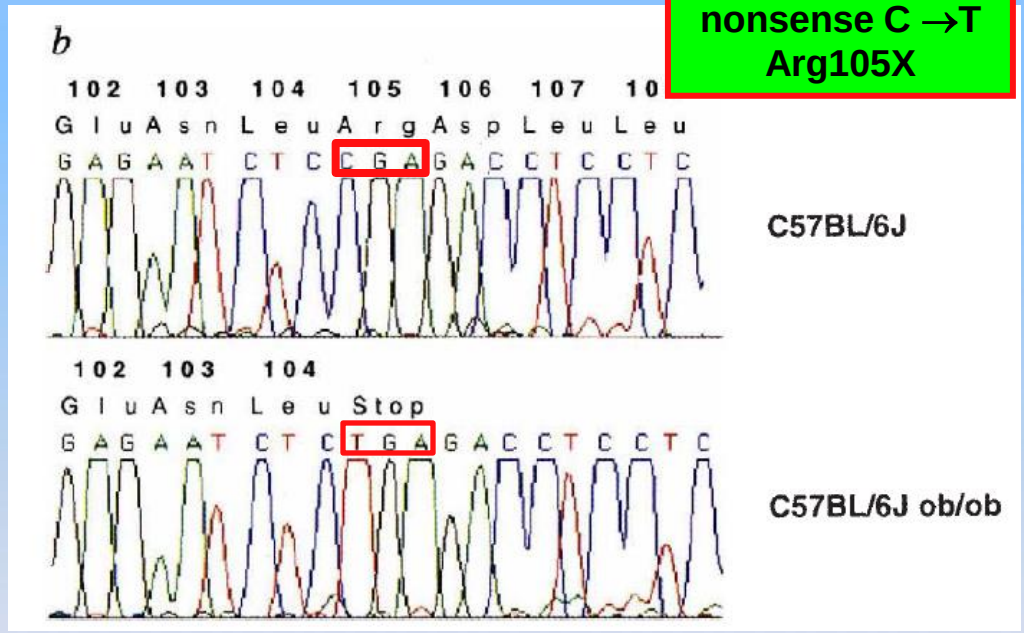
Positional cloning of the mouse *obese* gene and its human homologue

Yiying Zhang*†, Ricardo Proenca*†, Margherita Maffei†, Marisa Barone*†, Lori Leopold*† & Jeffrey M. Friedman*†‡

Nature, 1994

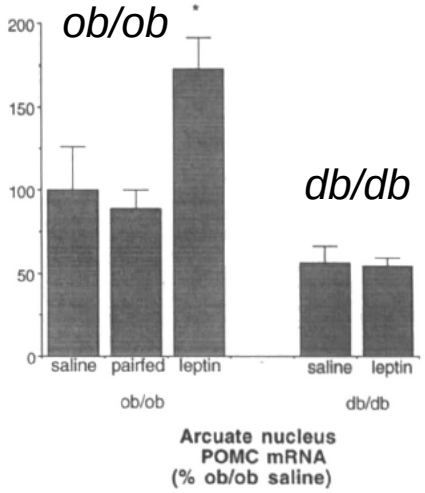


Mutação nonsense C →T Arg105X



Tartaglia LA et al. Identification and expression cloning of a leptin receptor, OB-R. Cell. 1995;83(7):1263-71.

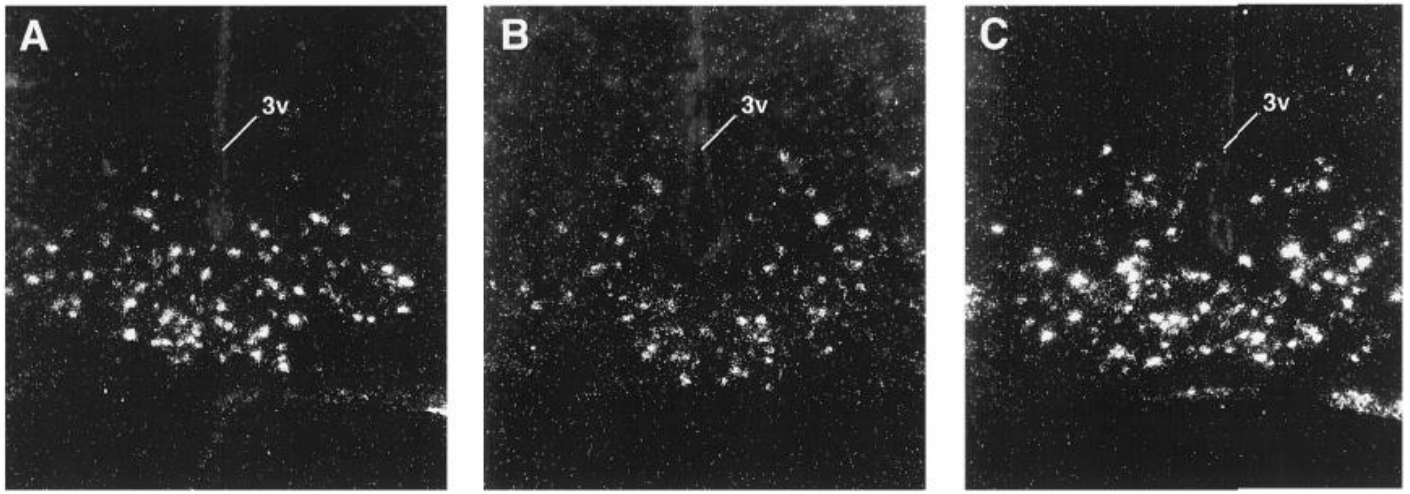
Leptin aumenta a expressão de mRNA da POMC no núcleo arqueado



Schwartz, et al, Diabetes, 1997

FIG. 2. POMC mRNA levels in the rostral arcuate nucleus of *ob/ob* and *db/db* mice receiving daily intraperitoneal injections of either 150 μg of recombinant murine leptin (leptin; $n = 8$) or saline for 5 days. Saline-treated mice were either fed ad libitum (saline; $n = 8$) or pair-fed to the food intake of leptin-treated mice (pair-fed; $n = 8$). *$P < 0.05$ vs. saline-treated *ob/ob* mice.

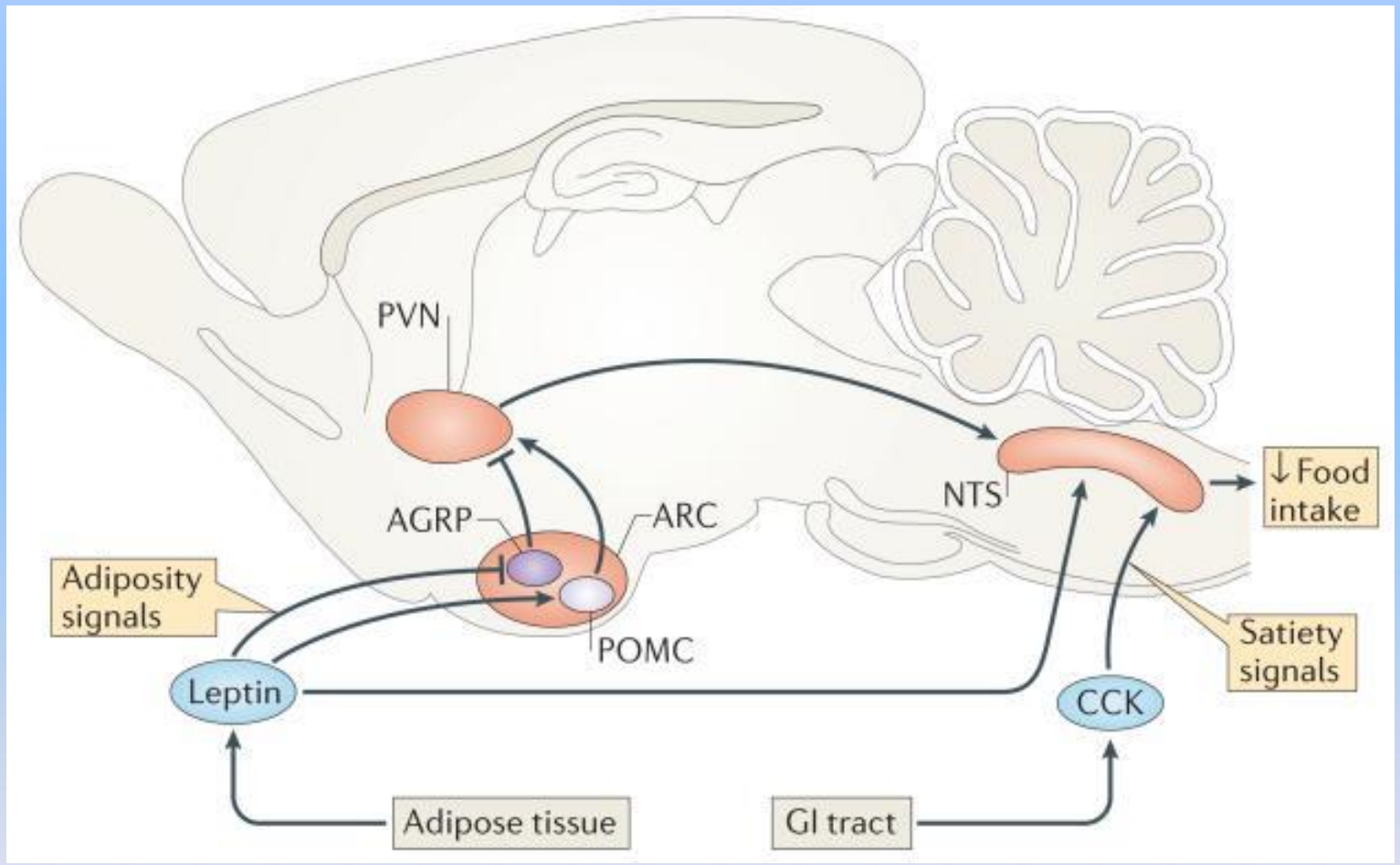
WT *ob/ob* *ob/ob* + leptin



Thorton, et al, Endocrinology, 1997

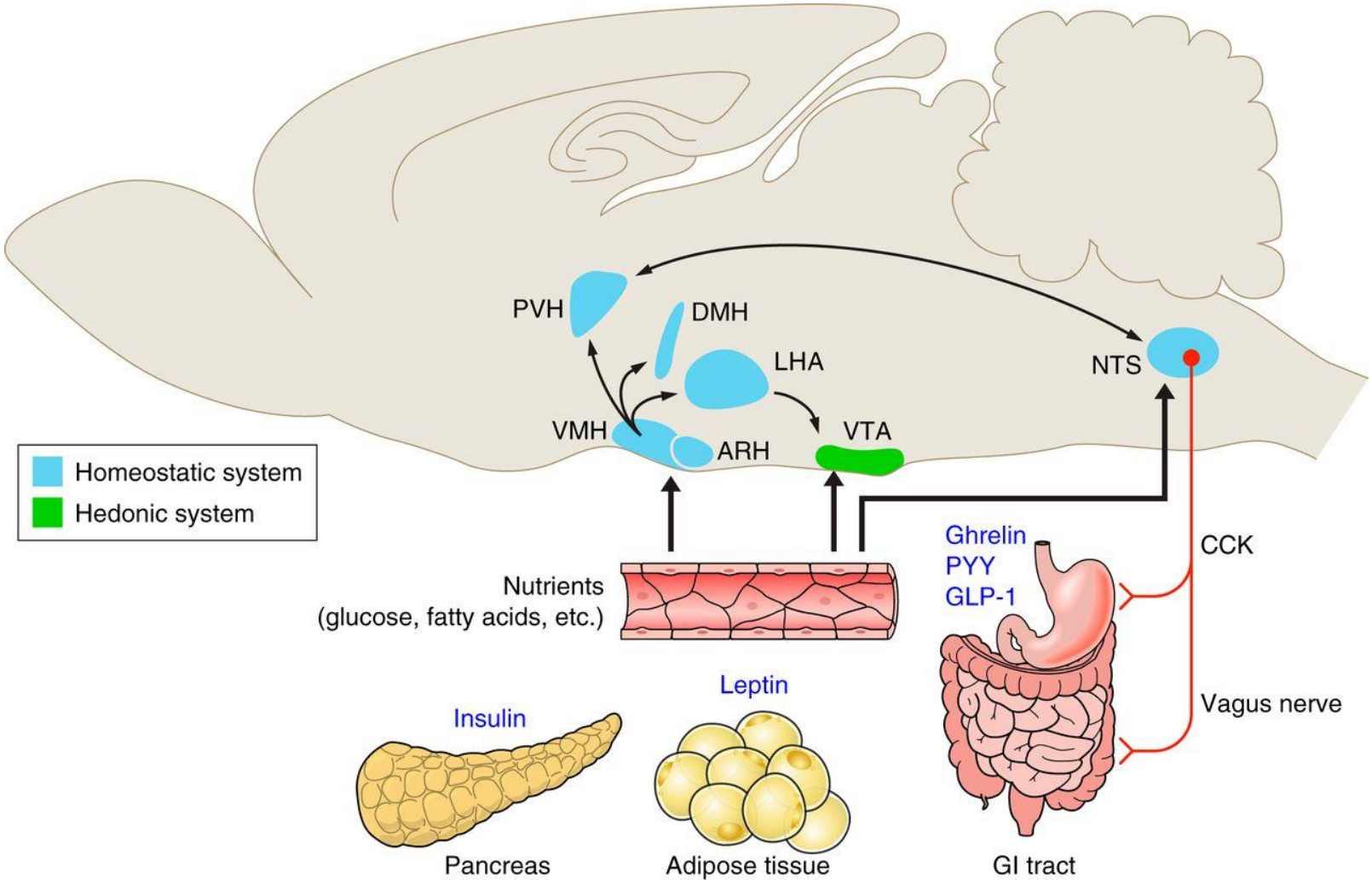
FIG. 1. Photomicrographs of POMC mRNA-containing cells in the rostral arcuate of A) wild-type lean control mice (vehicle-treated), B) *ob/ob* control mice (vehicle-treated and pair-fed), and C) *ob/ob* leptin-treated mice. Clusters of silver grains indicate the presence of cells containing POMC mRNA. Leptin significantly increased the number of grains/cell in the *ob/ob* mice to a level that was higher than that in the *ob/ob* controls ($p<0.0001$) and comparable to that in the lean control mice.

Integration of long-term homeostatic and short-term satiety signals



cholecystokinin (CCK), nucleus of the solitary tract (NTS), pro-opiomelanocortin (POMC), agouti-related protein (AGRP), arcuate nucleus (ARC), paraventricular nucleus (PVN).

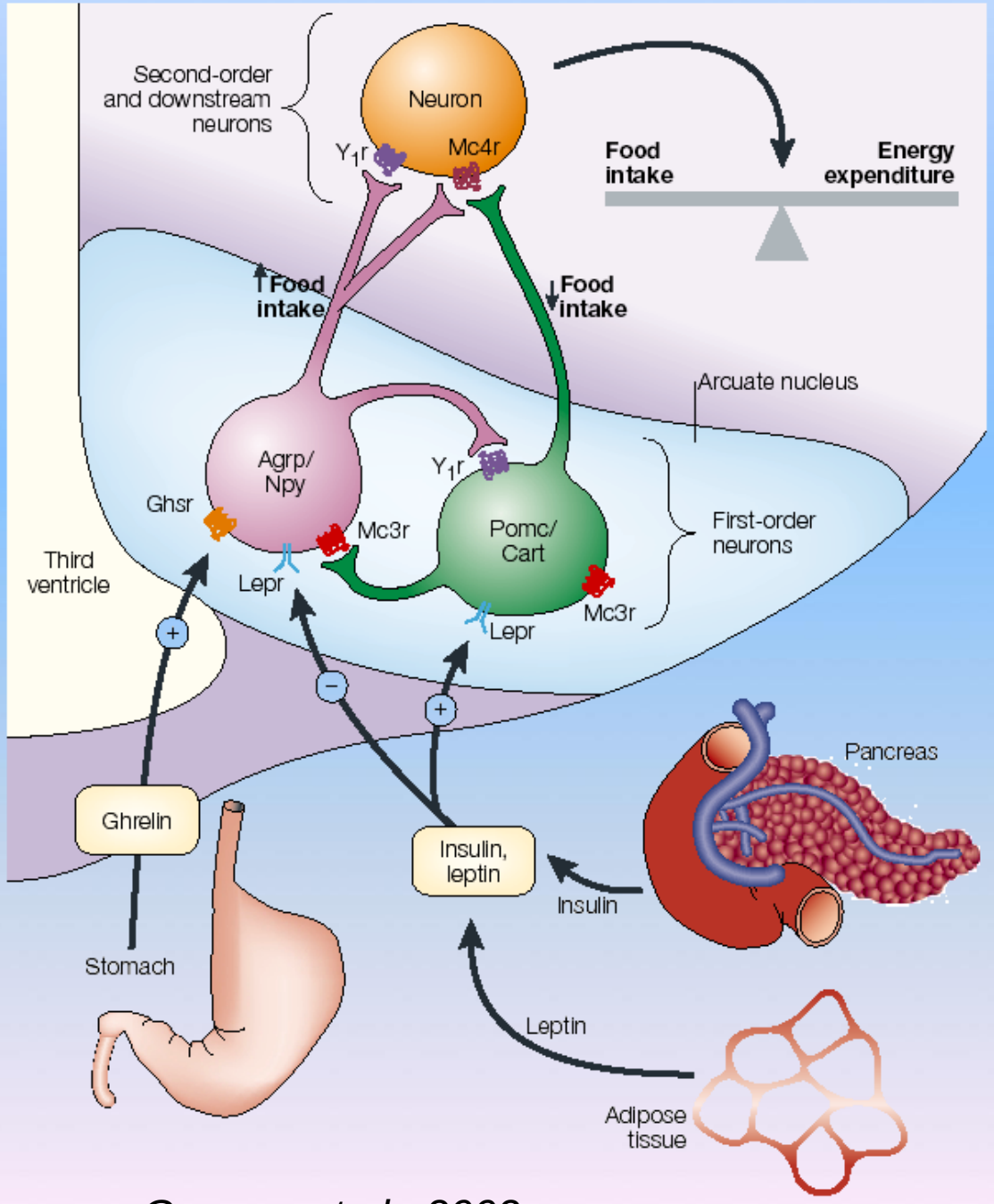
Major routes for regulation of feeding and energy balance.



Sebastien Bouret et al. Physiol Rev 2015;95:47-82

Physiological Reviews

Neurônios do Núcleo Arqueado



Gregory et al., 2002

NPY: neuropeptide Y

POMC: pro-opiomelanocortin

AgRP: agouti-related protein

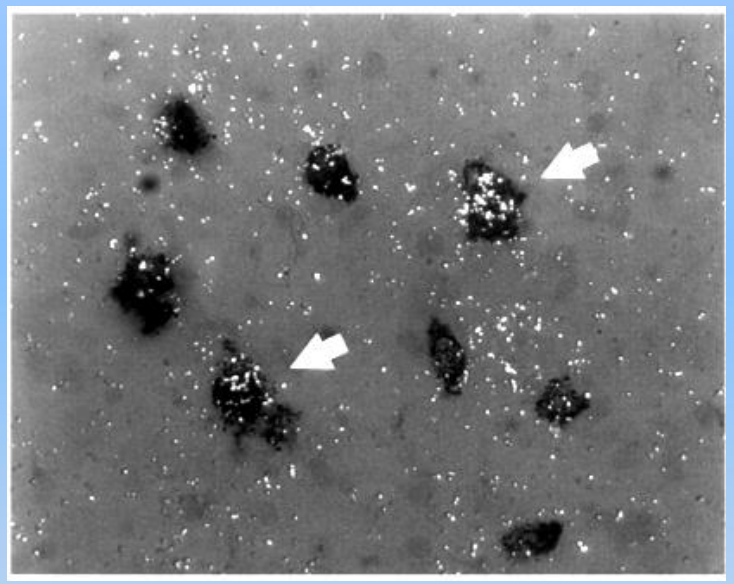
CART: cocaine- and amphetamine-regulated transcript

Lepr: leptin receptor

MC3R/MC4R: melanocortin 3/4 receptor

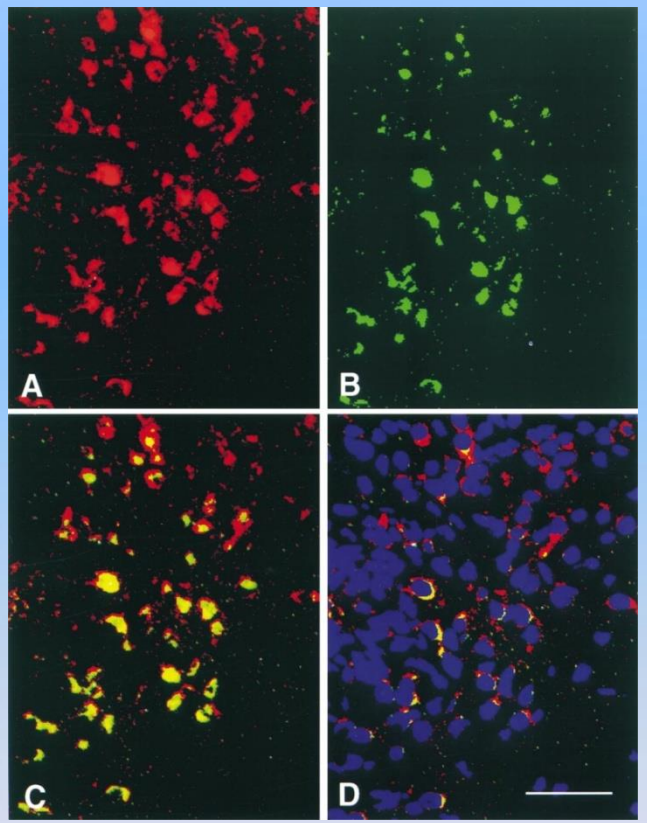
Y1r, neuropeptide Y1 receptor.

Leptina atua em neurônios que expressam Proopiomelanocortina (POMC) e Neuropeptídeo Y (NPY)



Co-localização de RNAm de **LepR** em neurônios **POMC**

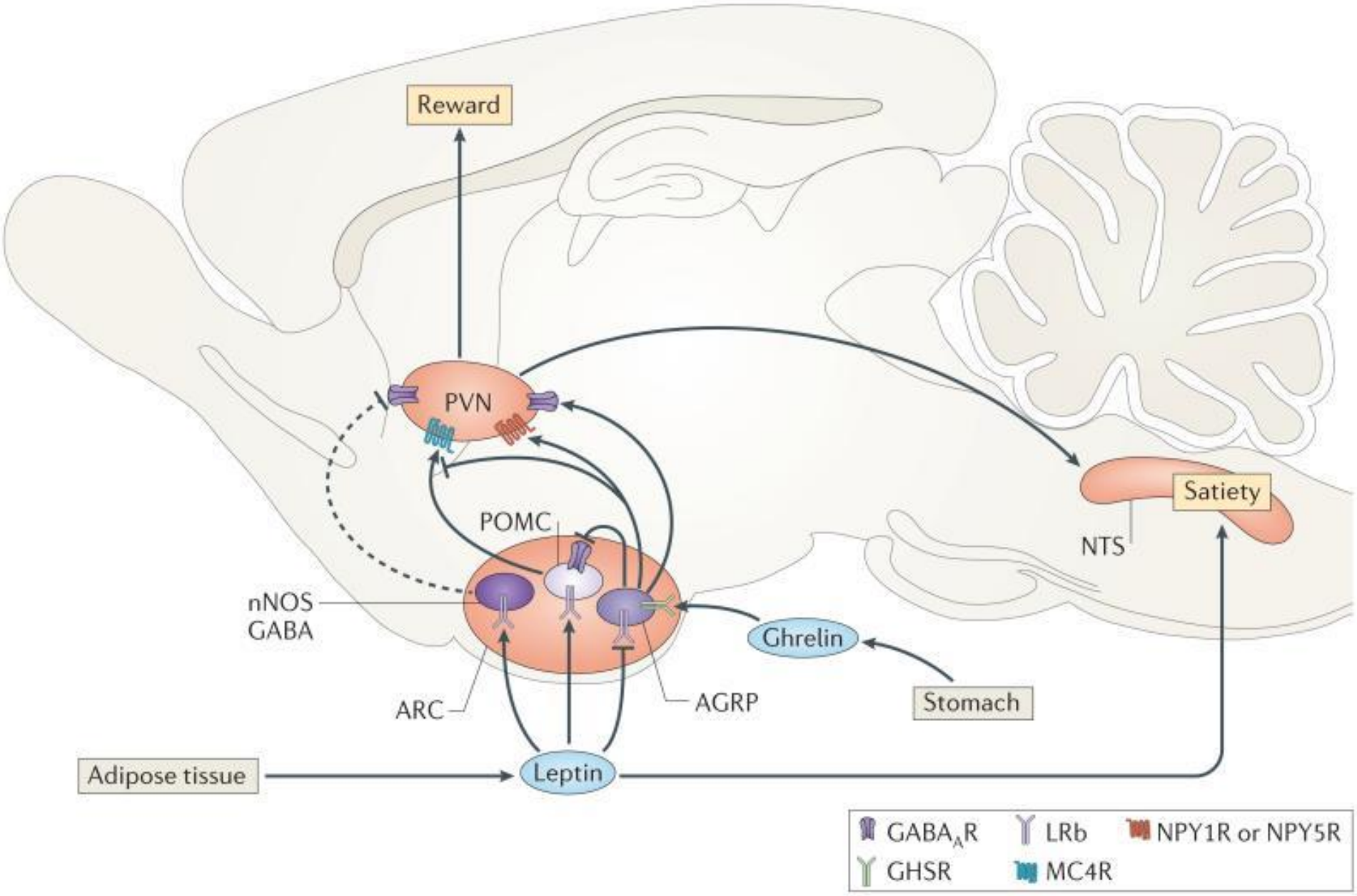
Cheung, et al., Endocrinology, 1997



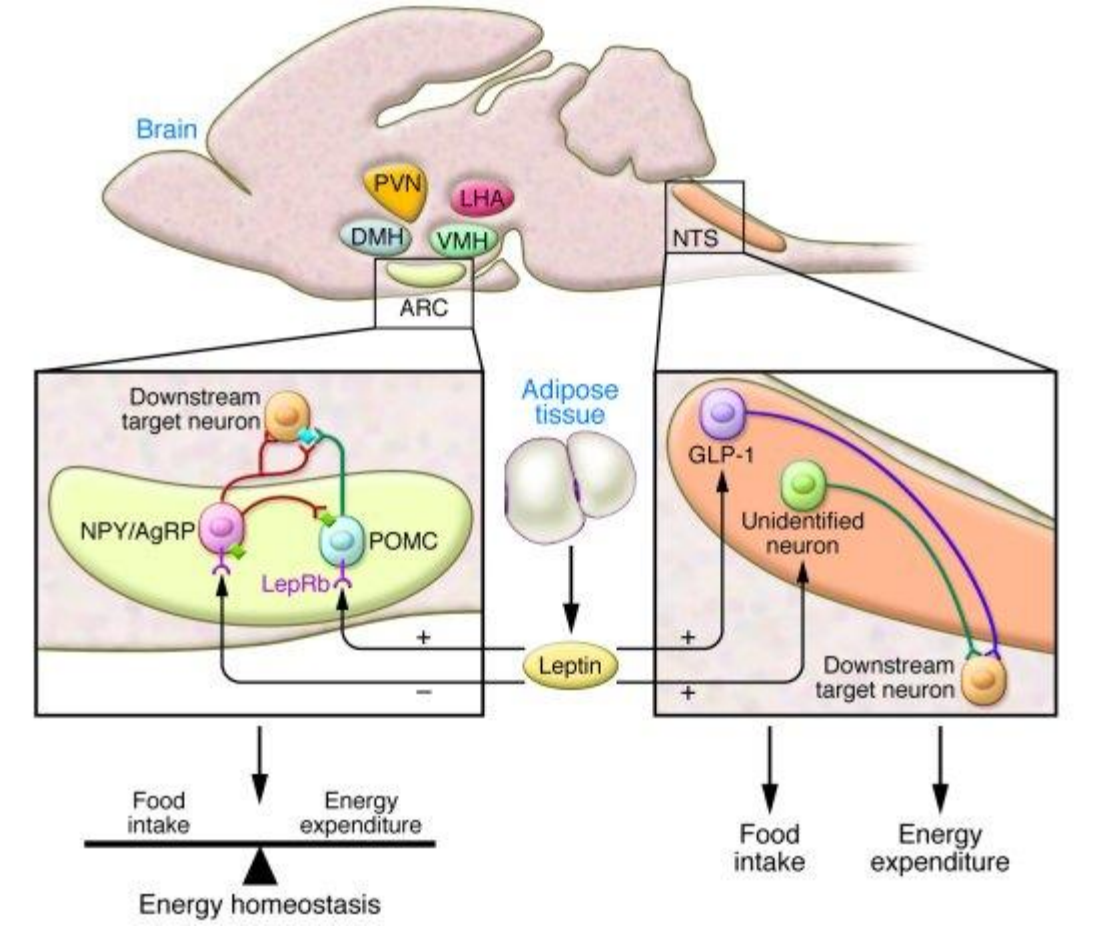
Co-localização de RNAm de **NPY** em neurônios que expressam **LepR**

Baskin, et al., J Histochem Cytochem, 1999

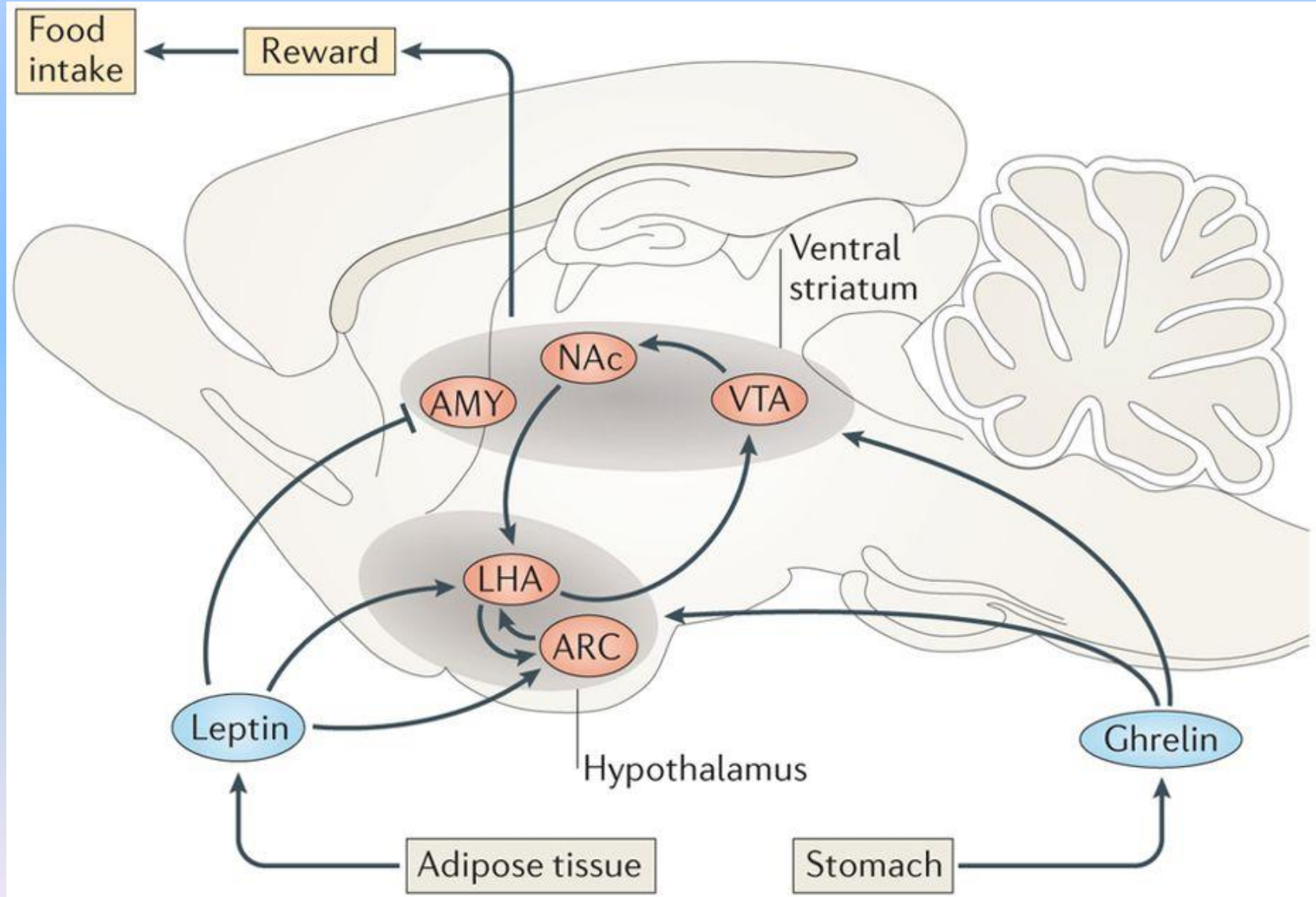
Neurocircuits involved in the homeostatic regulation of feeding.



Hypothalamic and hindbrain neurocircuits that regulate food intake and energy expenditure in response to input from the adipocyte hormone leptin.



Integration of homeostatic and reward-related inputs.



7. Citar causas monogênicas de obesidade.

Table 1
Obesity monogenes identified in Caucasians and their expression in the hypothalamus.

Gene	Gene name	Identification (bold) and mutation screen in locus	Expression hypothalamus[a]	GWAS hit?
LEP	Leptin	[**40**,45,51–53,55–57]; reviewed in: Ref. [58]	No	No
LEPR	Leptin receptor	[41,**45**,56,59]; reviewed in: Ref. [58]	Yes	No
MC4R	Melanocortin-4 receptor	[57,**62**–64,80]; reviewed in: Ref. [20]	Yes	Yes
BDNF	Brain-derived neurotrophic factor	[47,**140**]; reviewed in: Ref. [45]	Yes	Yes
NTRK2	Neurotrophin receptor TrkB	[47,**77**]; reviewed in: Ref. [48]	Yes	No
SH2B1	SH2B adaptor protein 2 isoform 1	[49,50,**96**]	Yes	Yes
POMC	Pro-opiomelanocortin	[**61**–64]; reviewed in Ref. [65]	Yes	Yes
PCSK1	Prohormone convertase 1 gene	[**59**,60]	Yes	Yes[b]
TUB	Tubby gene	[51,**96**]	Yes	Yes

[a] Analysed by http://biogps.org, Dataset GeneAtlas U133A.
[b] In a meta-analysis of 83,048 East Asian individuals [99].

Hinney et al., 2014

α – MSH

Papel no controle do comportamento alimentar e homeostase energética

- Injeção icv de α – MSH ou de seus agonistas suprime a ingestão alimentar em roedores

- Antagonistas sintéticos de α – MSH (SHU9119) aumentam o apetite

- Agouti e AGRP, antagonistas naturais do α – MSH, estimulam a alimentação

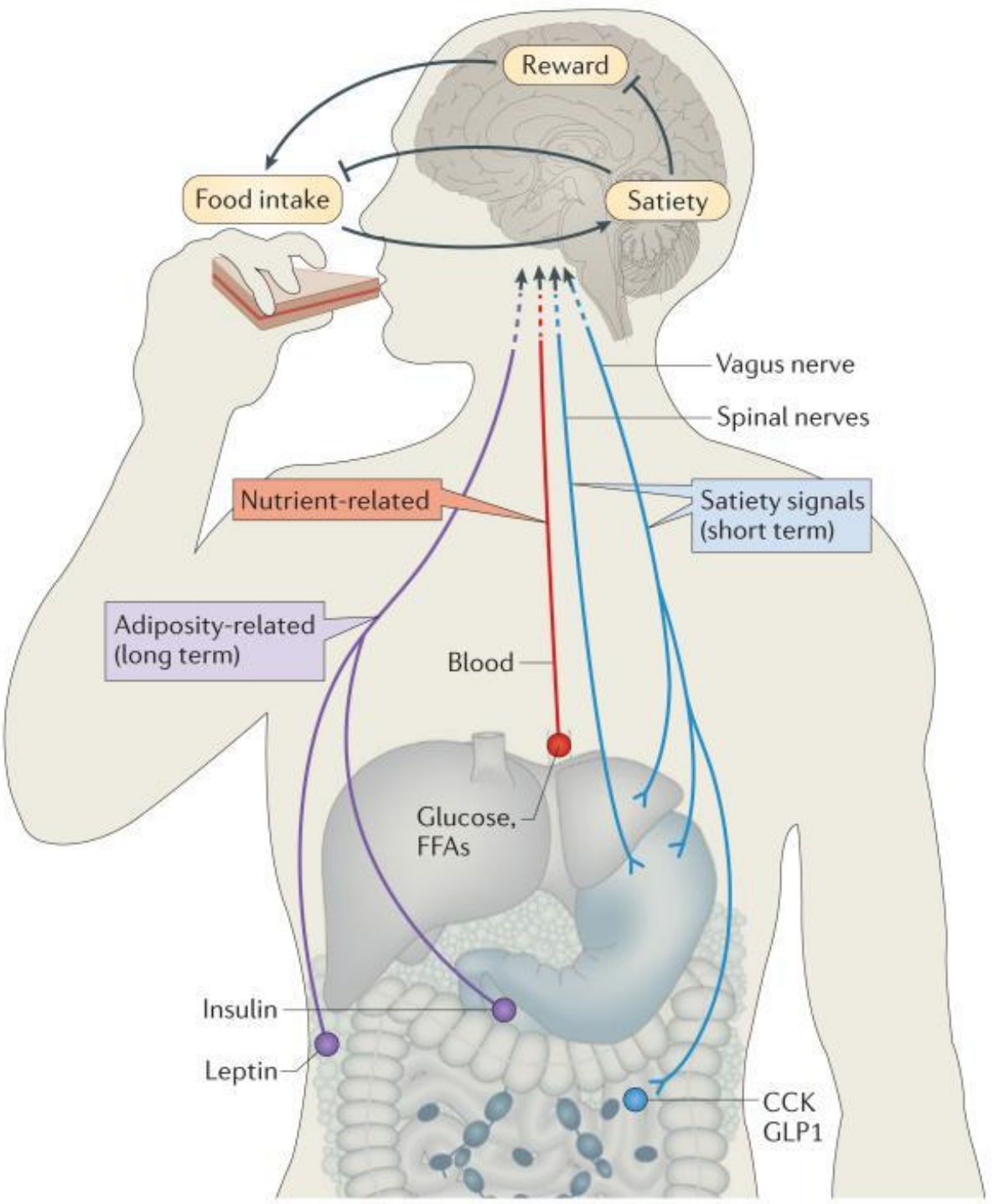
- Mutação do gene agouti (A^{Y}) no camundongo amarelo resulta em hiperfagia, hiperinsulinemia e obesidade (expressão ectópica de agouti no hipotálamo)

- Deficiência de POMC no homem resulta em insuficiência adrenal, cabelos ruivos e obesidade

- Leptina aumenta a expressão de RNAm da POMC no hipotálamo

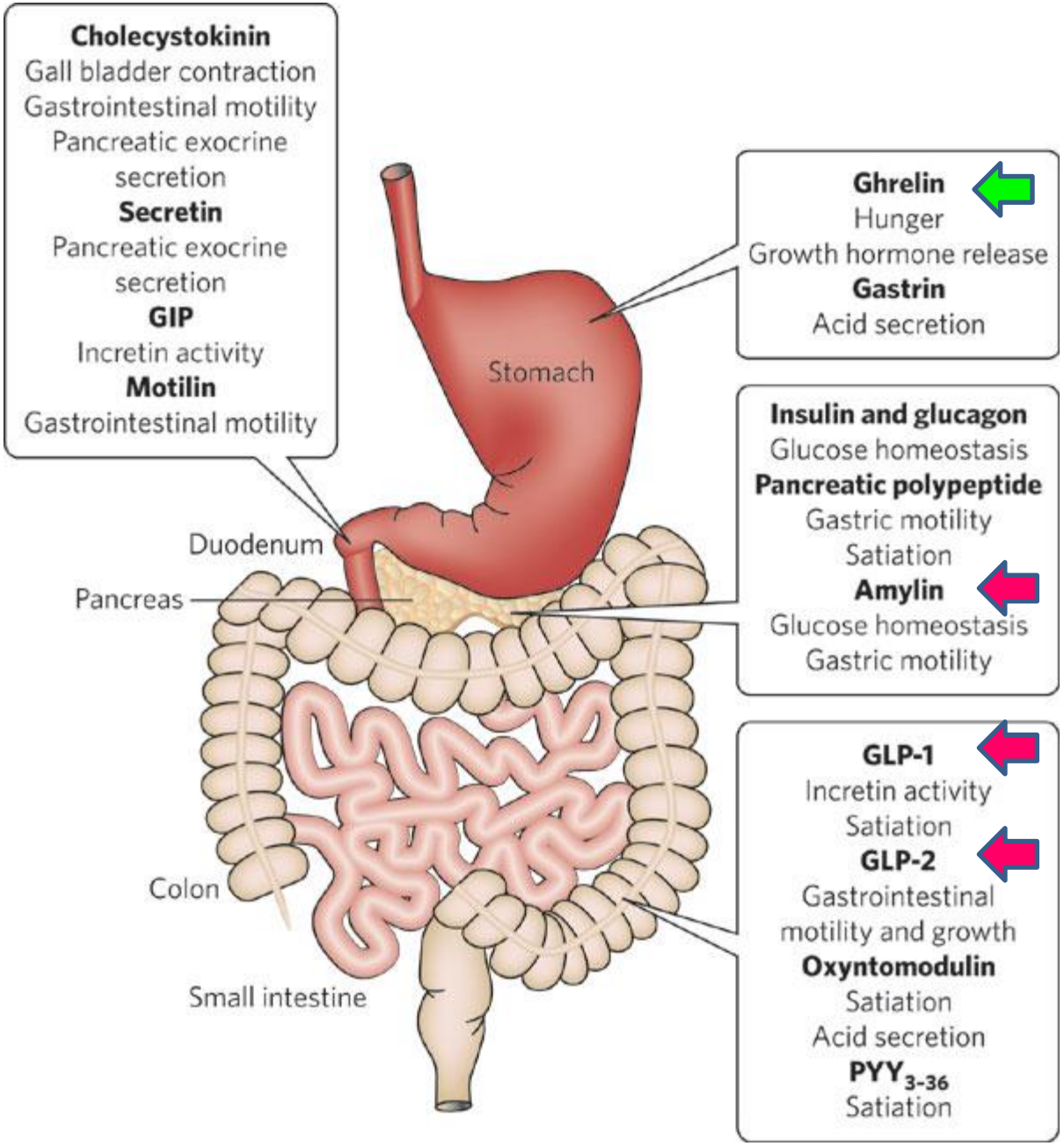
CNS regulation of energy homeostasis

Morton, et al., 2014

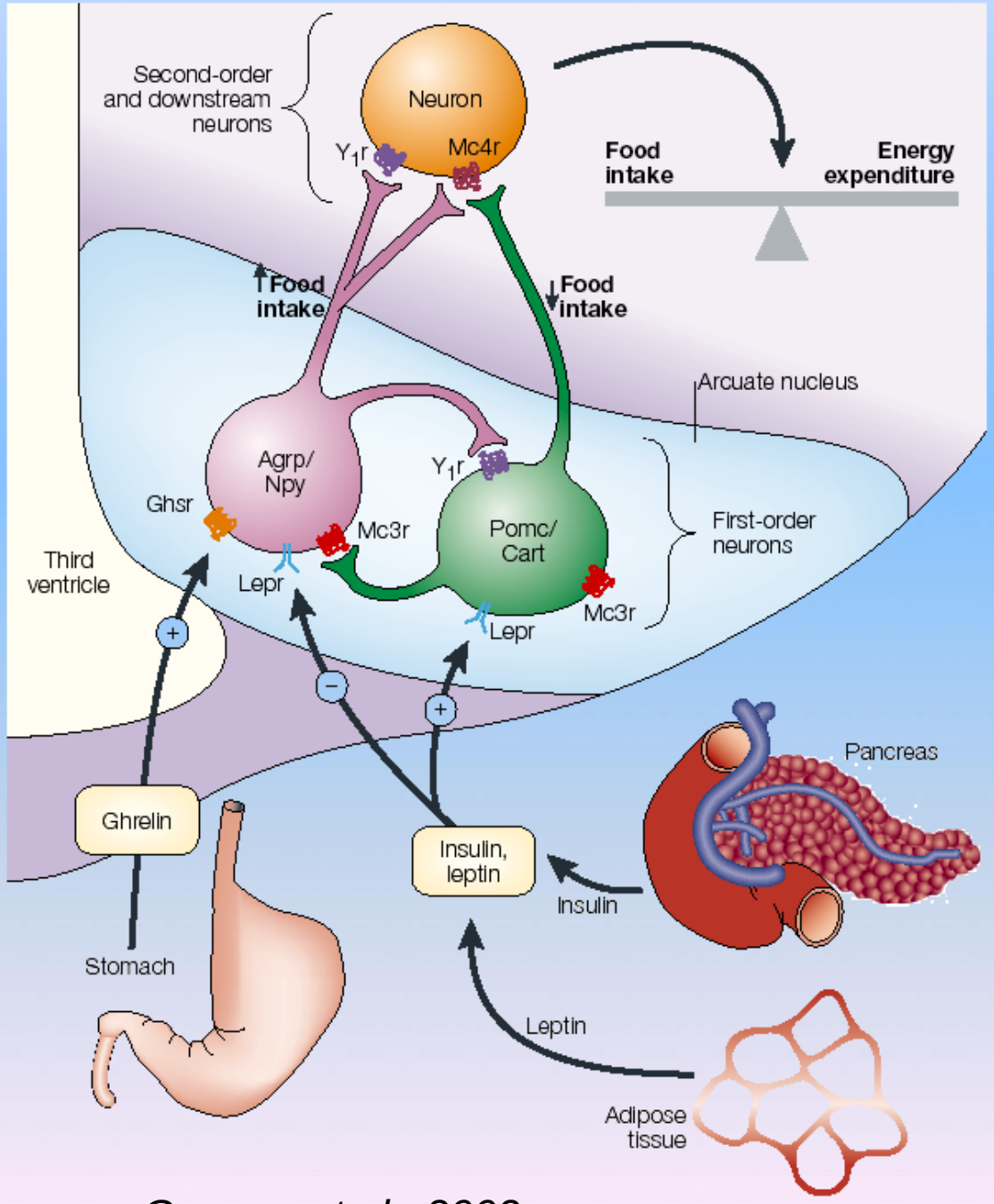


Gut hormones and the regulation of energy homeostasis

Kevin G. Murphy and Stephen R. Bloom



Neurônios do Núcleo Arqueado



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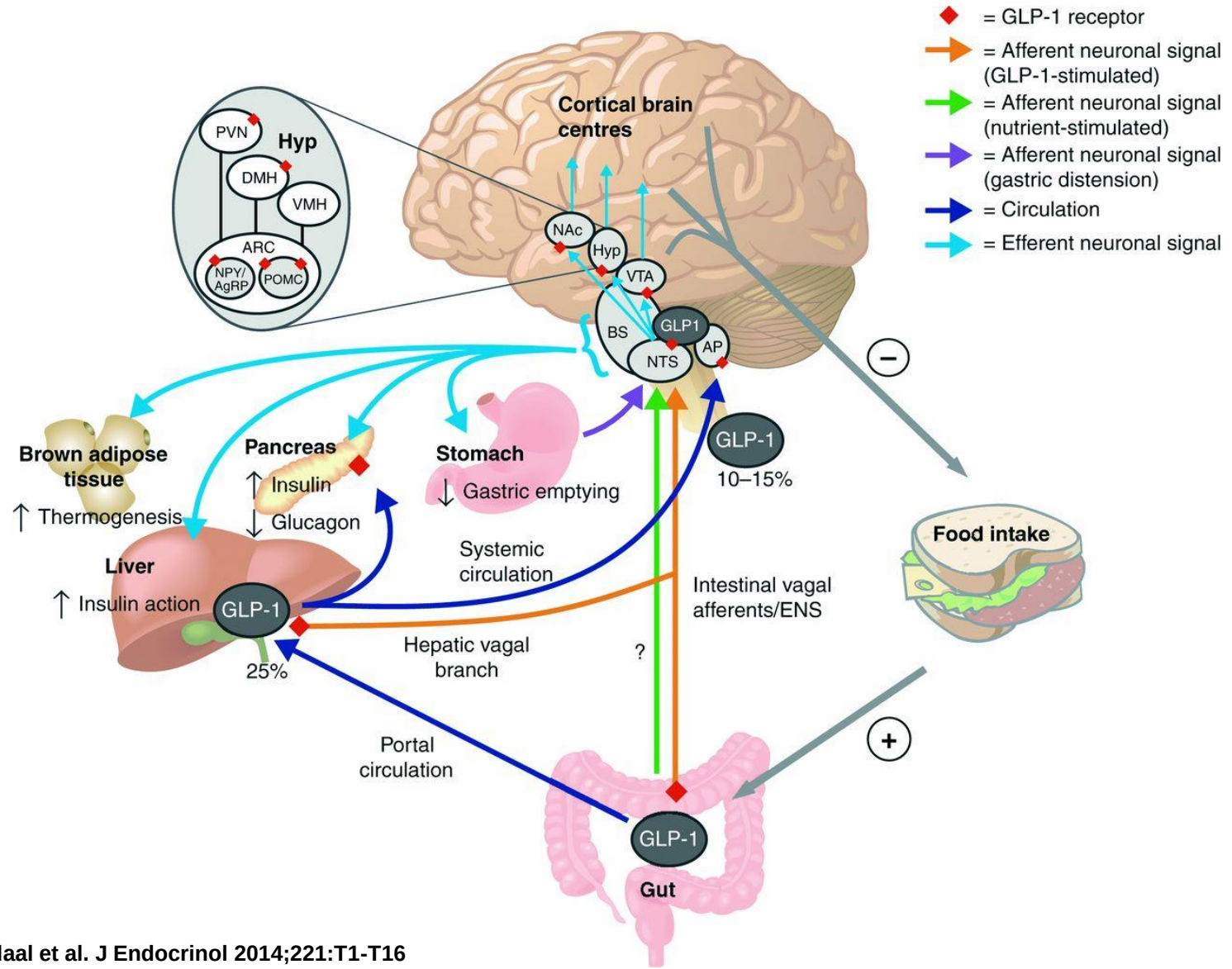
Y1r, neuropeptide Y1 receptor.

GLP-1

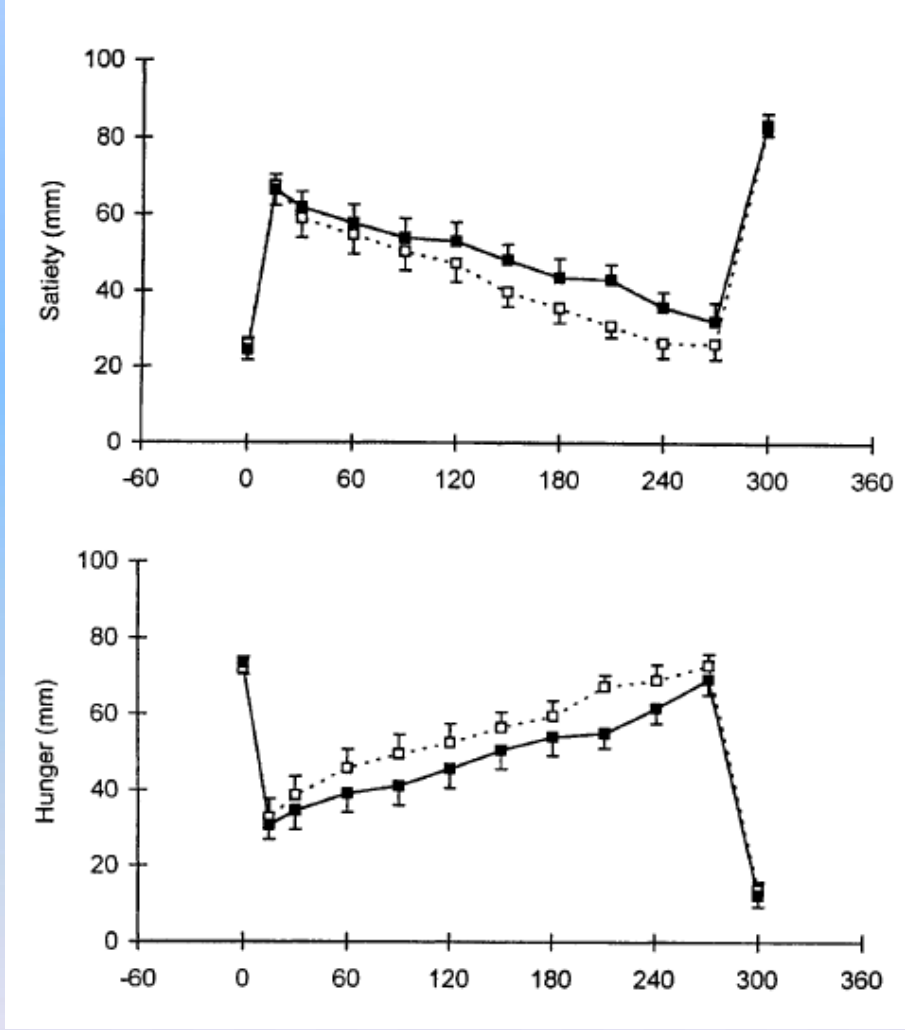
- Produto de clivagem de pre-proglucagon
- Secretado pelas células L do intestino delgado, neurônios do NTS
- Células L: sensíveis glicose, proteína, ácidos graxos e ácidos biliares, potentes liberadores de GLP-1.
- Degradação pela enzima DPP4 no fígado. Apenas 10-15% de GLP-1 liberada atinge a circulação sistêmica. Meia vida de 1-2 minutos.
- Receptor de GLP1: pâncreas, coração, rim, tecido adiposo, SNC.
- Diminui o esvaziamento gástrico e a motilidade intestinal.
- Células beta pâncreas: Potencializa a secreção de insulina estimulada pela glicose, proliferação de células beta, inibição de apoptose de células beta
- Ações na resposta de saciedade: ativação de GLP-1R em aferentes vagais, NTS, neurônios POMC (ativação) e NPY (inibição) do ARC

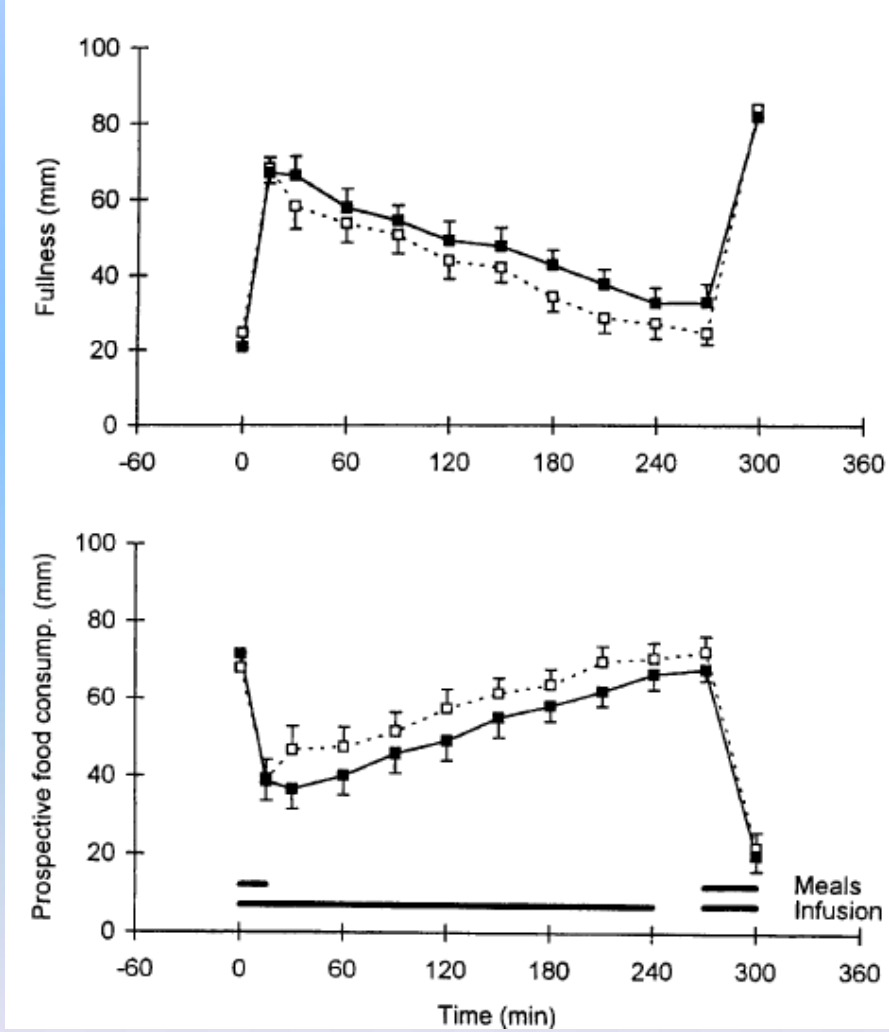
Proposed routes of action of GLP-1 in the central regulation of feeding and glucose metabolism.



L van Bloemendaal et al. J Endocrinol 2014;221:T1-T16

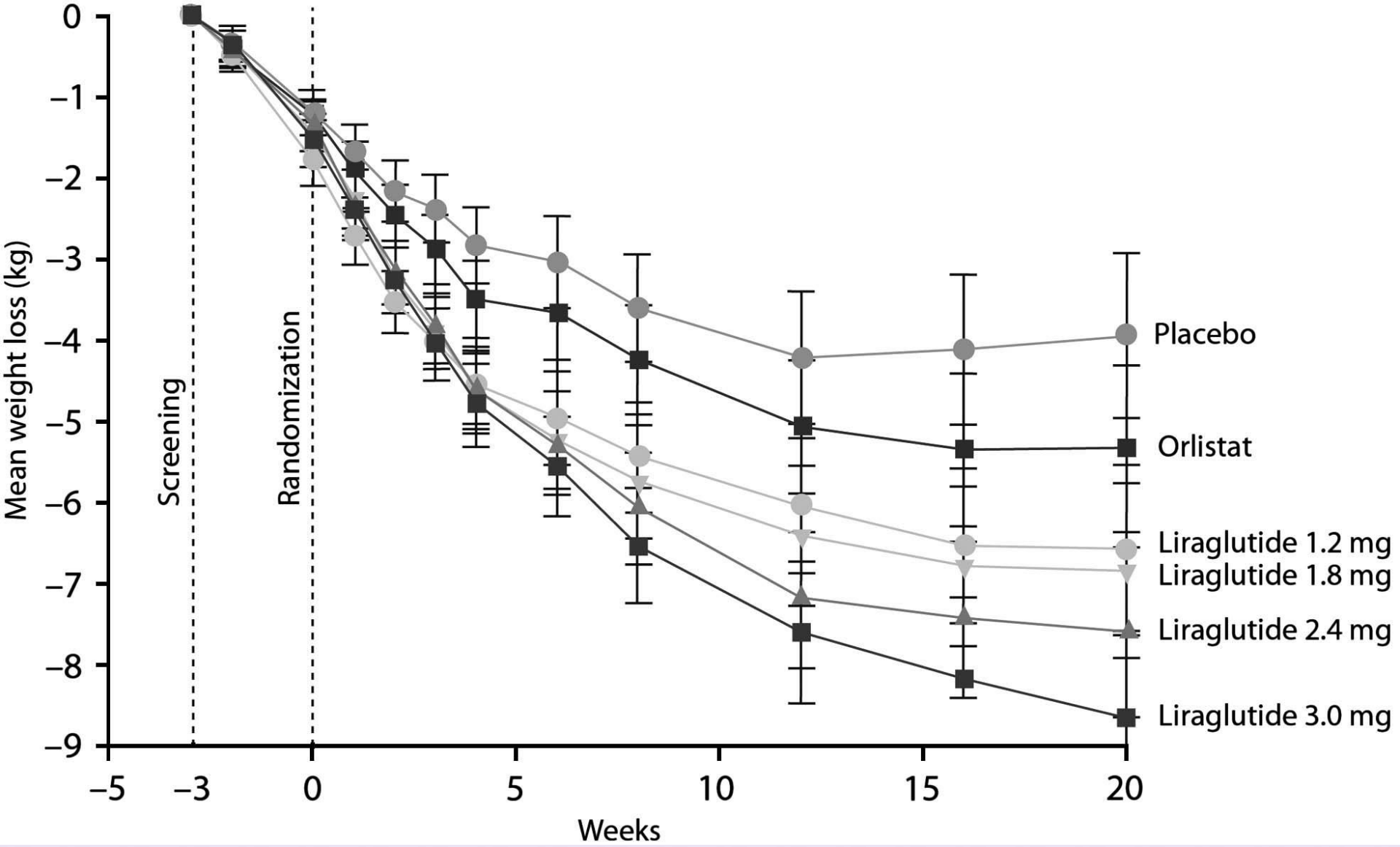
Glucagon-like Peptide 1 Promotes Satiety and Suppresses Energy Intake in Humans

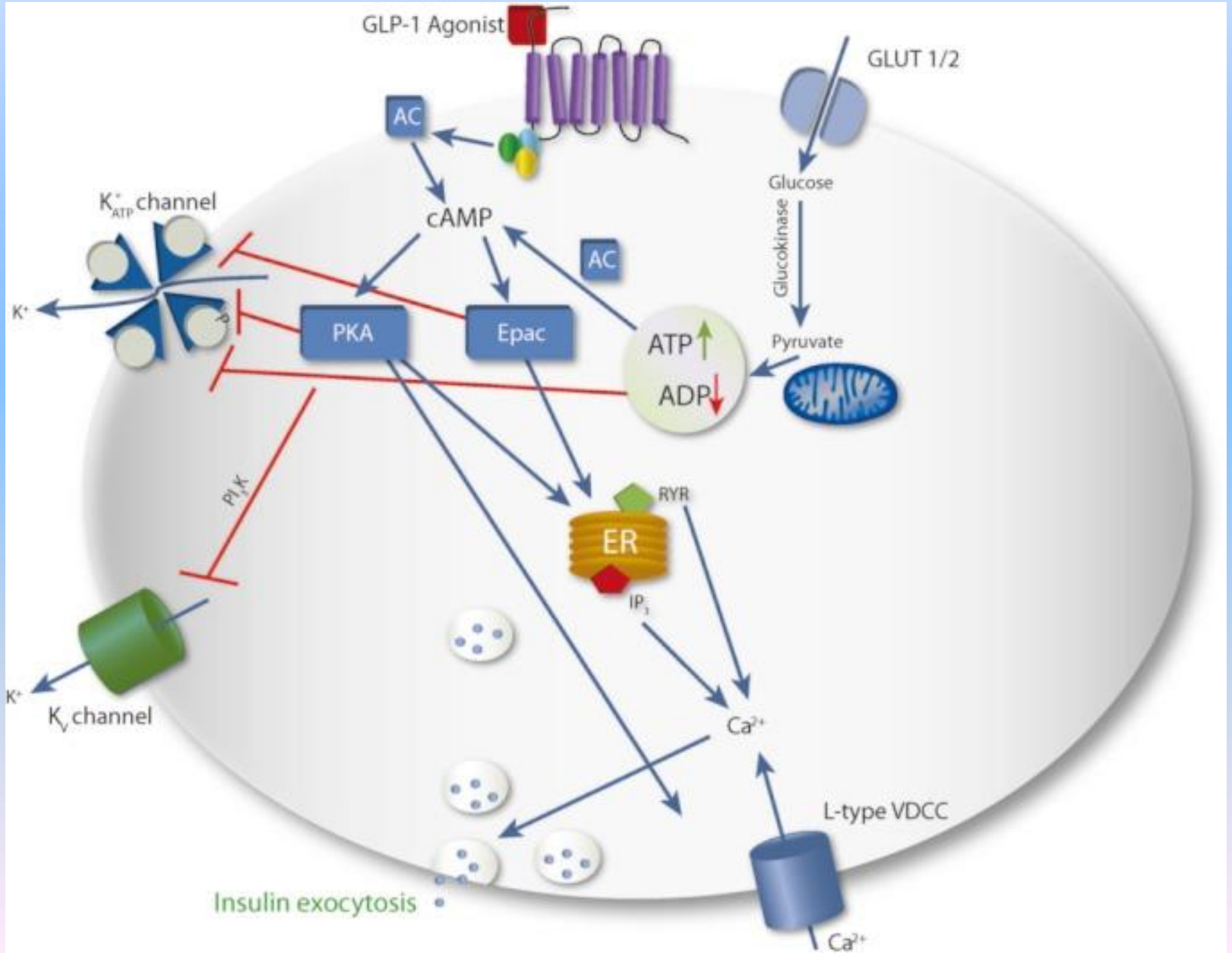




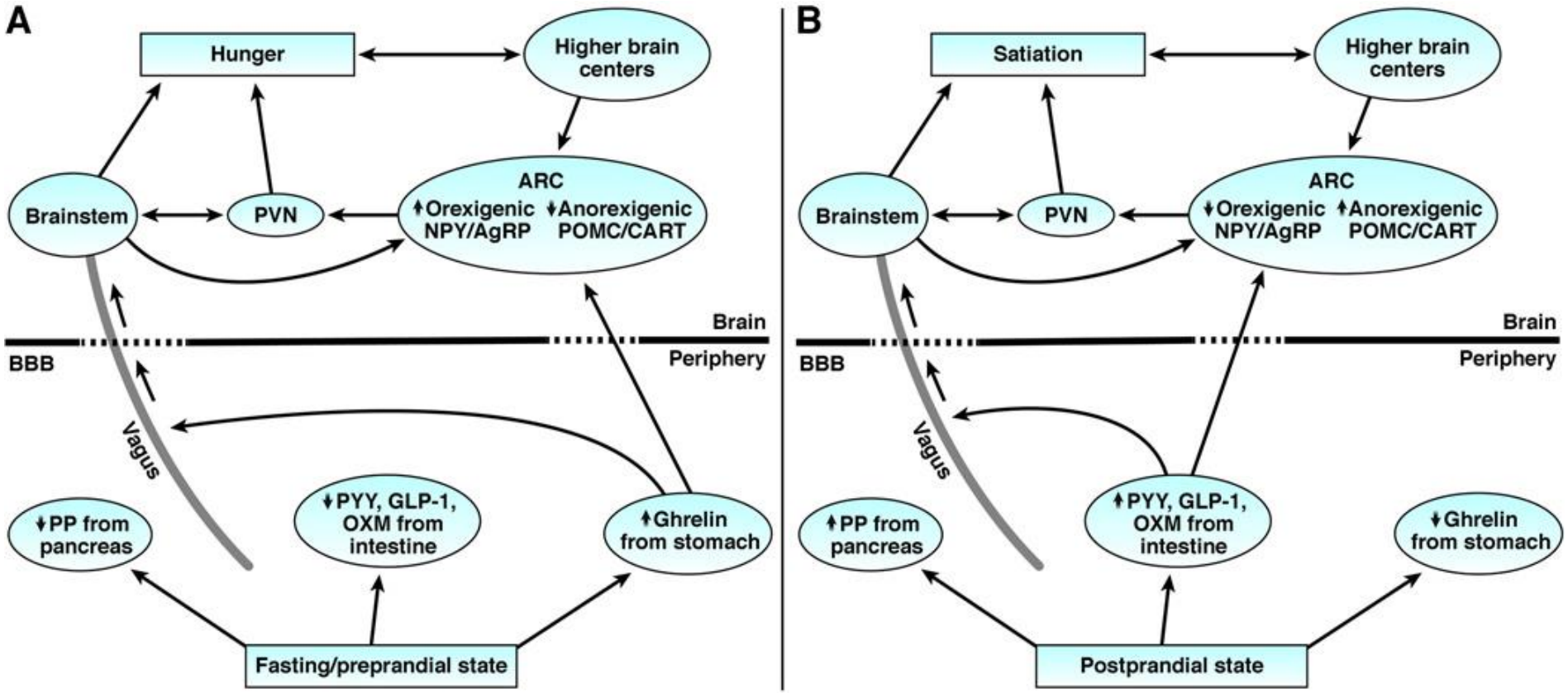
Anne Flint et al., JCI, 1998

Mean changes in body weight with liraglutide long-acting human GLP-1 analogue



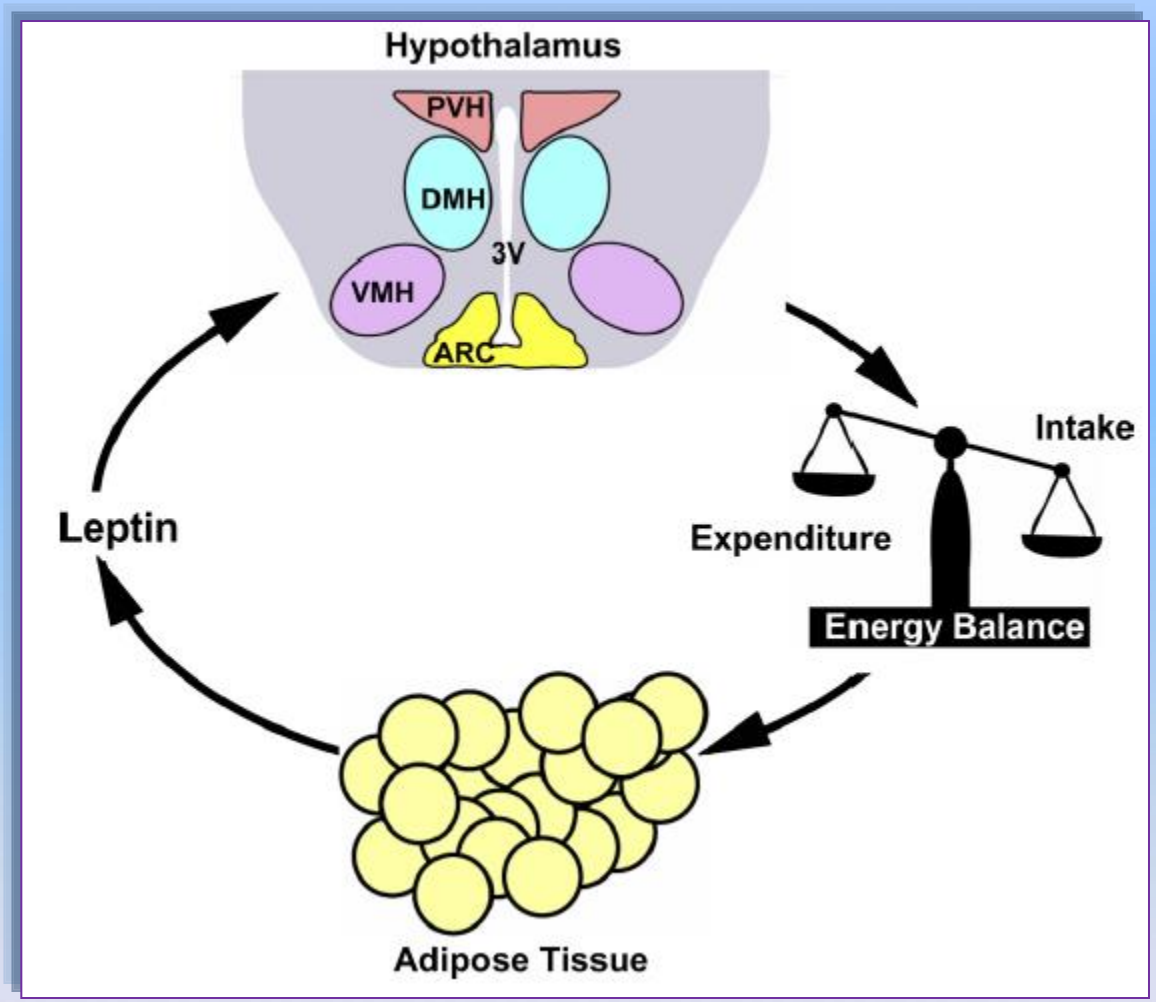

GLP-1 Agonist
GLUT 1/2
AC
Glucose
K^+_{ATP} channel
cAMP
Glucokinase
AC
K^+
PKA
Epac
ATP
ADP
Pyruvate
PI_3K
RYR
ER
IP_3
K^+
K_V channel
Ca^{2+}
L-type VDCC
Insulin exocytosis
Ca^{2+}

PERIPHERAL MECHANISMS IN APPETITE REGULATION



Camilleri, 2015

Leptina: regulação da homeostase energética e do peso corporal

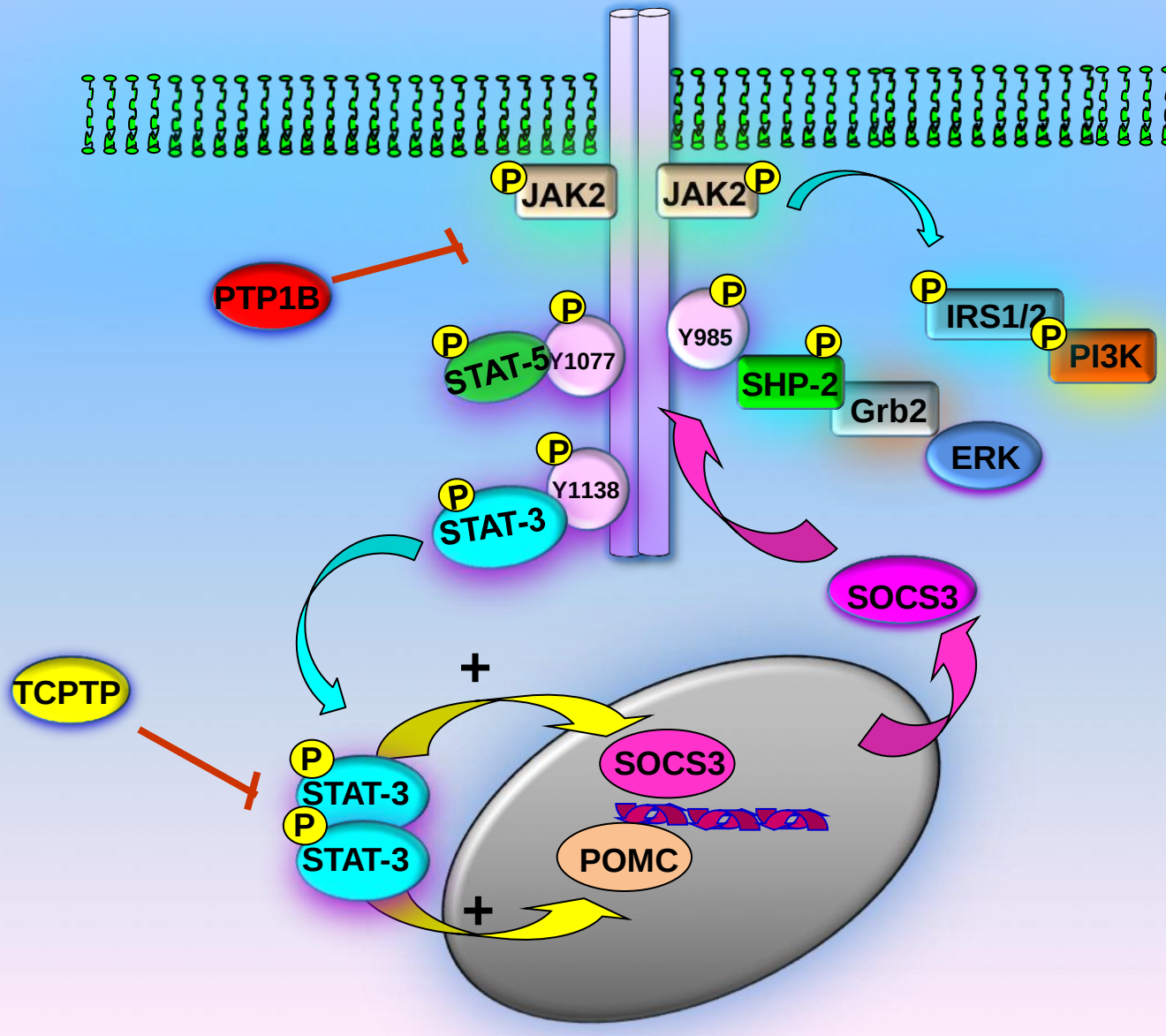


Núcleo arqueado (ARC)
Hipotálamo ventromedial (VMH)
Núcleo paraventricular (PVH)

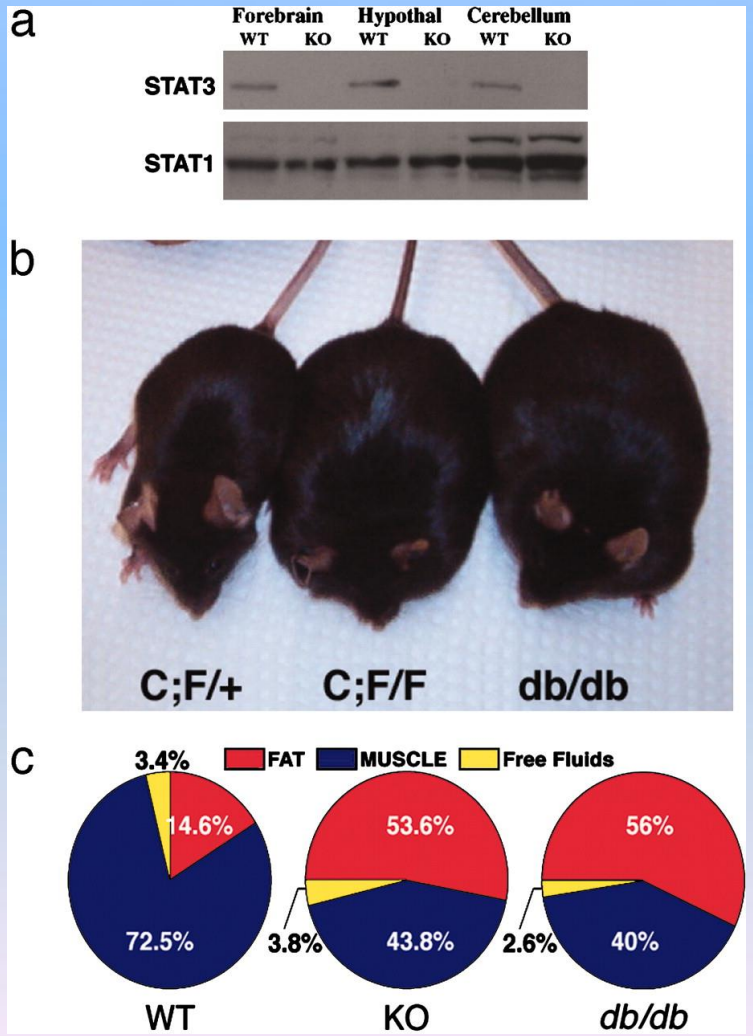
Morris and Rui,
AJP Endocrinol Metab, 2009

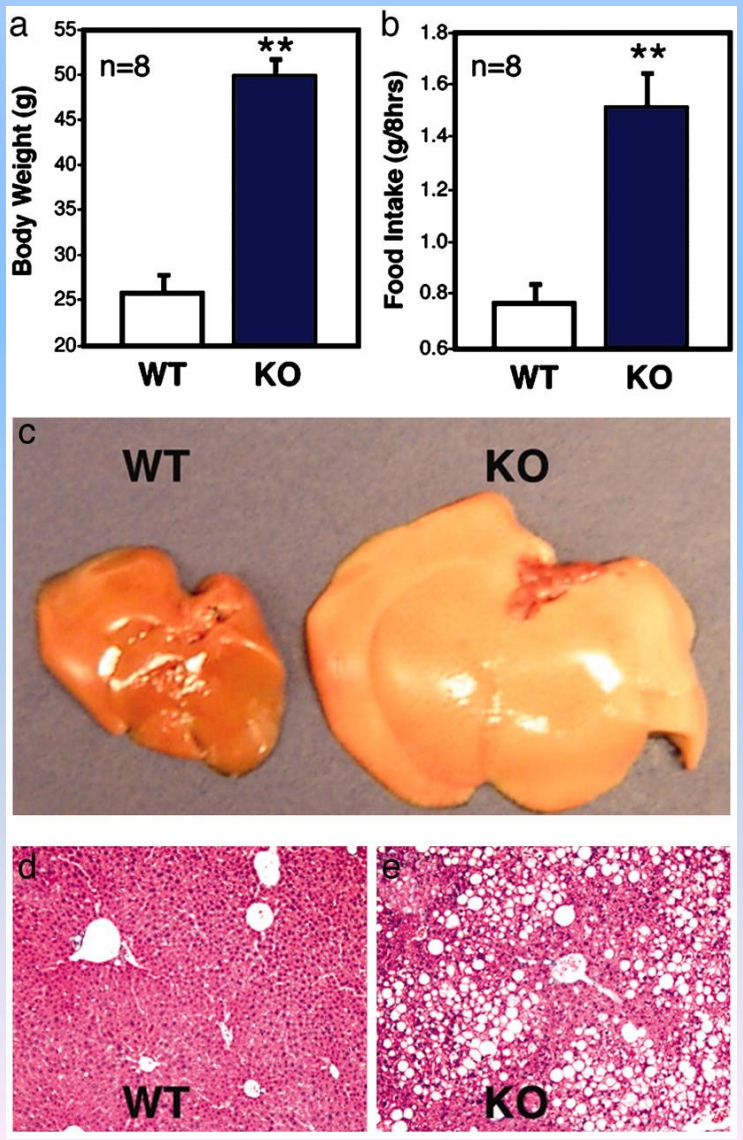
SINALIZAÇÃO DA LEPTINA

STAT3 como marcador da ativação central de LepRb



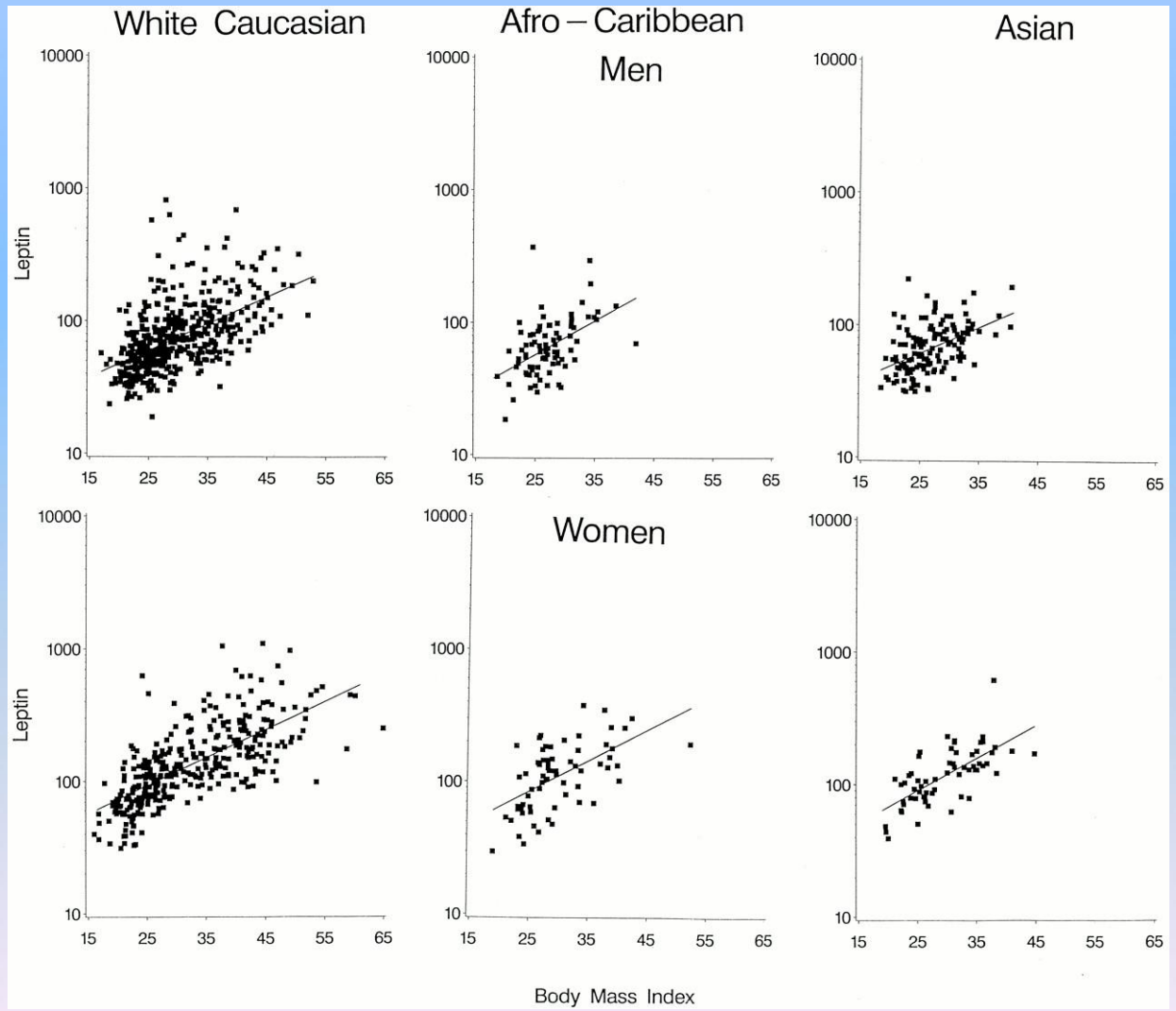
STAT3 no SNC tem função essencial na regulação da homeostase energética





Gao et al. PNAS, 2004

UK Prospective Diabetes Study (UKPDS): Leptina plasmática, obesidade e DM2



N= 1187 indivíduos

Correlação positiva entre leptina e adiposidade

Insensibilidade à leptina endógena

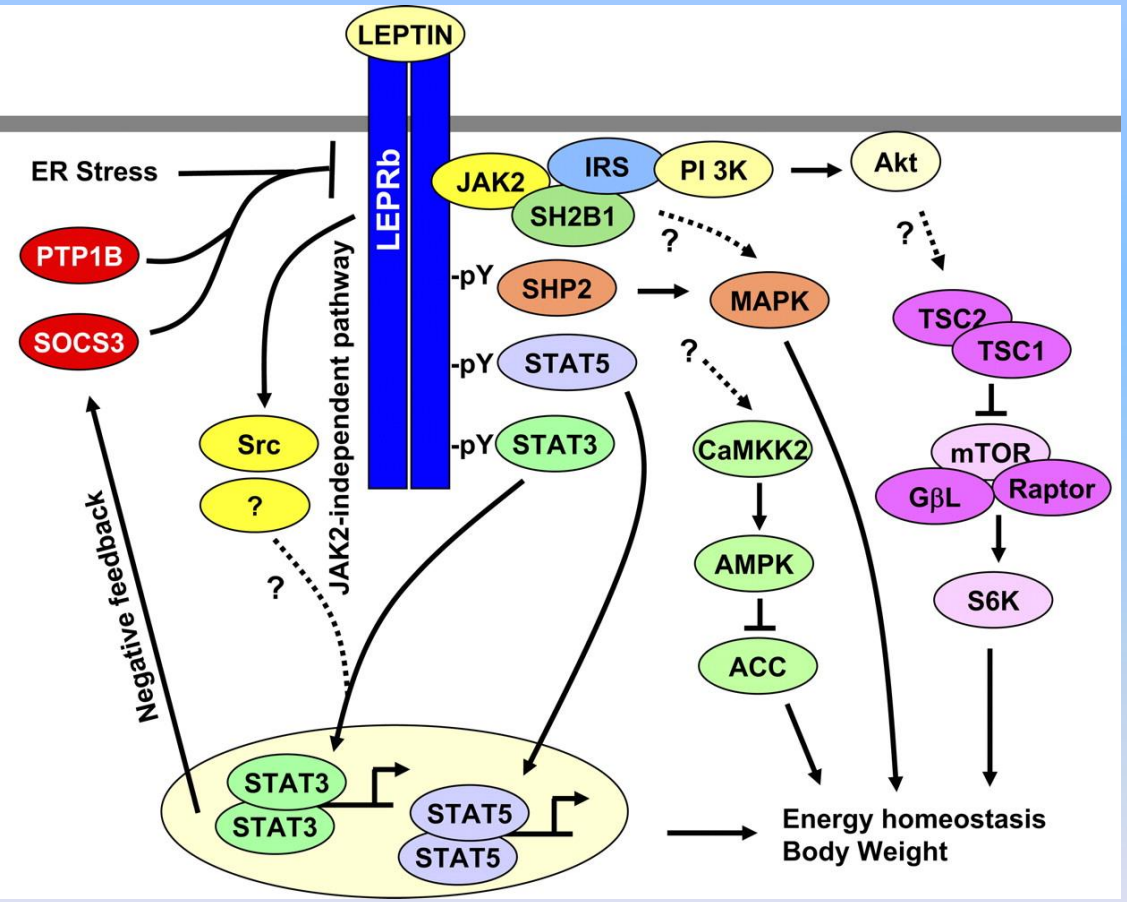
Resistência

Widjaja A et al., JCEM 1997

Resistência à Leptina:

Mecanismos Moleculares?

A model of leptin signaling and leptin resistance.



Leptin Resistance Is Induced by Multiple Mechanisms:

Impaired leptin transport

Impaired LEPRb trafficking
(Bardet-Biedl syndrome protein – mediated LEPRb trafficking)

Impaired LEPRb signaling
(SOCS3, PTP1B)

Endoplasmic reticulum stress

Defects in leptin-targeted neural circuitry
(MC4R and TrkB neurons)

Morris D L , Rui L Am J Physiol Endocrinol Metab 2009;297:E1247-E1259

AMERICAN JOURNAL OF PHYSIOLOGY
Endocrinology and Metabolism

Leptin Resistance Is Induced by Multiple Mechanisms:

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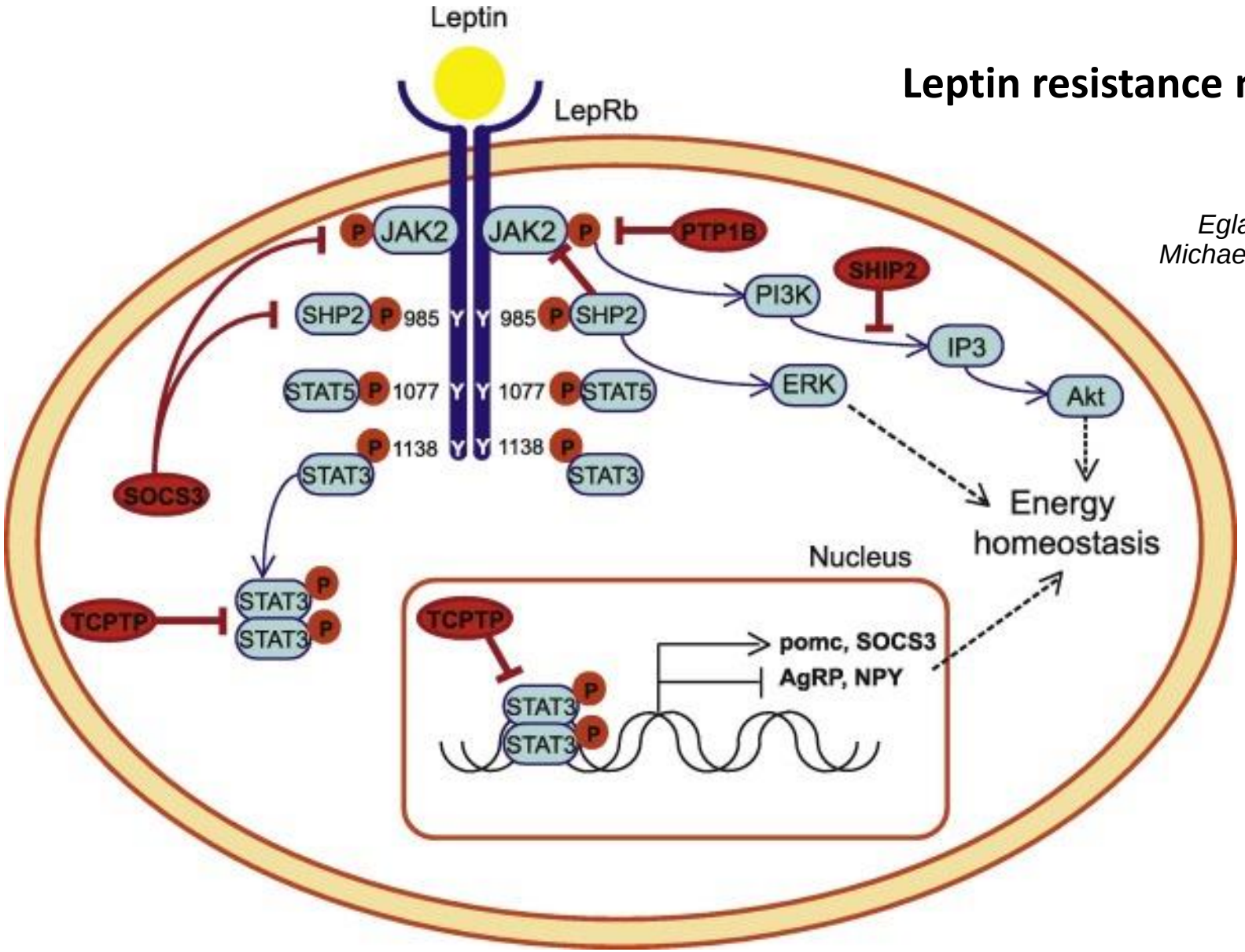
Defects in leptin-targeted neural circuitry
(MC4R neurons)

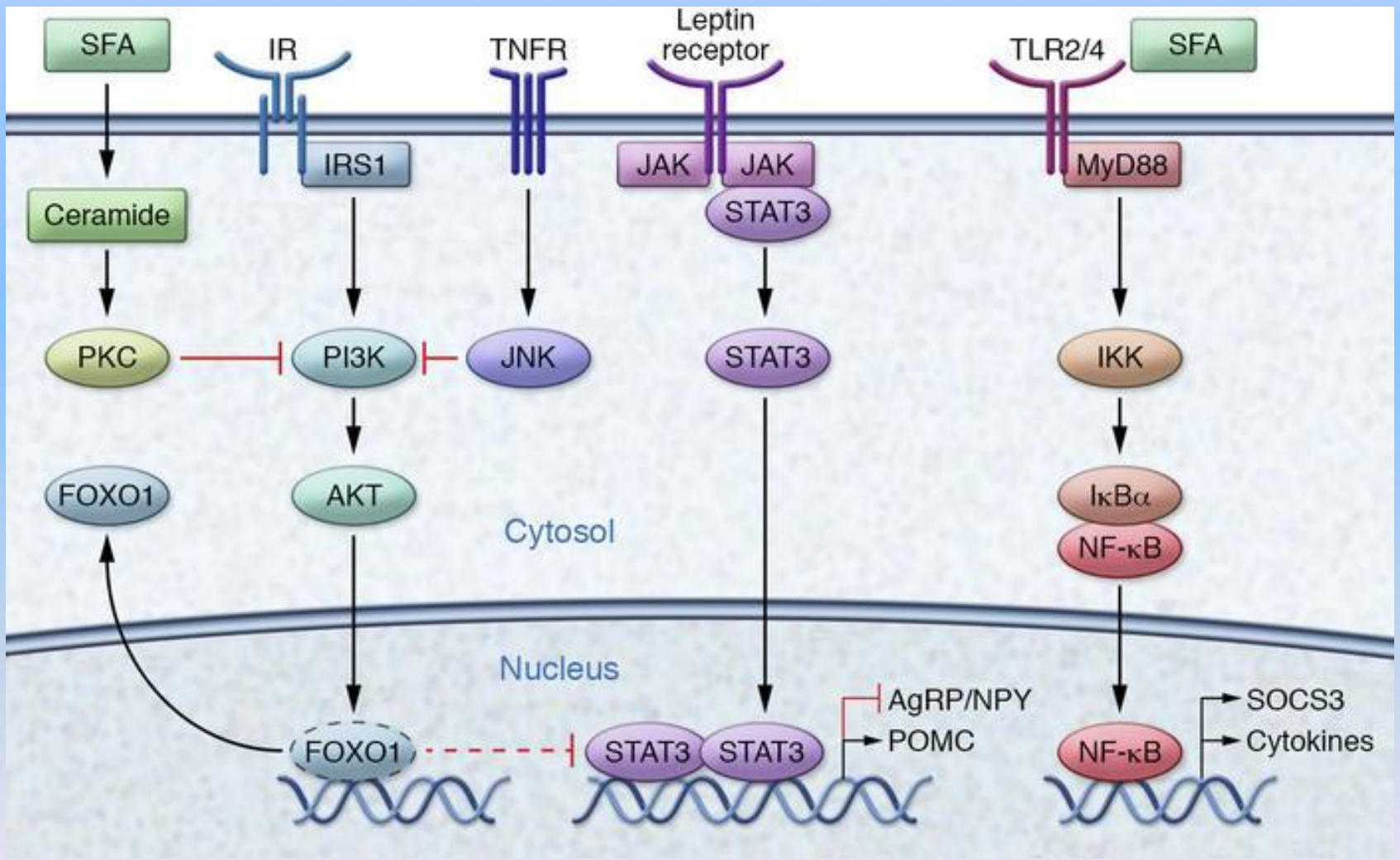
Impaired LEPRb signaling
(SOCS3, PTP1B, TCPTP)

Leptin resistance mechanisms



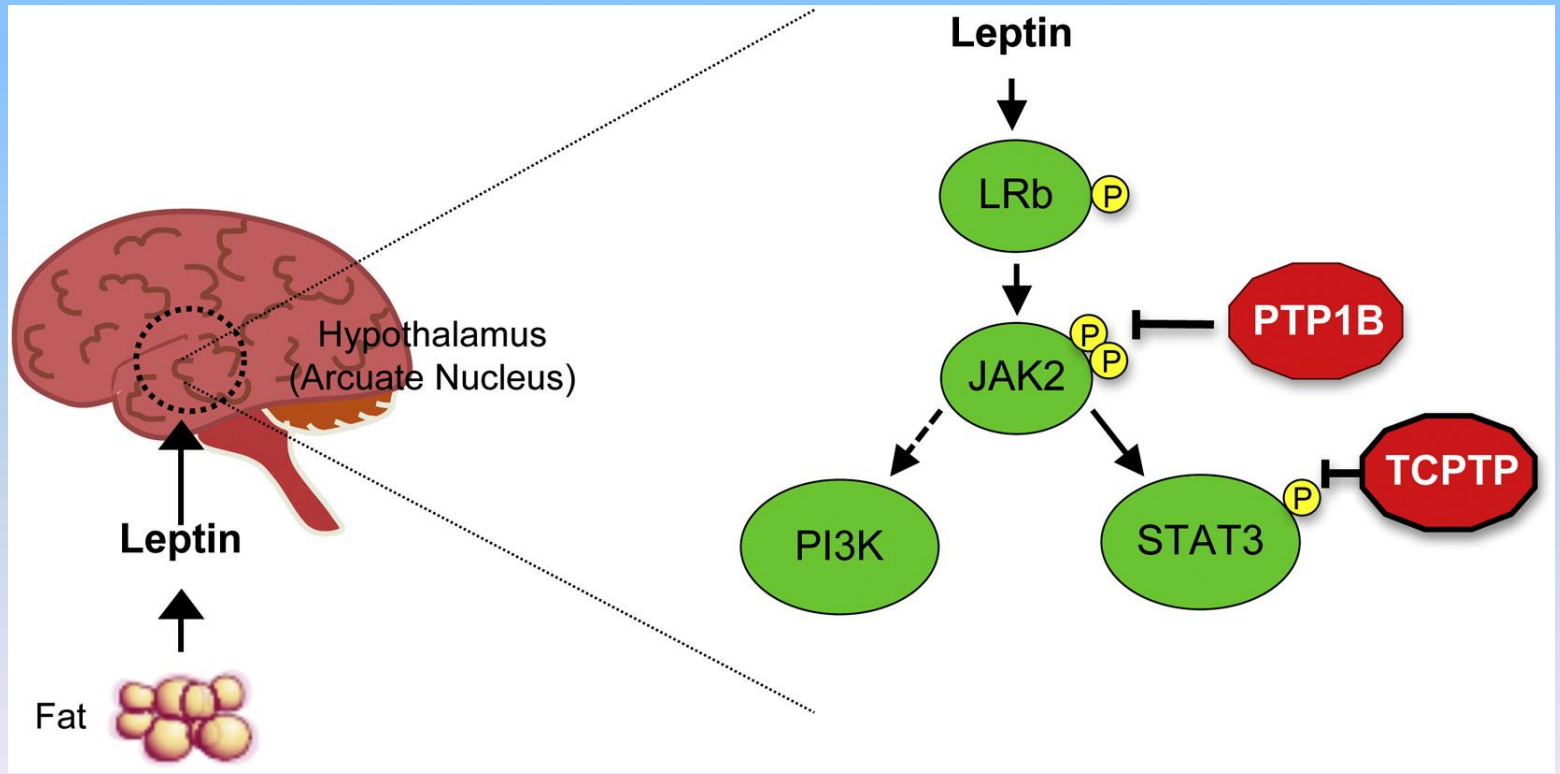
Eglantine Balland, Michael A. Cowley, 2015

***LepRb**: Leptin receptor **b,TCPTP**: T cell protein tyrosine phosphatase, **PTP1B**: Protein tyrosine phosphatase 1B, **SOCS3**: Suppressor of cytokine signalling 3, **PI3K**: Phosphoinositide 3-kinase , **JAK2** Janus kinase 2, **ERK**: Extracellular signal-regulated kinase , **STAT** – Signal transducer activator of transcription, **SHP2**"Protein tyrosine phosphatase 2*


SFA
IR
TNFR
Leptin receptor
TLR2/4
SFA
IRS1
JAK
JAK
MyD88
Ceramide
STAT3
PKC
PI3K
JNK
STAT3
IKK
FOXO1
AKT
IκBα
Cytosol
NF-κB
Nucleus
AgRP/NPY
SOCS3
FOXO1
STAT3
STAT3
POMC
NF-κB
Cytokines

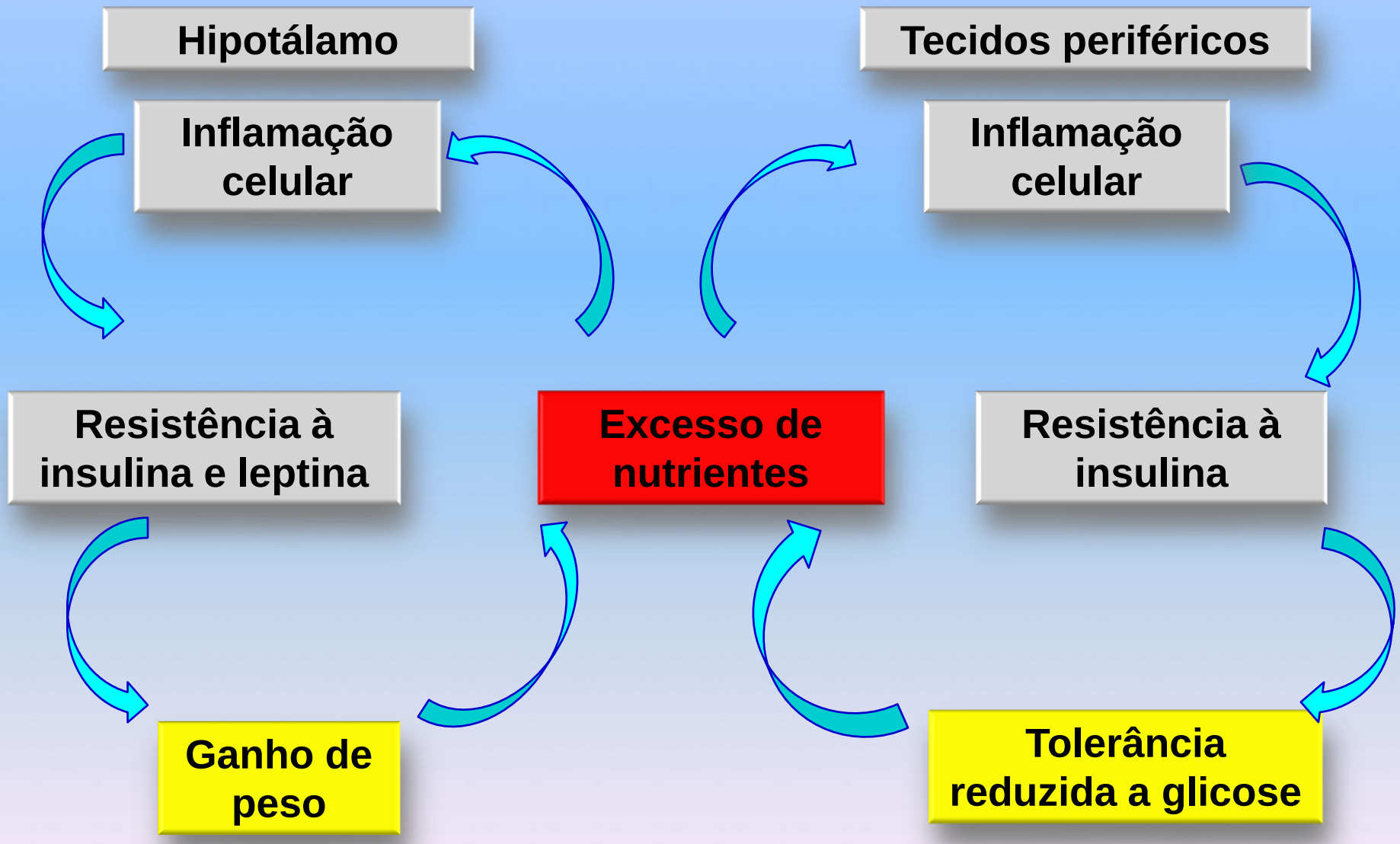
Aumento da expressão de PTP1B e TCPTP no hipotálamo contribui para a resistência à leptina

Combined PTP1B/TCPTP deletion has additive effects on leptin sensitivity and obesity



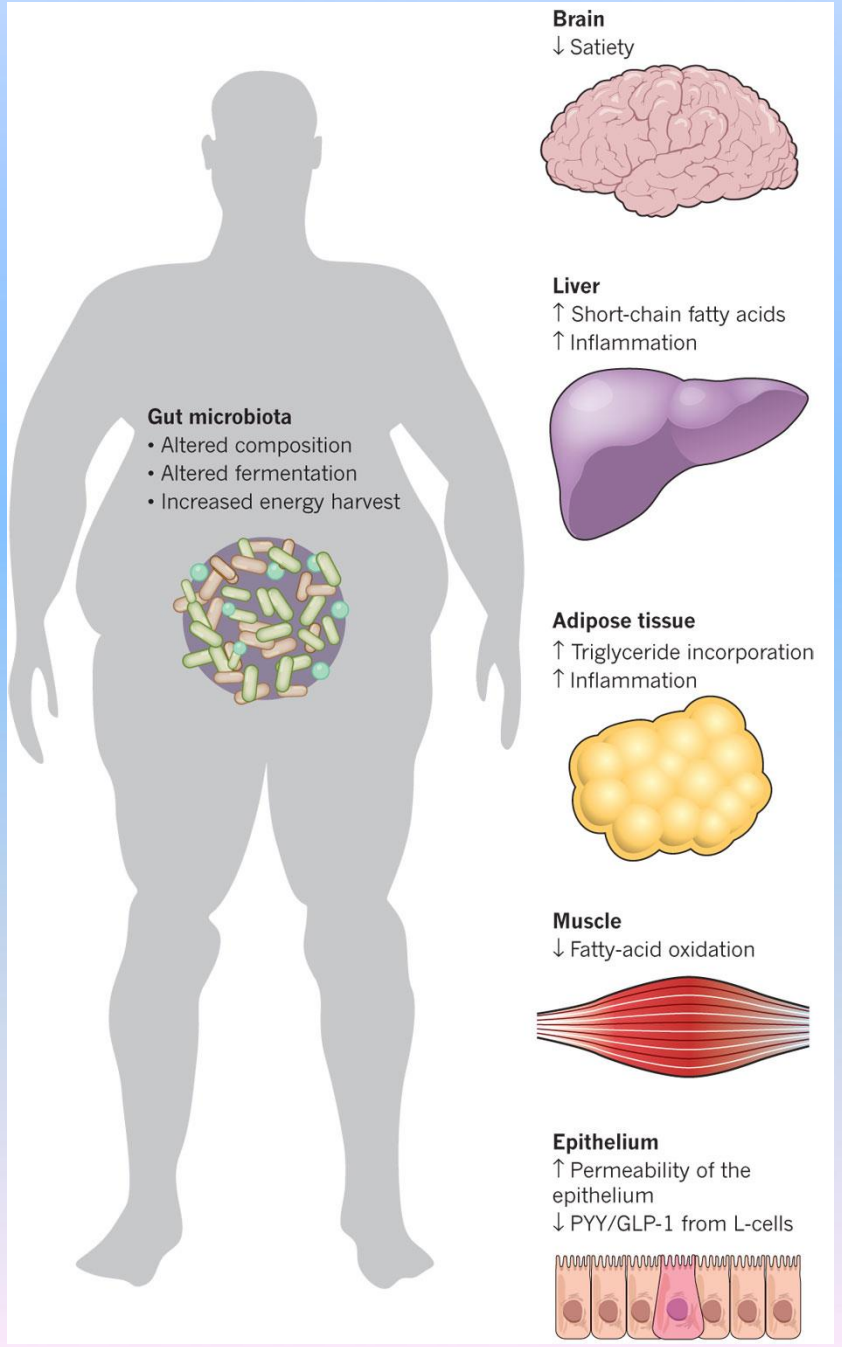
Loh et al., 2011

Inflamação e Patogênese da Obesidade



Modificado de Thaler and Schwartz, Endocrinology, 2010

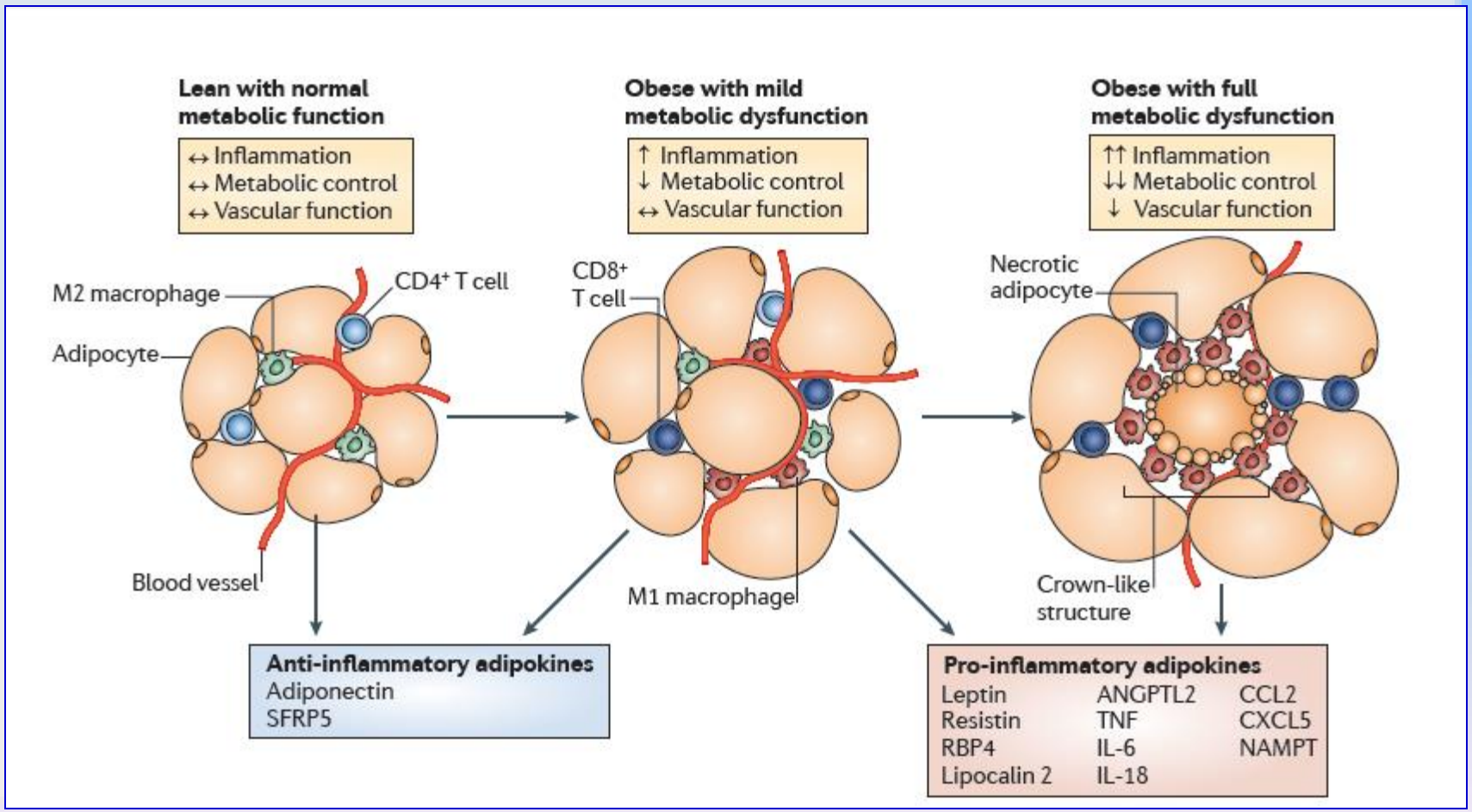
O que causa a inflamação na obesidade?



Alterações na microbiota gastrointestinal na patogênese da obesidade

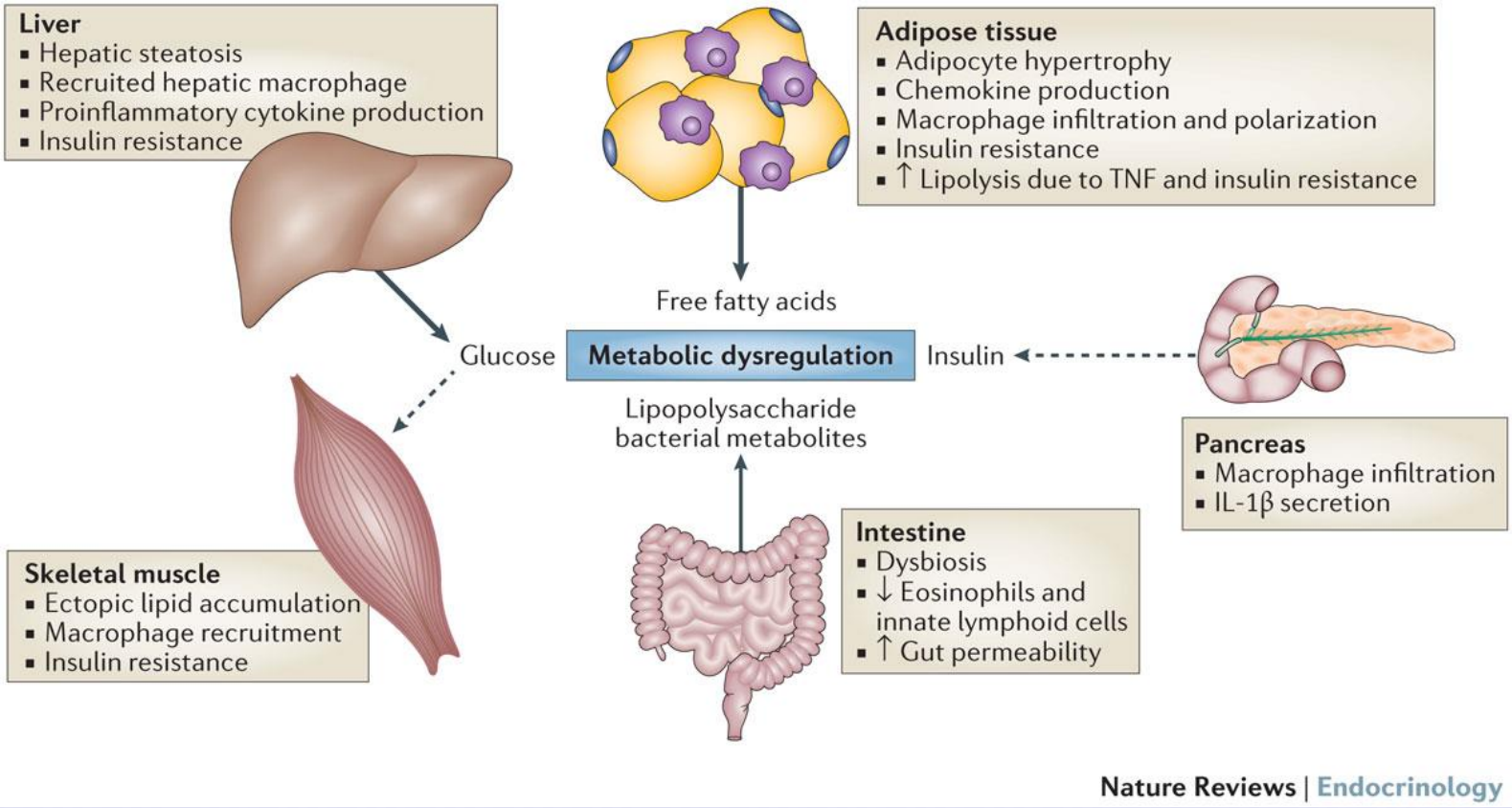
Tramaroli and Bäckhed, Nature , 2012

Obesidade:
Inflamação Crônica Subclínica



Ouchi et al., Nature Rev, 2011

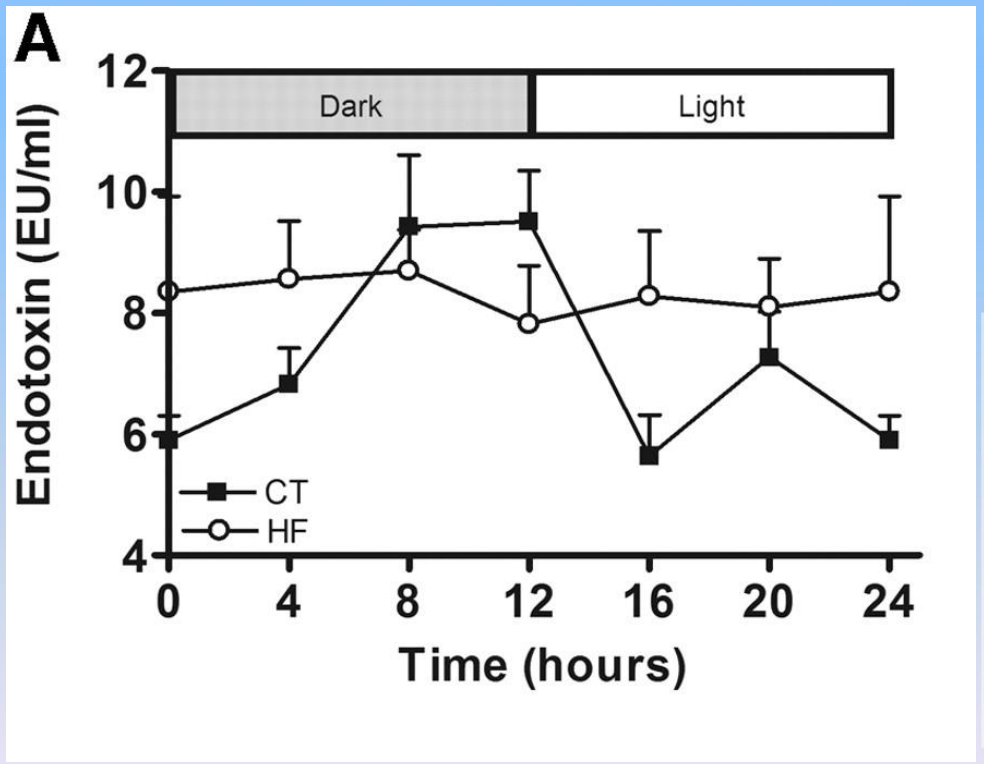
Figure 2 Obesity induces inflammation in adipose tissue, the liver, skeletal muscle and the pancreas to cause dysbiosis in the intestine



Lackey, D. E. & Olefskyl, J. M. (2015) Regulation of metabolism by the innate immune system
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2015.189

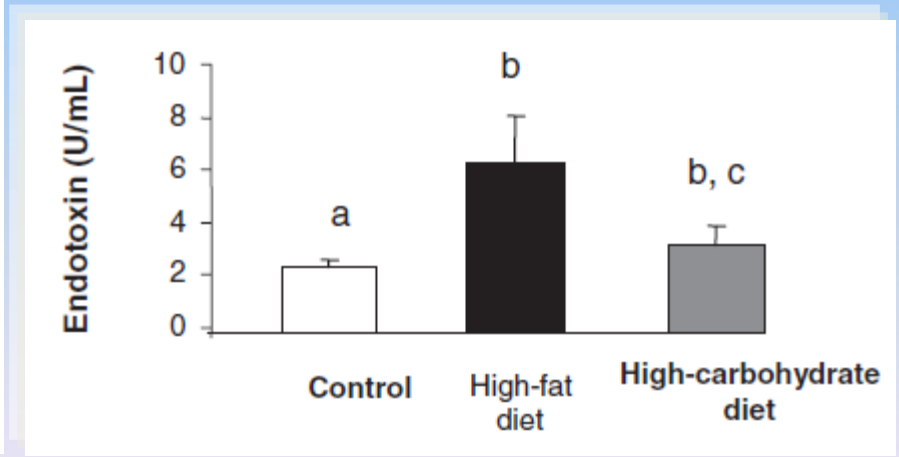
ENDOTOXEMIA METABÓLICA

Dieta hiperlipídica aumenta endotoxina no plasma



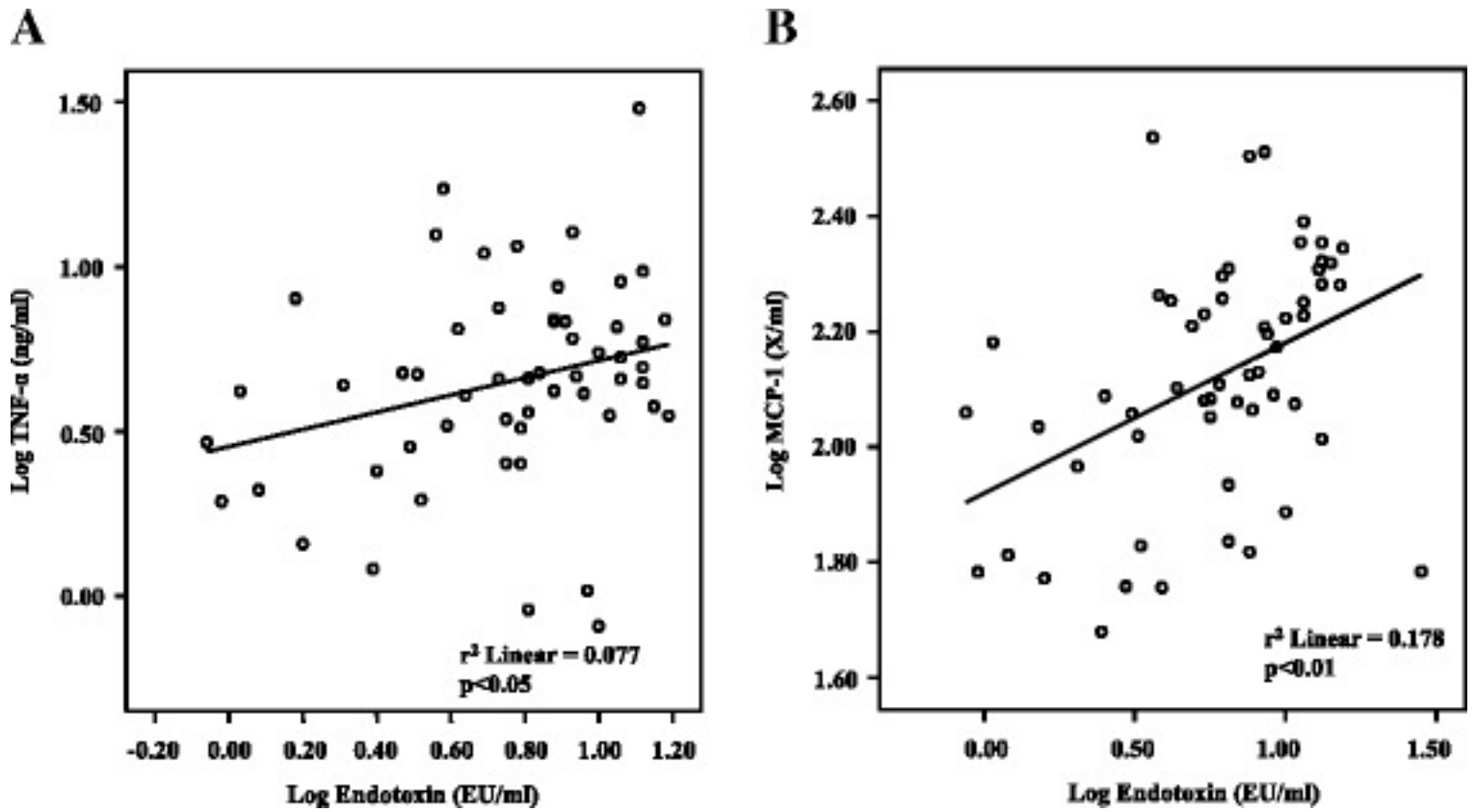
Cani, et al,
Diabetes, 2007

Influência da dieta na concentração de endotoxina no plasma



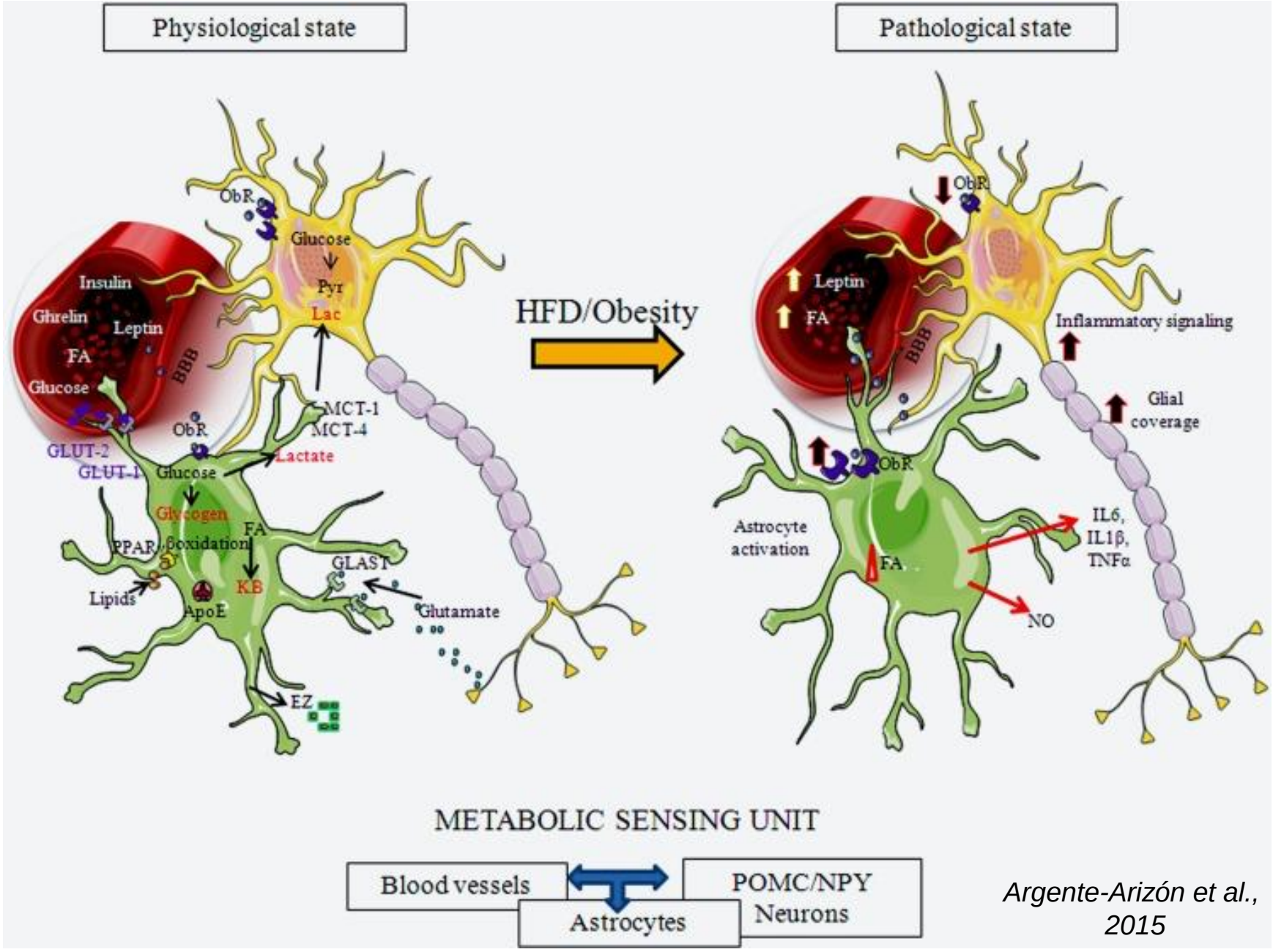
Amar et al.,
Am J Clin Nutr, 2008

Correlation between serum endotoxin levels and the inflammatory markers in children and adolescents



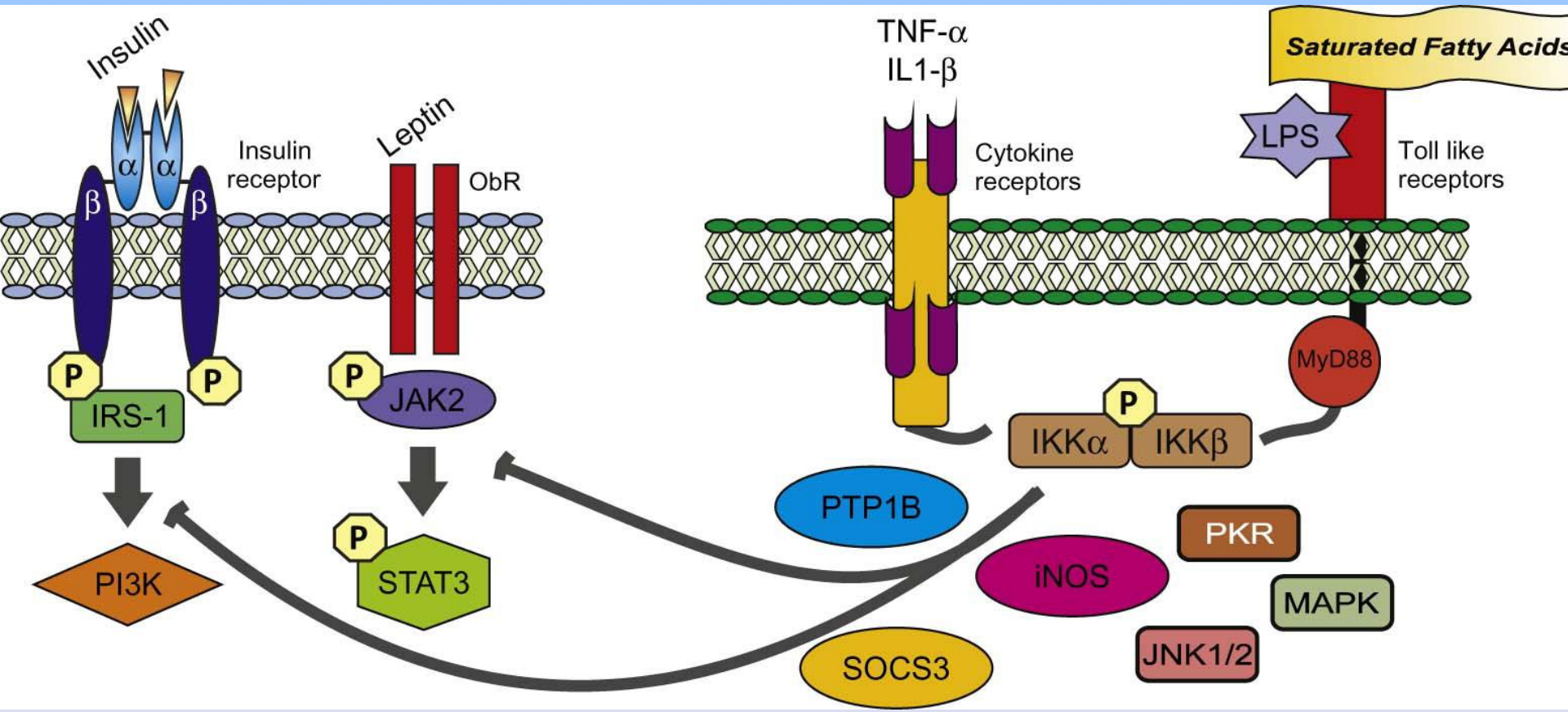
Varma et al., 2015

Role of Non-Neuronal Cells in Body Weight and Appetite Control



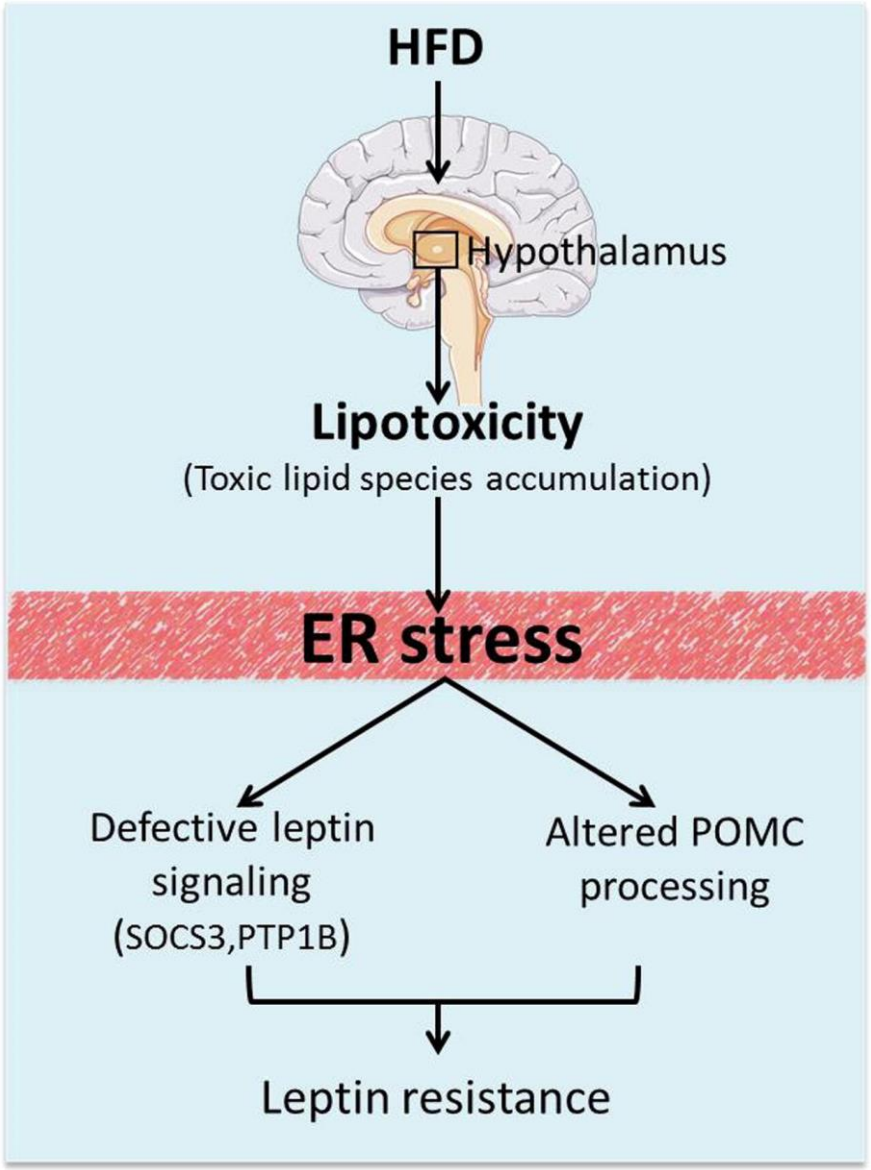
Argente-Arizón et al., 2015

LEPTIN RESISTANCE



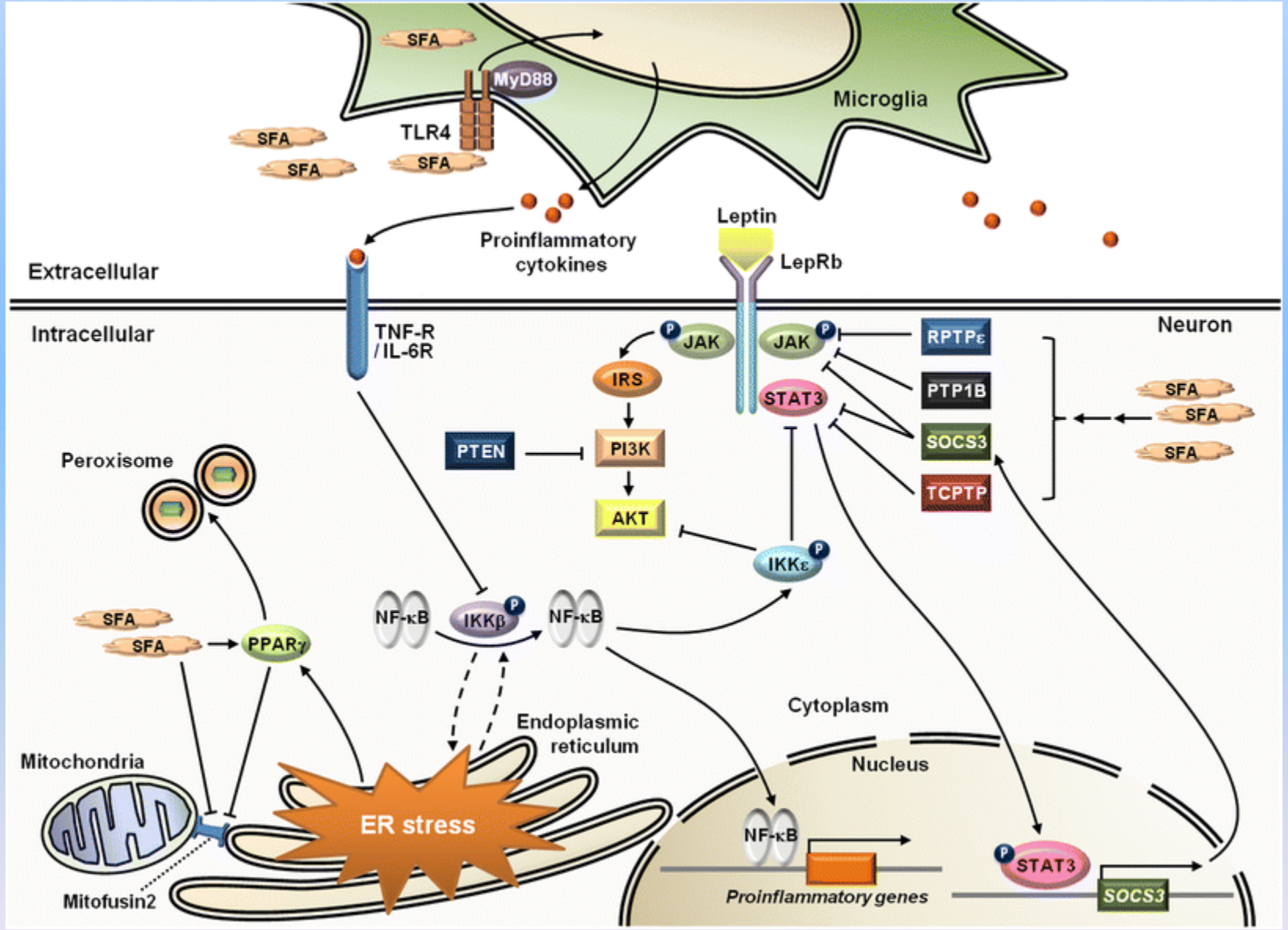
Pimentel, et al., 2014

Hypothalamic ER stress, leptin resistance and obesity

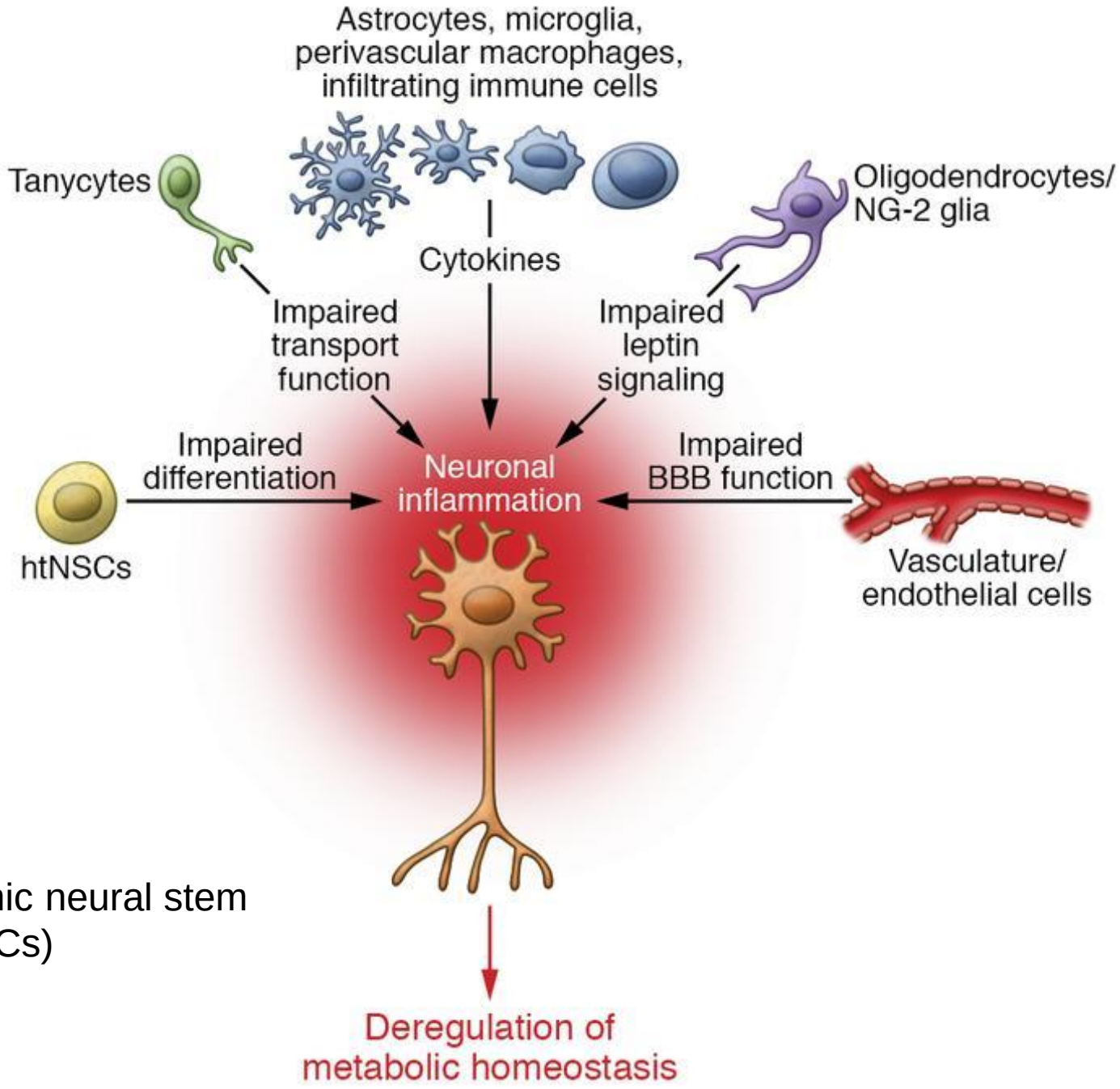


Ramirez, Claret, 2015

Signaling molecules which negatively regulate leptin signaling.

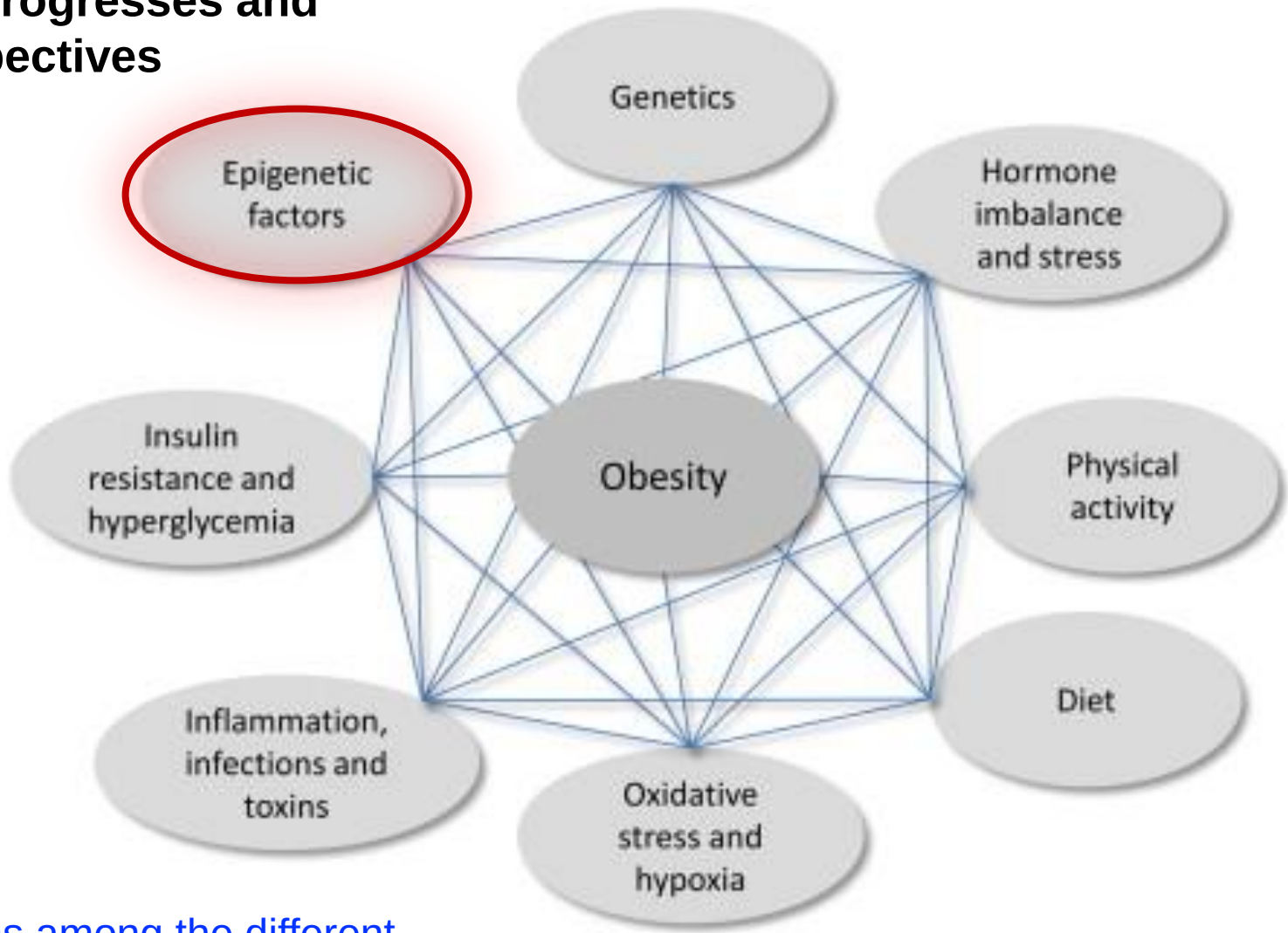


Several signaling pathways are activated in the hypothalamus of DIO mice and attenuate signaling cascades downstream from the leptin receptors via interactions with JAK2, STAT3, IRS2, and PI3K. *IKKβ* IκB kinase-β, *NFκB* nuclear factor-κB, *PKC-ϑ* protein kinase-θ, *PPARγ* peroxisome proliferator activated transcript-γ, *PTP1B* protein tyrosine phosphatase 1B, *SOCS3* suppressor of cytokine signaling 3, *PTP1B* protein-tyrosine phosphatase 1B, Tyrosine phosphatase ε (RPTPε) , T cell PTP (TCPTP), myeloid-differentiation primary-response gene 88 (MyD88),



hypothalamic neural stem cells (htNSCs)

Dietary factors, epigenetic modifications and obesity outcomes: Progresses and perspectives

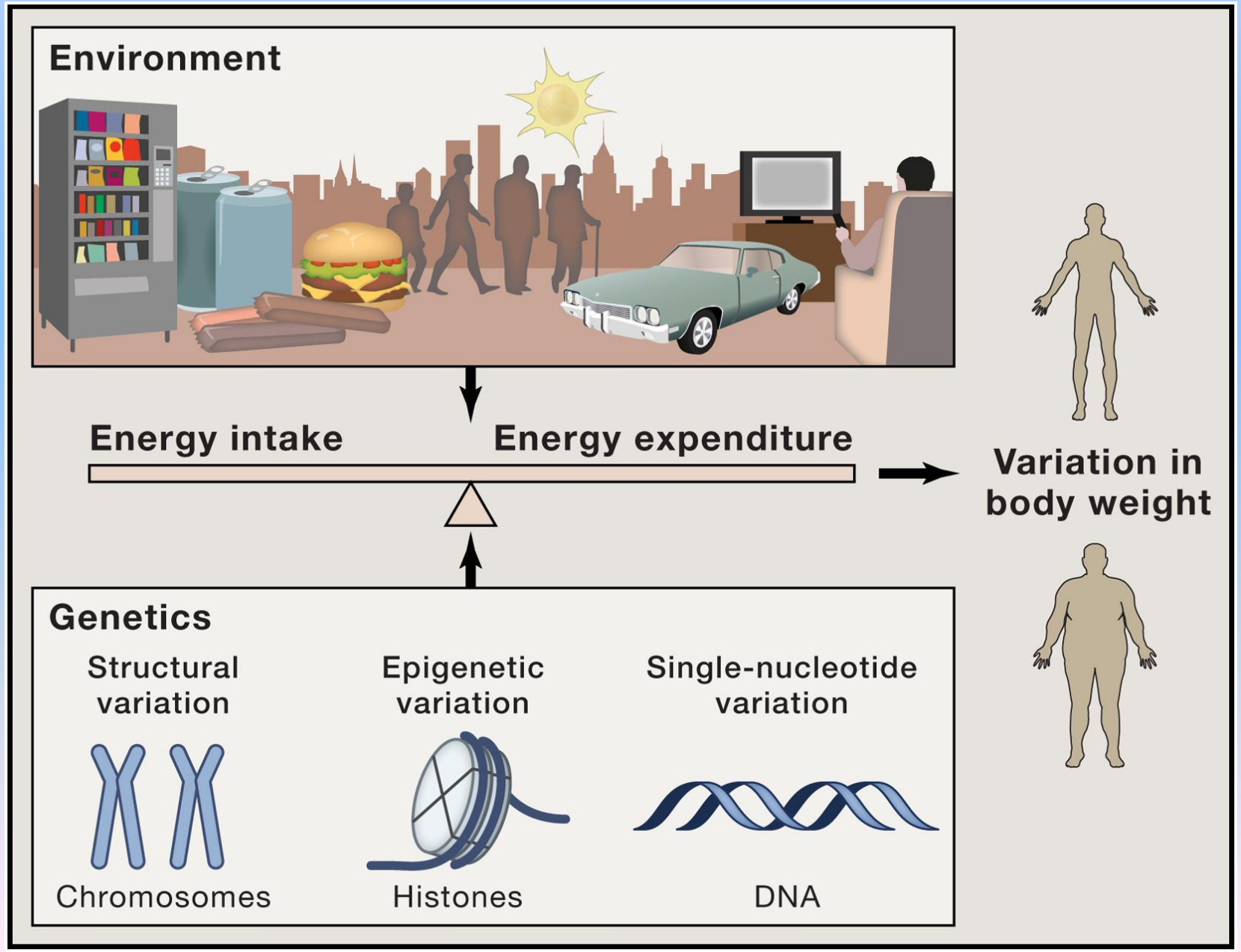


Interactions among the different factors that are involved in the onset and development of obesity.

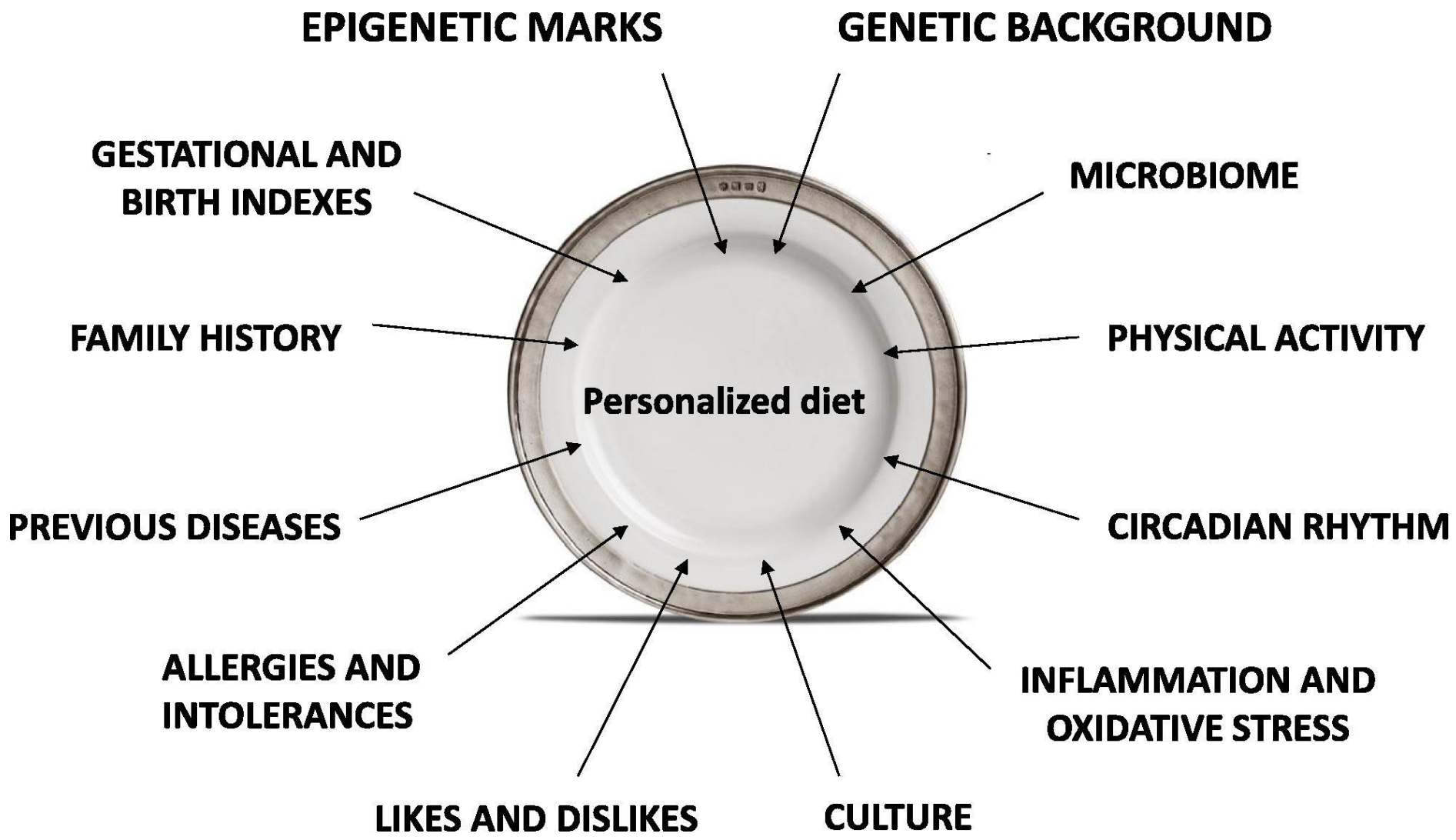
F.I. Milagro, M.L. Mansego, C. De Miguel, J.A. Martínez, 2013

PATHWAYS TO OBESITY

Klaauw, Farooq, 2015



Dietary factors, epigenetic modifications and obesity outcomes: Progresses and perspectives



F.I. Milagro, M.L. Mansego, C. De Miguel, J.A. Martínez

Molecular Aspects of Medicine, 2013