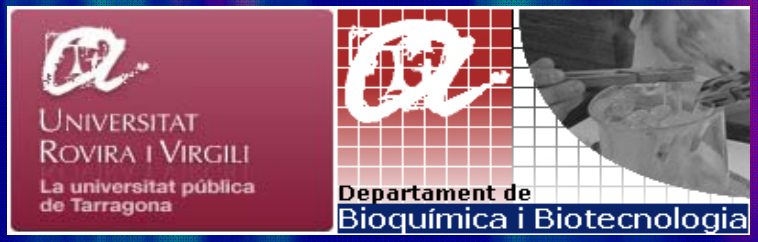
EFECTES PROTECTORS DE LA LEPTINA EN LES MALALTIES NEURODEGENERATIVES



Una lección de Claude Bernard (León Lhermitte, 1889)

Es la tendencia de los organismos vivos y otros sistemas a adaptarse a las nuevas condiciones y a mantener el equilibrio a pesar de los cambios.

Irina Matveikova, médica especializada en Endocrinología y Nutrición Clínica

Victor-M Amela, Ima Sanchís, Lluís Amiguet

"Tenemos dos cerebros: el de la cabeza y el del estómago"

06/02/2012 - 00:00

Foto: Xavier Gómez

IMA SANCHÍS

El universo interior

Leyendo *Inteligencia digestiva* (La Esfera de los Libros) me entero de que la capacidad de mi estómago de generar ácido clorhídrico puede llegar a niveles industriales, mi zumo gástrico puede disolver un trozo de metal, y el plástico en pocas horas. Me entero de que tenemos un "estado microbiano" inteligente con

Mi estómago es inteligente?

Absolutamente, es una red extensa de neuronas (100 millones) interconectadas.

¿Un segundo cerebro?

Sí, su estructura neuronal posee la capacidad de producir y liberar los mismos neurotransmisores, hormonas y moléculas químicas que produce el cerebro superior.

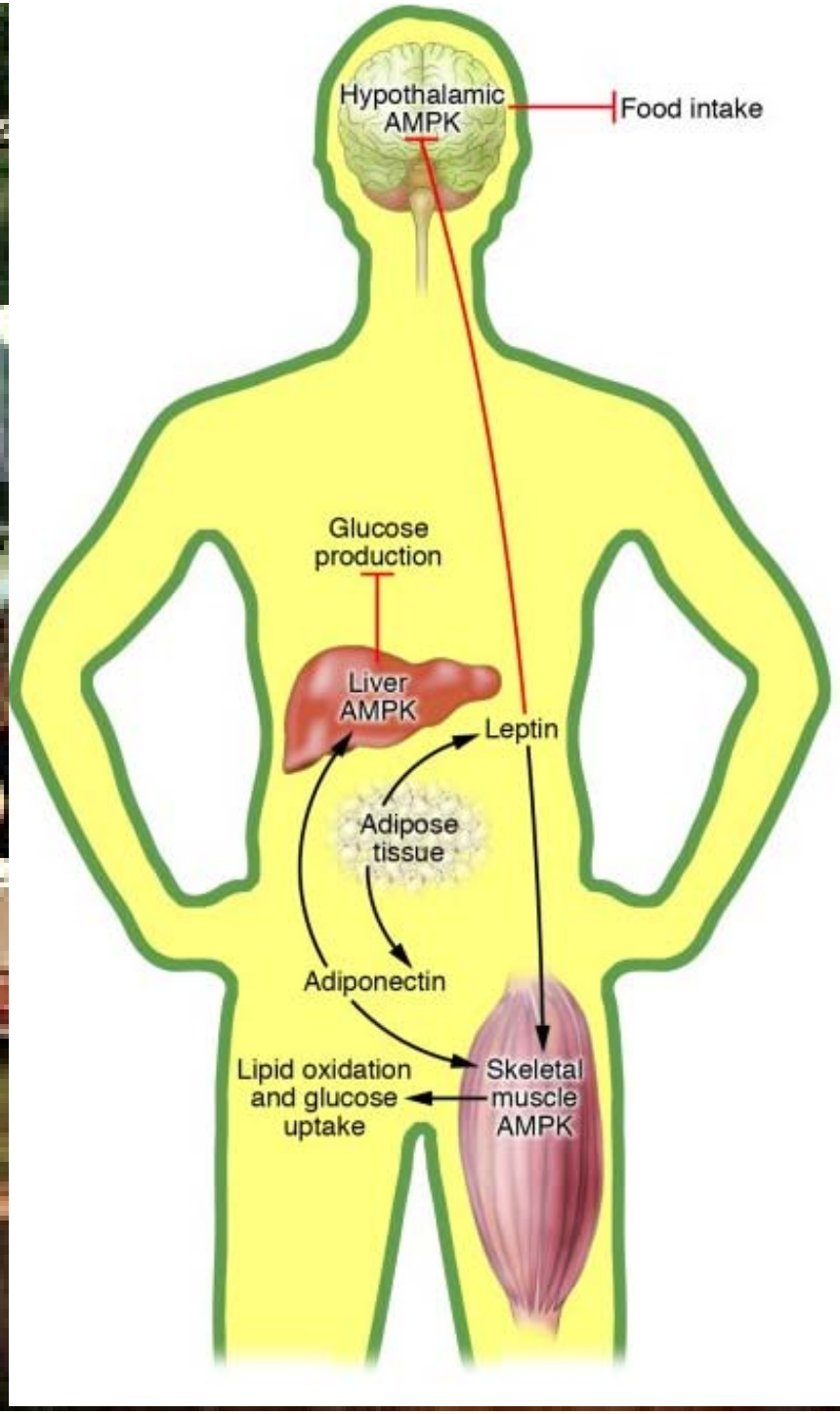
¿Mi barriga tiene emociones?

En nuestro sistema digestivo se produce y almacena el 90% de la serotonina de nuestro cuerpo; su función es esencial: absorción, aporte nutricional y movimientos

- Tengo 46 años. Nací en Rusia. He vivido en Polonia, Praga y Alemania. Desde el 2003 vivo en Madrid. Casada, tengo un hijo (23). Los políticos deben involucrarse más en la vida ciudadana -sentirse ciudadanos- y los ciudadanos más en la política. Somos pequeñas partes de Dios.

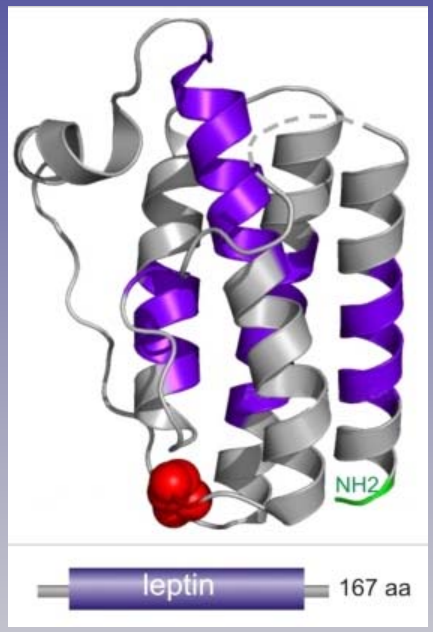
El banquete en los pinares
Botticelli

El banquete en los pinares
Botticelli

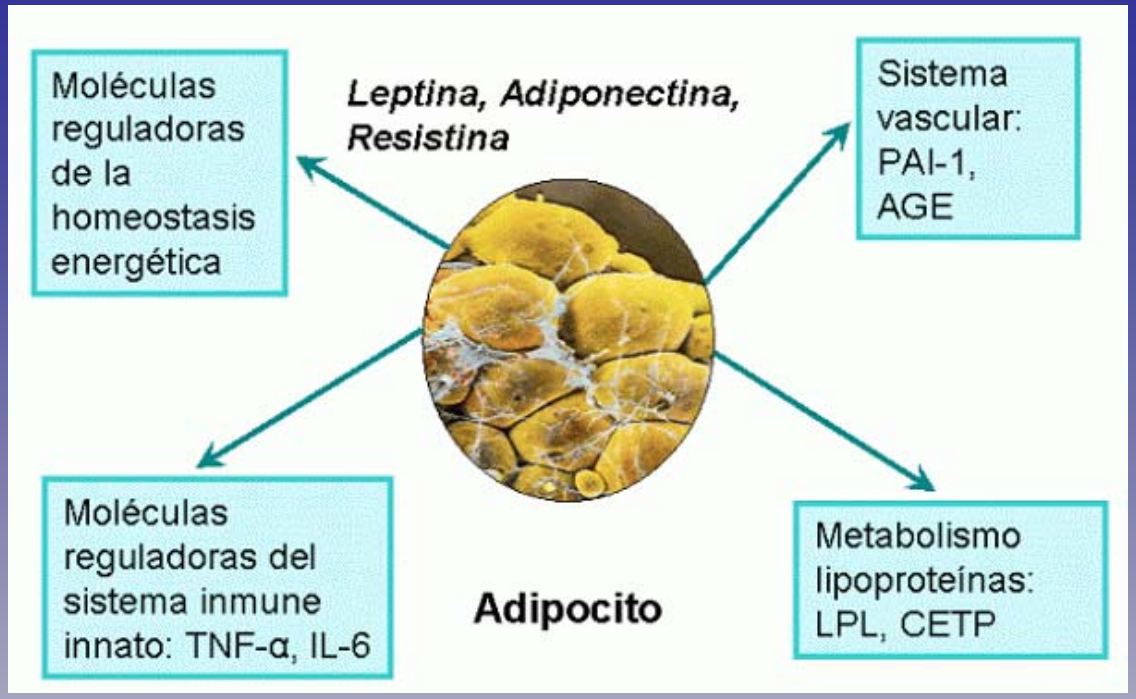


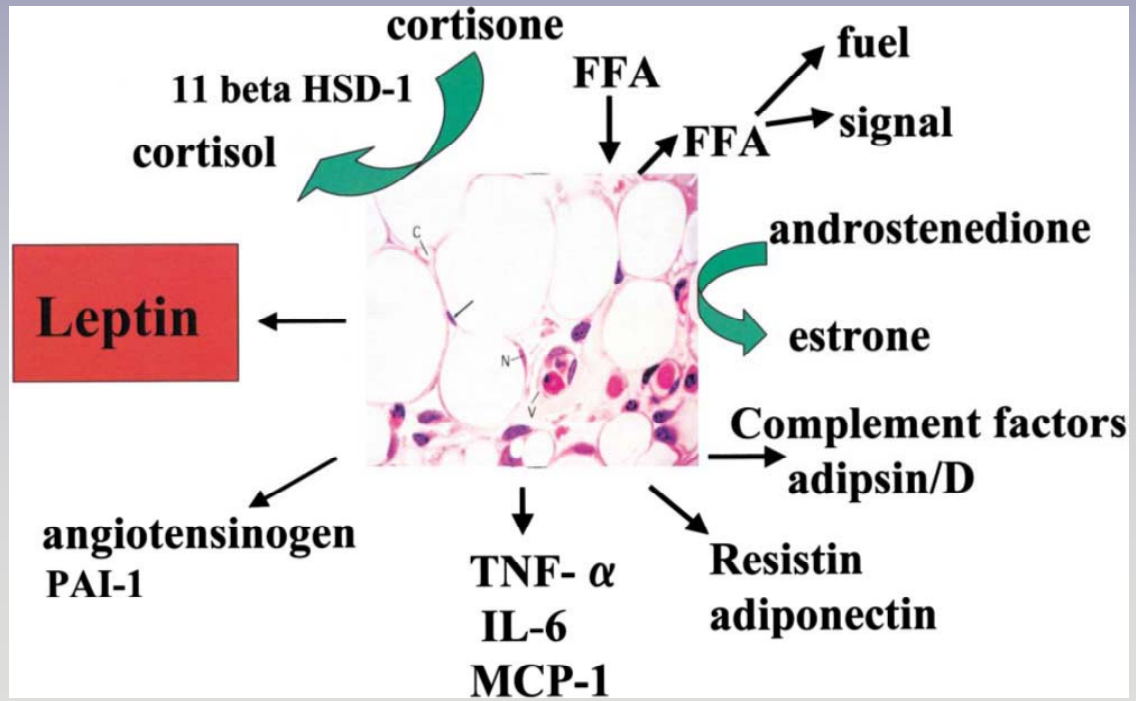
Ingalls AM, Dickie MM, Snell GD (December 1950).
"Obese, a new mutation in the house mouse".
J. Hered. **41** (12): 317–8.

Jackson Laboratory

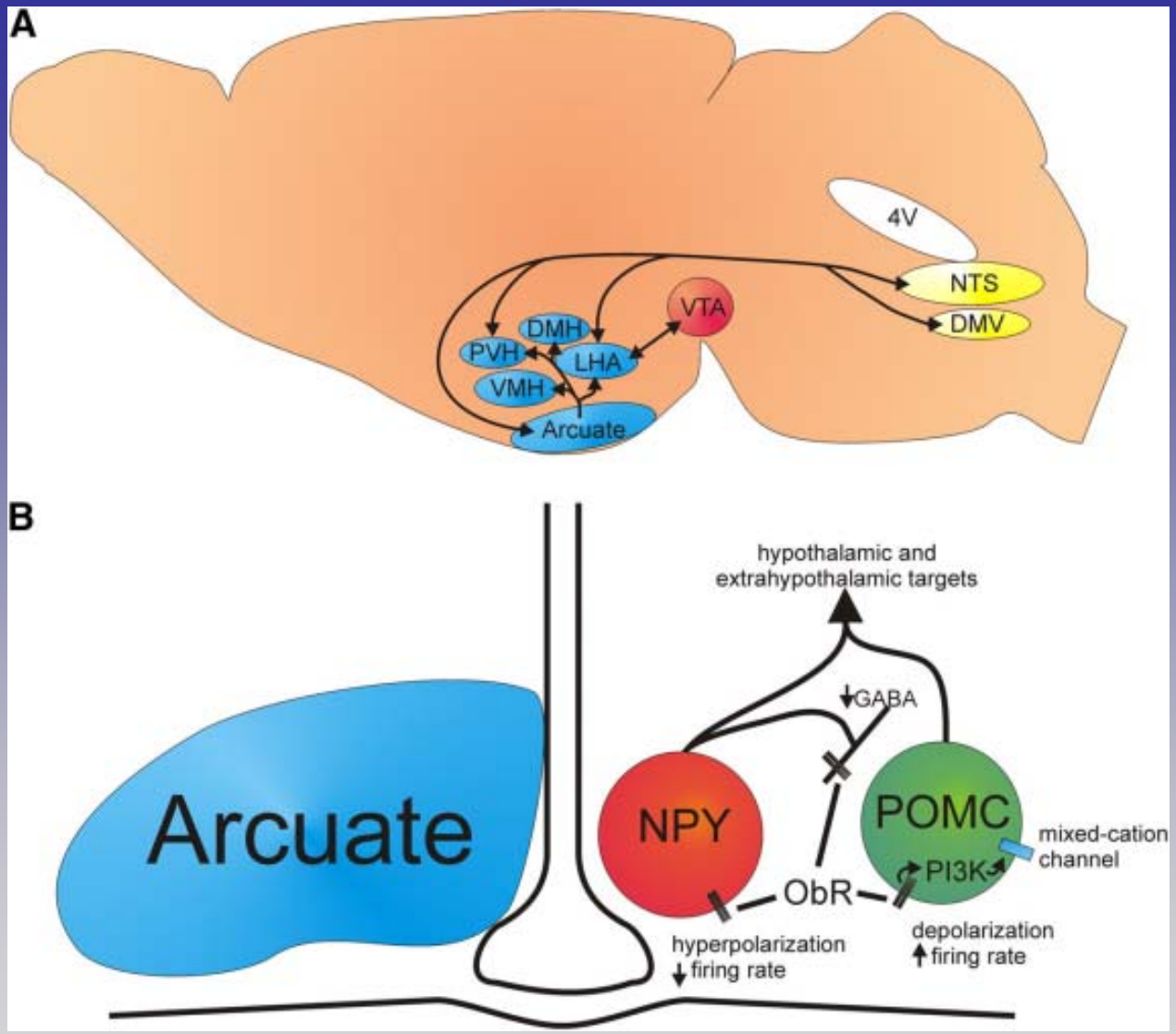


Estructura tridimensional de la molécula de leptina. De *Institut Européen de Chimie et Biologie*, http://www.cellbiol.net/





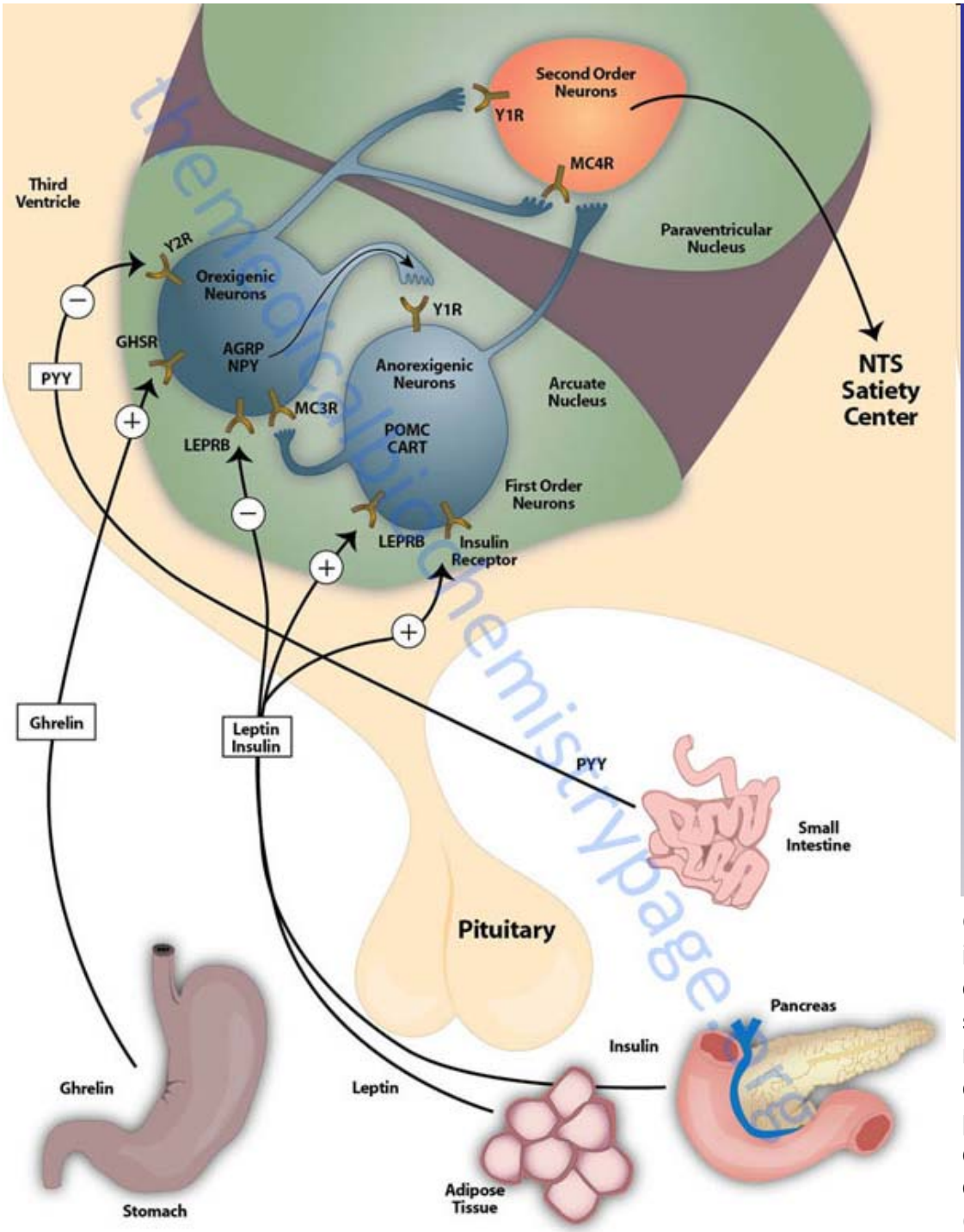
The Adipocyte as an Endocrine Cell. Jeffrey S. Flier. Obesity Wars: Molecular Progress. Cell, Vol. 116, 337–350, January 23, 2004.



Targets of leptin action in the brain.

(A) Illustration shows hypothalamic (blue) and extrahypothalamic (yellow and red) sites of leptin action that are or may be involved in the control of energy and glucose homeostasis.

(B) Illustration shows our current understanding of the pro-opiomelanocortin (POMC) and neuropeptide Y–Agouti-related peptide (NPY-AgRP) circuit in the arcuate nucleus.



Circuitos hormonales en el intestino (estómago, intestino delgado, y páncreas) y grasa (tejido adiposo) que afectan a las sensaciones del hambre y la saciedad que se ejercen a través de las vías neuroendocrino hipotálamo. La grelina desde el estómago, la leptina del tejido adiposo, la insulina del páncreas, y péptido tirosina tirosina (PYY) del intestino delgado se unen a los receptores sobre las neuronas orexigénicos y / o anorexígenos en el núcleo arqueado (ARC) de el hipotálamo.

Únicamente saciedad??

HIPÓTESIS:

Las enfermedades neurodegenerativas pueden constituir la manifestación neurológica de una disfunción sistémica relacionada con la regulación del metabolismo energético.

En ese contexto, moléculas como la leptina y la insulina tendrían un papel significativo.

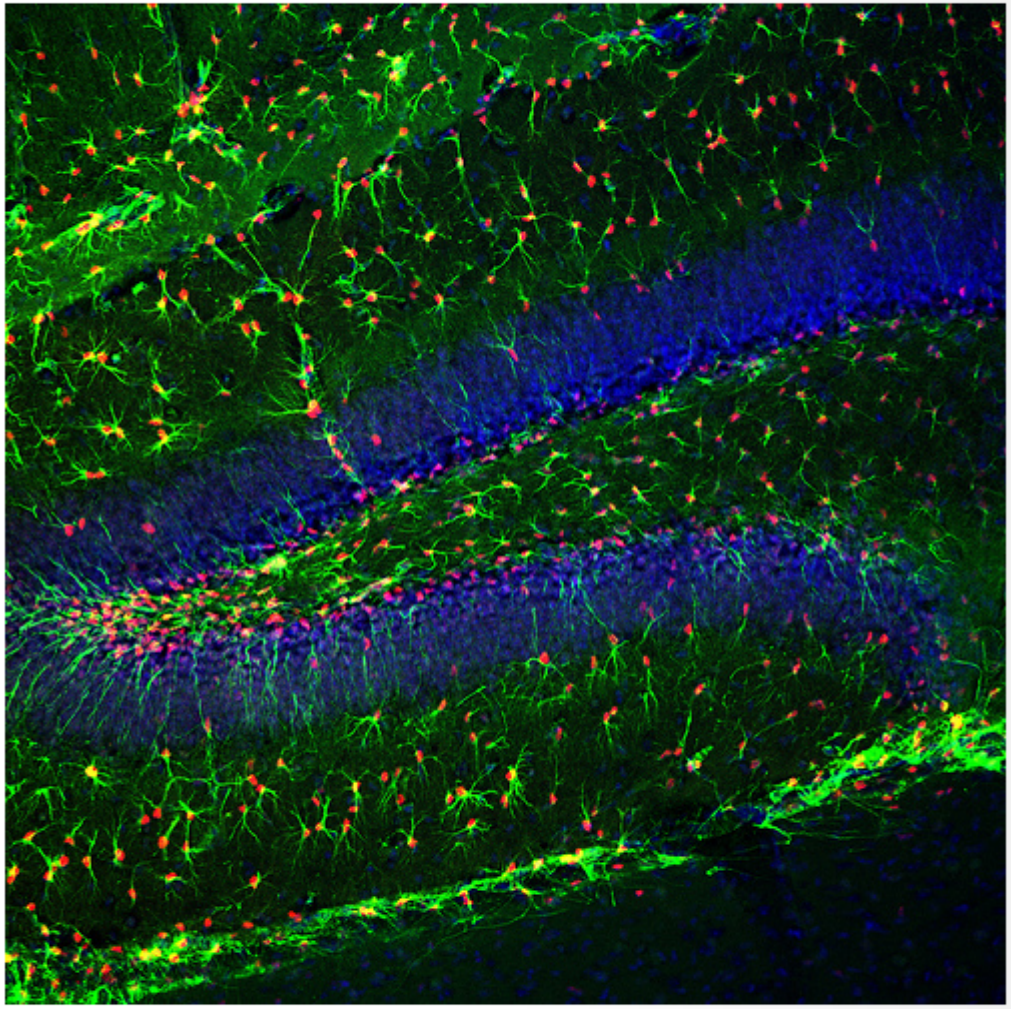
"No deben preocuparnos las arrugas del rostro sino las del cerebro. Estas no las refleja el espejo, pero las perciben nuestros amigos..."

Santiago Ramón y Cajal ***(El Mundo Visto a los Ochenta Años)***

"En el cerebro, todo puede morir, pero ninguna célula se regenera".

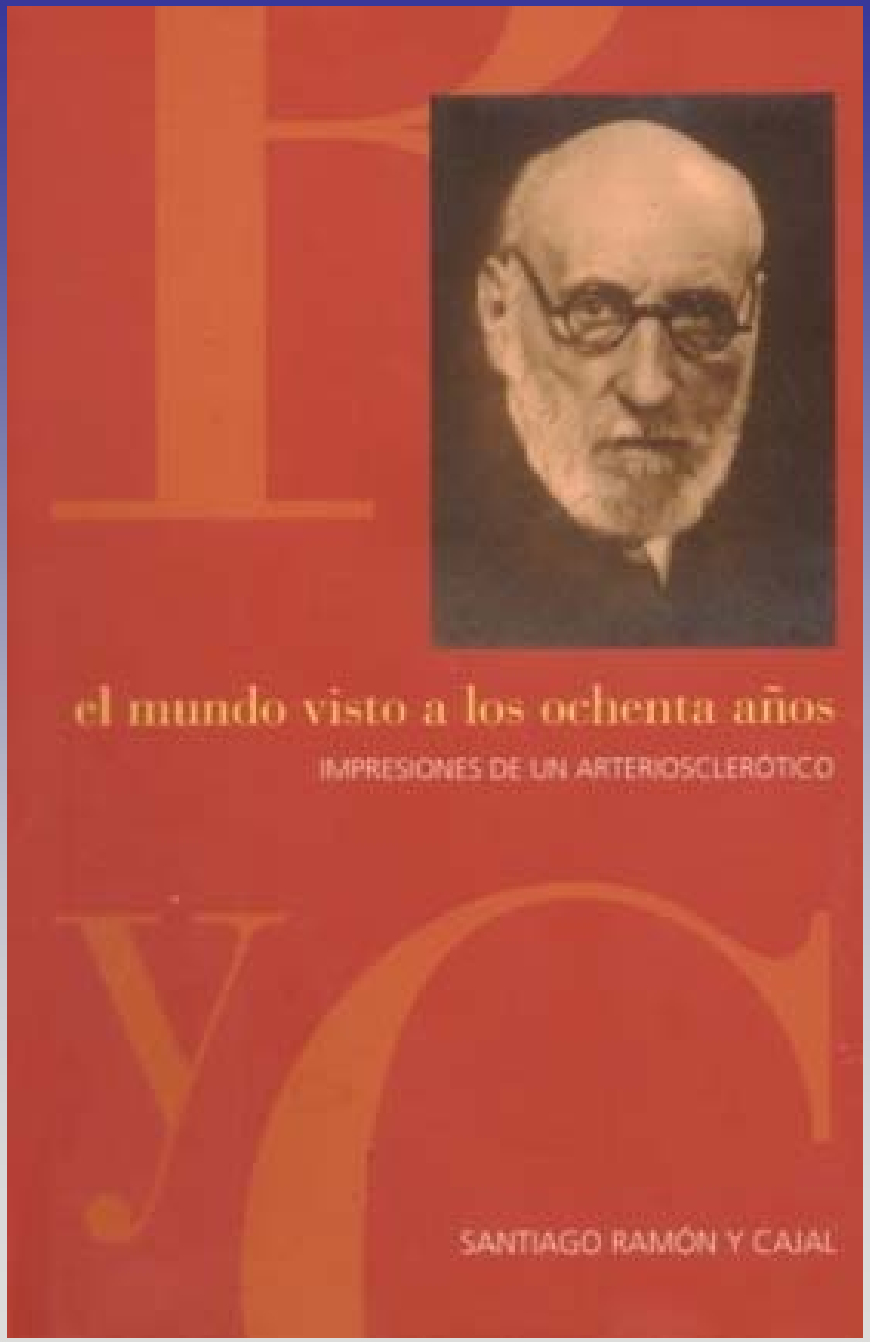
In press: The neurogenesis-depression hypothesis, confirmed.

Jason Snyder | 07/13/2011

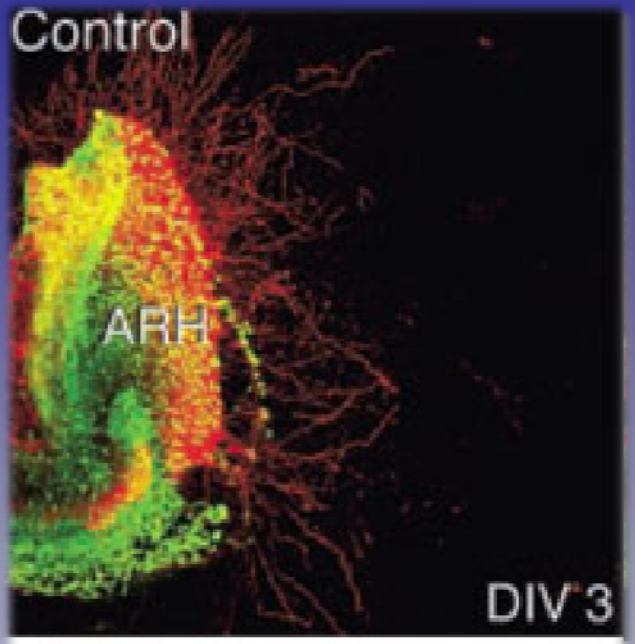


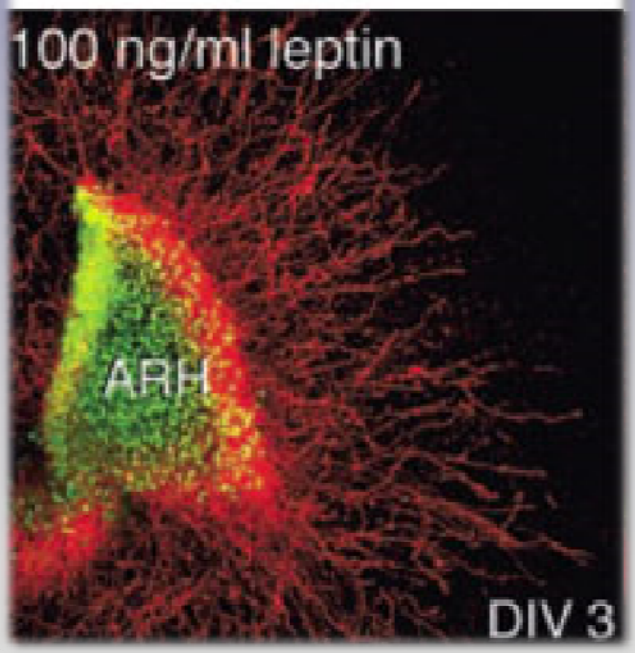
The idea that adult neurogenesis protects individuals from depression is perhaps the single greatest motivator driving neurogenesis research. Not surprisingly, "neurogenesis depression" is the most common behavioral keyword that brings people to this blog (followed closely by "pattern separation"). So I'm excited to say that we will soon be publishing what (I think) is the best evidence that impaired adult neurogenesis actually causes depressive symptoms (in mice). The neurogenesis-depression hypothesis is over 10 years old and yet there is largely

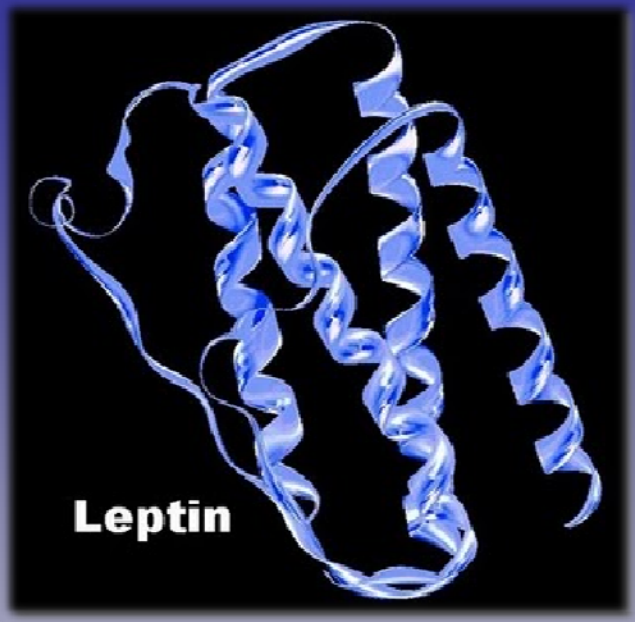
Snyder JS, Soumier A, Brewer M, Pickel J, Cameron HA. **Adult hippocampal neurogenesis buffers stress responses and depressive behaviour.** Nature. 2011 Aug 3;476(7361):458-61. doi: 10.1038/nature10287.



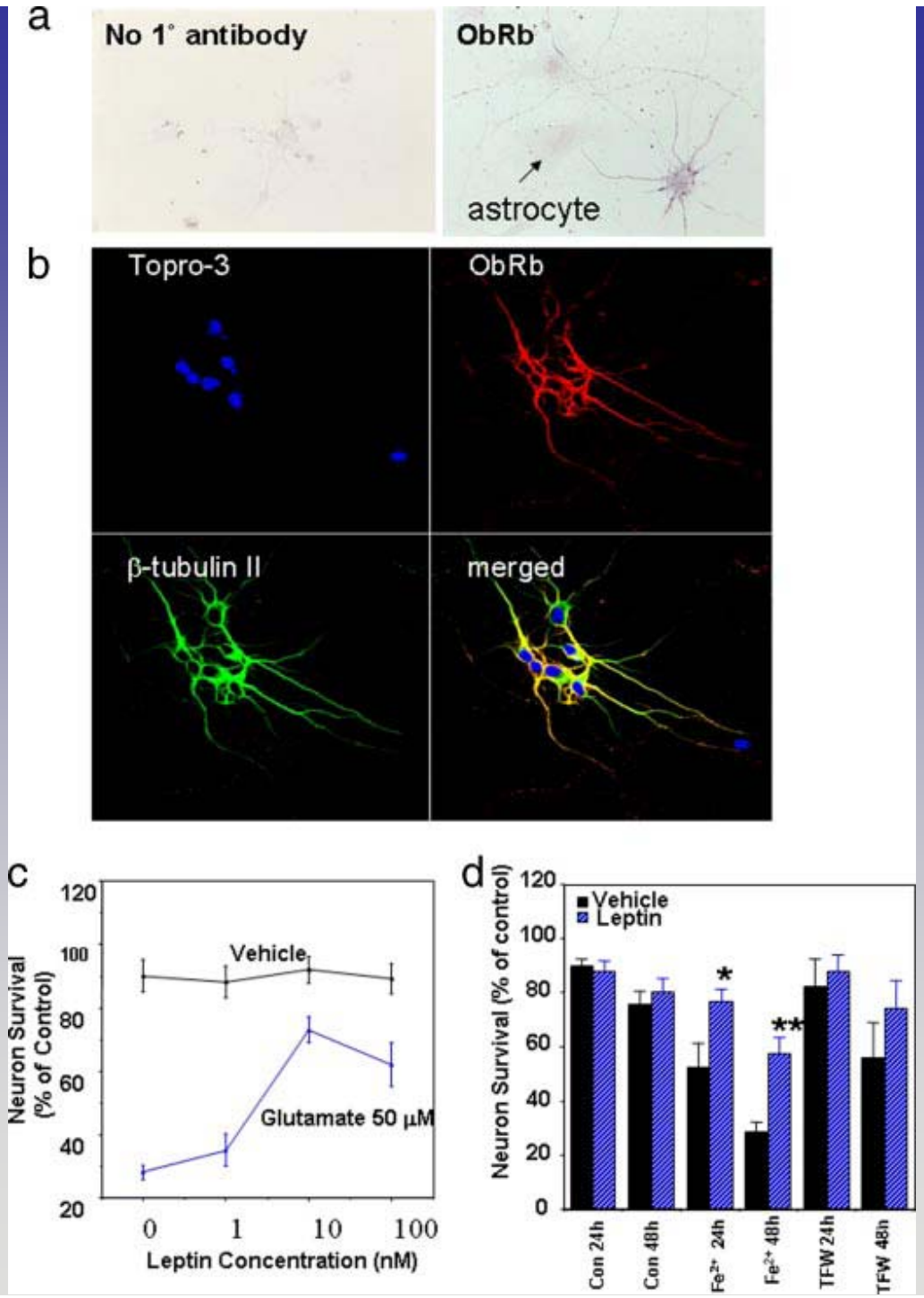
...."la clave es hacer un esfuerzo muy grande por no perder la curiosidad por las cosas de la vida e incluso inventarse nuevas curiosidades, siempre está uno a tiempo de inventarse nuevas aficiones"







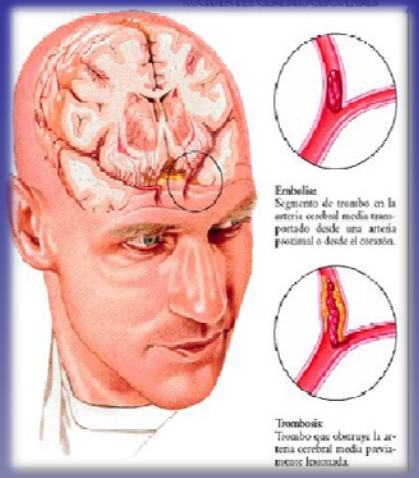
Leptin promotes the growth of mouse neurons. Images show growth patterns without leptin (top) and with leptin. Image courtesy Science.

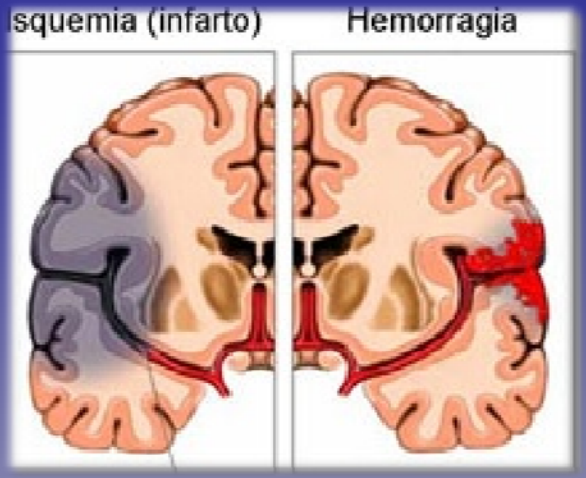


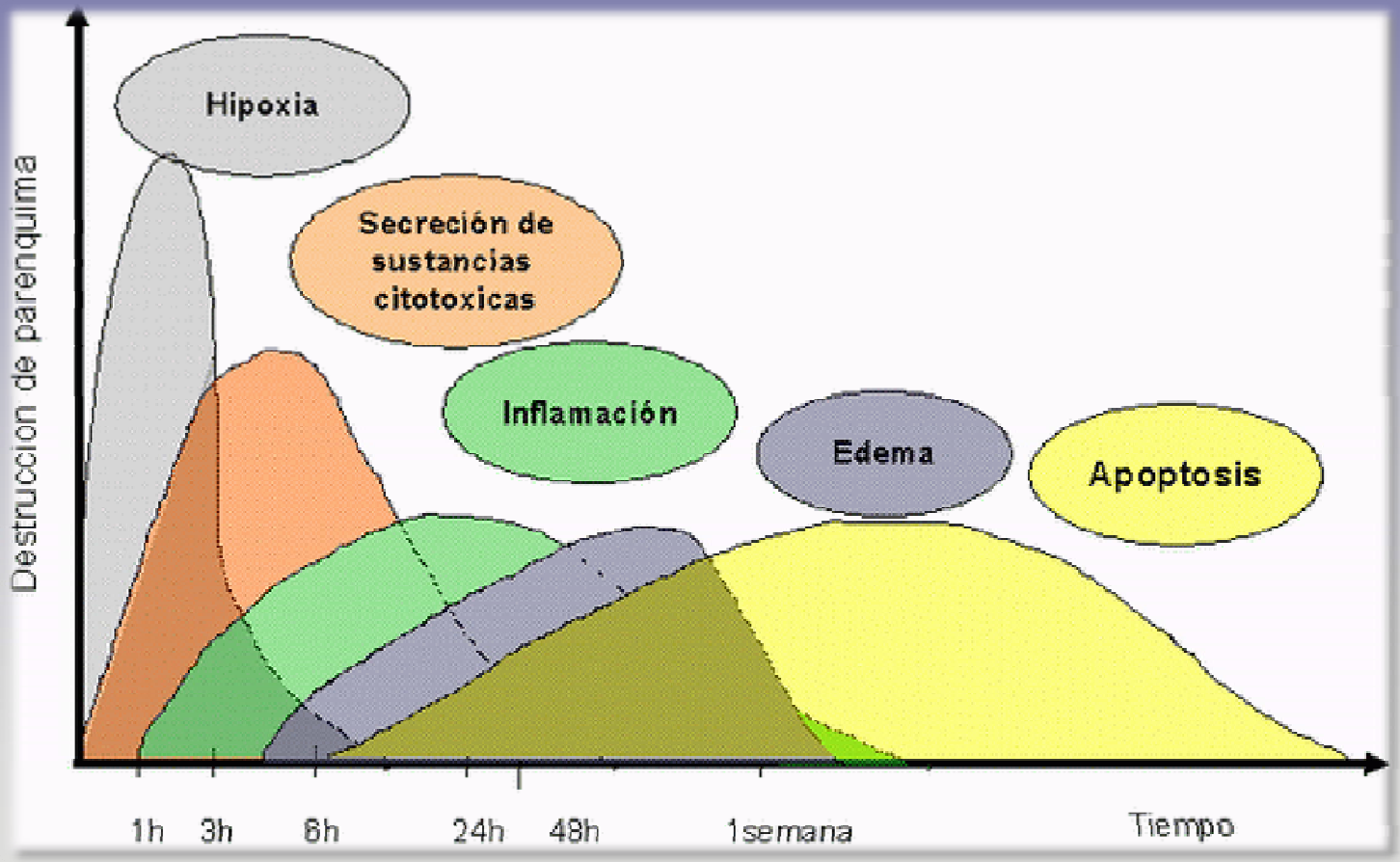
Zhihong Guo et al., Leptin-mediated Cell Survival Signaling in Hippocampal Neurons Mediated by JAK STAT3 and Mitochondrial Stabilization. THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 283, NO. 3, pp. 1754–1763, January 18, 2008

Ictus cerebral

Giuseppe Fortunino Francesco Verdi
(La Roncole, Busseto, 10 de octubre de 1813 – Milán, 27 de enero de 1901)


Embolia:
Trombosis:


squemia (infarto)
Hemorragia


Hipoxia
Secreción de sustancias citotoxicas
Inflamación
Edema
Apoptosis
Destruccion de parenquima
1h
3h
6h
24h
48h
1semana
Tiempo

Curr Neurovasc Res. 2010 May;7(2):136-43.

Leptin reduces infarct size in association with enhanced expression of CB2, TRPV1, SIRT-1 and leptin receptor.

Avraham Y, Davidi N, Porat M, Chernoguz D, Magen I, Vorobeiv L, Berry EM, Leker RR.

Department of Human Nutrition and Metabolism, Braun School of Public Health, Hebrew University-Hadassah Medical School, Jerusalem, Israel. yosefa@md.huji.ac.il

Abstract

Brain ischemia is associated with detrimental changes in energy production and utilization. Therefore, we hypothesized that leptin, an adipokynin hormone protecting against severe energy depletion, would reduce infarct volume and improve functional outcome after stroke. Male Sabra mice underwent permanent middle cerebral artery occlusion (PMCAO) by photothrombosis. Following initial dose-response and time-window experiments animals were treated with vehicle or leptin, were examined daily by a neurological severity score (NSS) and were sacrificed 72 hours after stroke. Infarct volume was determined and the expression of key genes involved in neuroprotection and survival including the cannabinoid receptors CB1, CB2 and TRPV1, SIRT-1, leptin receptor and Bcl-2 was quantified in the cortex. A separate group of mice were examined with the neurological severity scale 1, 24 and 48 hours and 1, 2 and 3 weeks after stroke, and were killed 3 weeks post stroke to examine metabolic status in the peri-infarct area. Leptin given at a dose of 1mg/kg intra-peritoneally 30 minutes after PMCAO significantly improved neurological disability and reduced infarct volume. Leptin treatment led to increased expression of CB2 receptor, TRPV1, SIRT-1 and leptin receptor and reduced expression of CB1 receptor. There was also a non-significant increase in Bcl-2 gene expression following leptin administration. These results suggest that leptin may be used for attenuating ischemic injury after stroke via induction of an anti-apoptotic state.

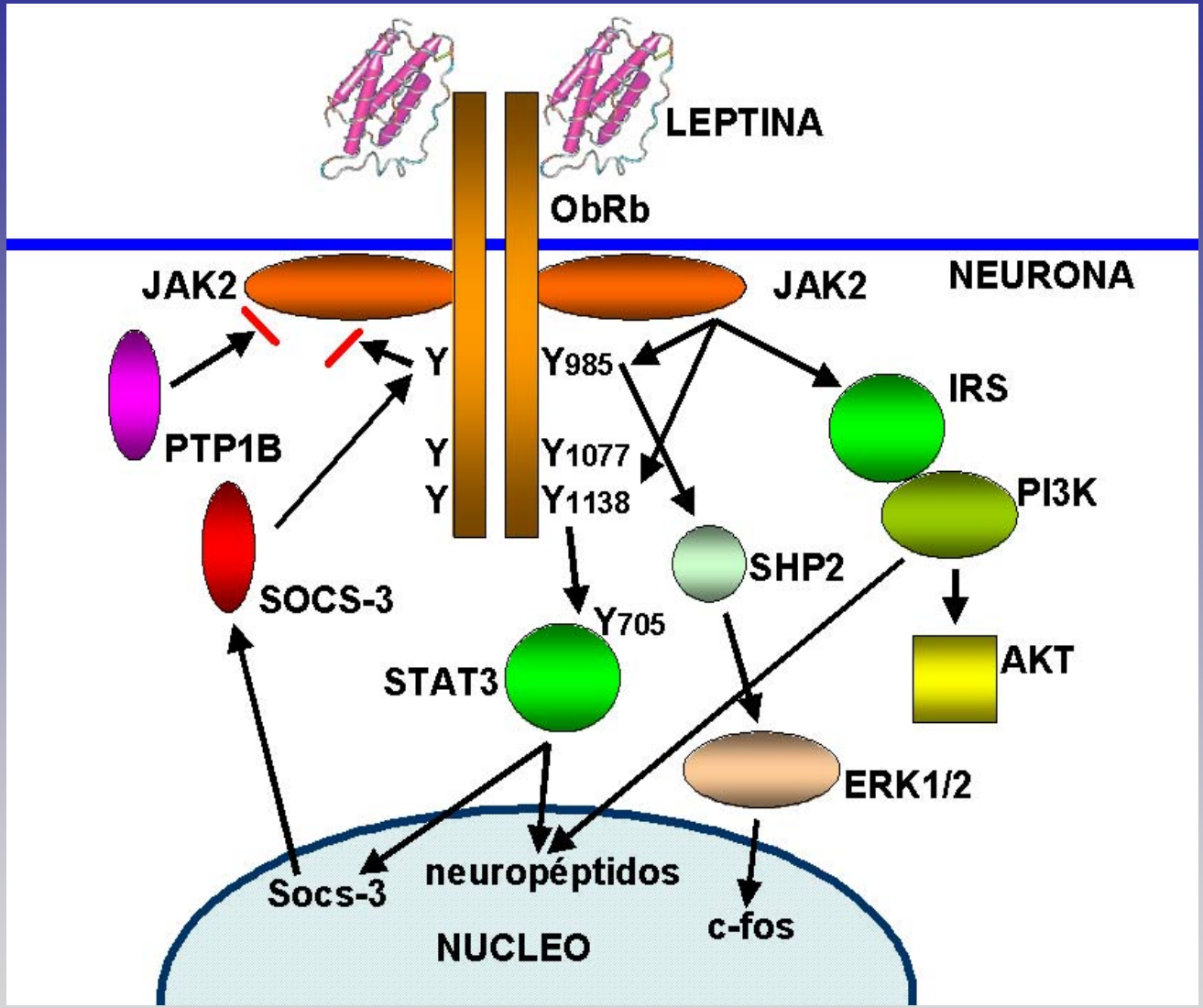
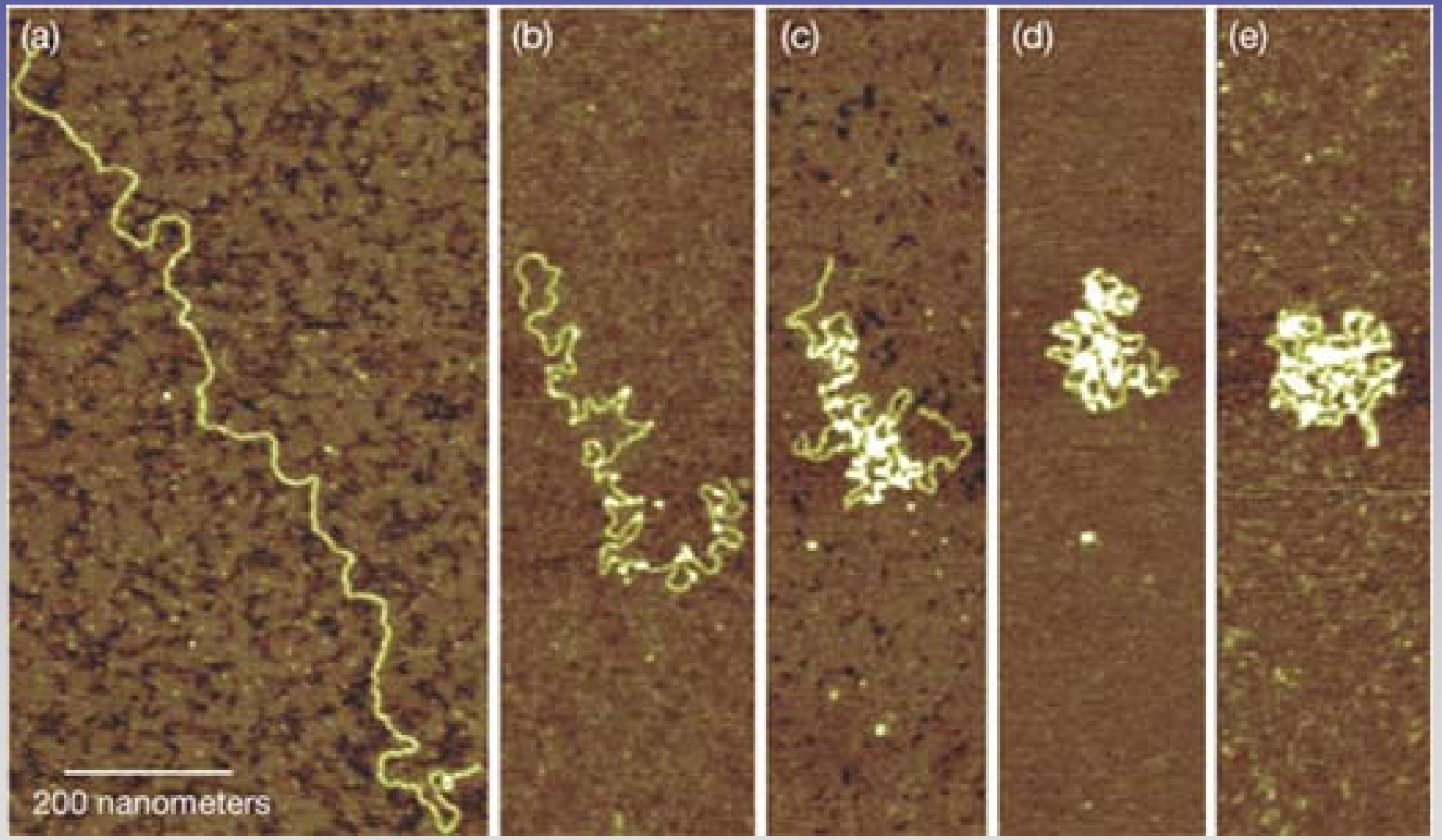


Figura 5. Mecanismo de señalización del receptor de leptina. La activación del Ob-Rb por leptina incrementa la actividad de las quinasas JAK2 que fosforilan diversos sustratos intracelulares como Y985 y Y1138 (pertenecientes a Ob-Rb) y a Y705 (perteneciente a STAT3). Adaptado de Bjørbaek y Kahn, 2004.

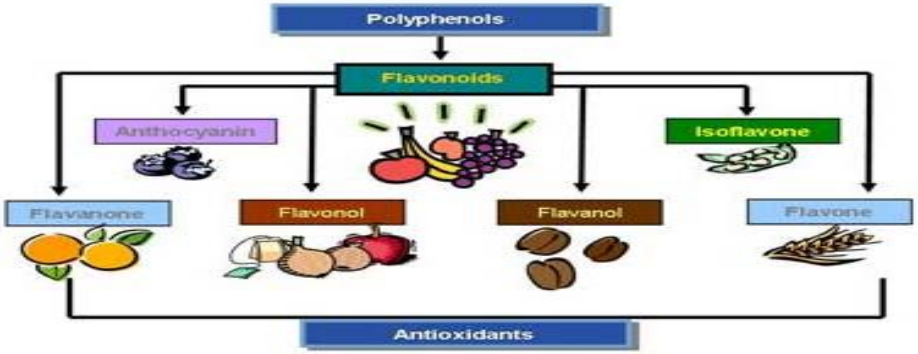
SIRTUÍNA 1
NAD-dependent class Histone deacetylase III family



Braz. J. Plant Physiol., 18(1):23-36, 2006

Table 1. Main classes of phenolic compounds in higher plants.

Classes and sub-classes	Examples of specific compounds
Non-flavonoid compounds	
Phenolic acids	
Benzoic acids	Gallic acid; protocatechuic acid; *p*-hydroybenzoic acid
Hydroxycinnamic acids	Coumaric acid; caffeic acid; ferulic acid; sinapic acid
Hydrolyzable tannins	Pentagalloylglucose
Stilbenes	Resveratrol
Lignans	Secoisolariciresinol, matairesinol, lariciresinol, pinoresinol
Flavonoid compounds	
Flavonols	Kaempferol; quercitin; myricetin
Flavones	Apigenin; luteolin
Flavanones	Naringenin; hesperetin
Flavanols	Catechins; gallocatechins
Anthocyanidins	Pelargonidin; cyanidin; malvidin
Condensed tannins or proanthocyanidins	Trimeric procyanidin, prodelphinidins
Isoflavones	Daidzein; genistein; glycitein

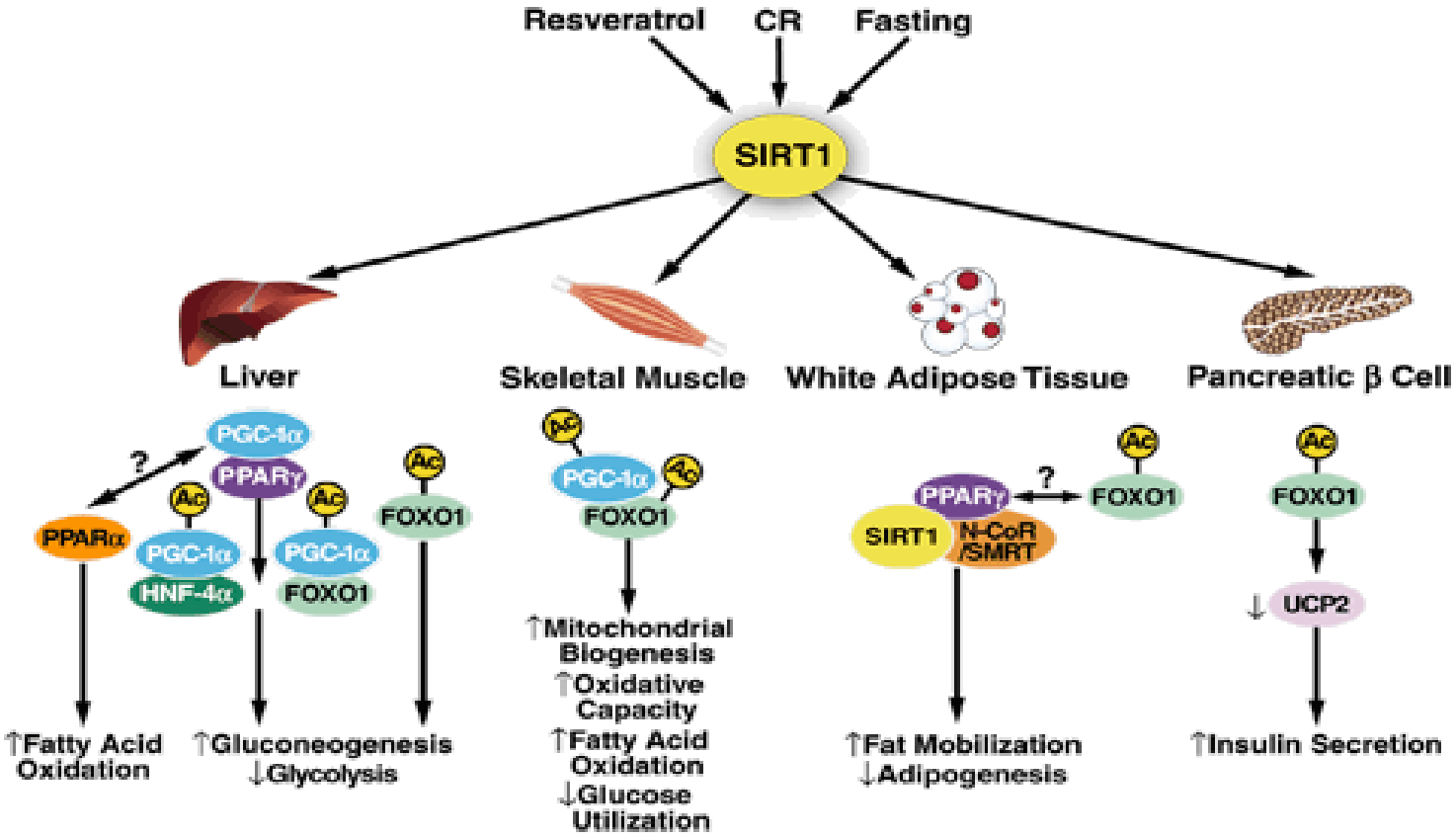


Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-γ

Frédéric Picard[1], Martin Kurtev[1], Namjin Chung[1], Acharawan Topark-Ngarm[2], Thanaset Senawong[2], Rita Machado de Oliveira[1,3], Mark Leid[2], Michael W. McBurney[4] & Leonard Guarente[1]

[1]*Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA*
[2]*Laboratory of Molecular Pharmacology, Department of Pharmaceutical Sciences,*

methylxanthine, we observed that Sirt1 protein levels increased and peaked at day 5 after hormonal stimulation (Fig. 1a). *Sirt1* expression in 3T3-L1 cells was then modified through retroviral infection with either pBABE–*Sirt1* or pSUPER–*Sirt1* RNA interference (RNAi) for overexpression (tenfold) or downregulation (sevenfold) of the *Sirt1* gene, respectively (Fig. 1b). 3T3-L1 cells undergo one or two mitotic divisions after induction as a prelude to terminal differentiation[9,10]. This occurred normally in cells that overexpressed or underexpressed Sirt1 as evaluated by 5-bromodeoxyuridine (BrdU) incorporation (data not shown). However, compared with cells infected with the control vector, stable 3T3-L1 cells overexpressing Sirt1 accumulated much less fat as determined by Oil red O staining after 7 days of differentiation (Fig. 1c) or direct measurement of intracellular triglyceride content (Fig. 1d). In contrast, downregulation of Sirt1 expression resulted in a significant



Biochimica et Biophysica Acta xxx (2010) xxx–xxx

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/bbagrm

Review

Sirtuin activators: Designing molecules to extend life span

Antoni Camins [a,*], Francesc X. Sureda [b], Felix Junyent [a,c], Ester Verdaguer [a], Jaume Folch [c], Carme Pelegri [e], Jordi Vilaplana [e], Carlos Beas-Zarate [d], Mercè Pallàs [a]

[a] Unitat de Farmacologia i Farmacognòsia Facultat de Farmàcia, Institut de Biomedicina (IBUB), Centros de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Universitat de Barcelona, Nucli Universitari de Pedralbes, 08028 Barcelona, Spain

[b] Unitat de Farmacología, Centros de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Facultat de Medicina i Ciències de la Salut, Universitat Rovira i Virgili, C./ St. Llorenç 21 43201 Reus, Tarragona, Spain

[c] Unitat de Bioquímica, Facultat de Medicina i Ciències de la Salut, Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED),

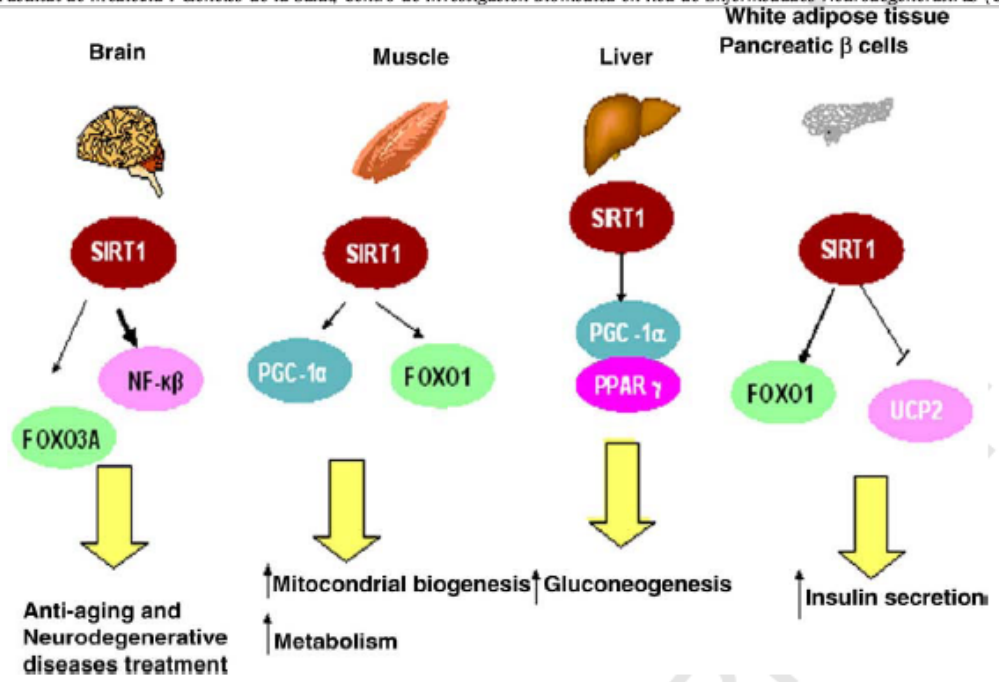
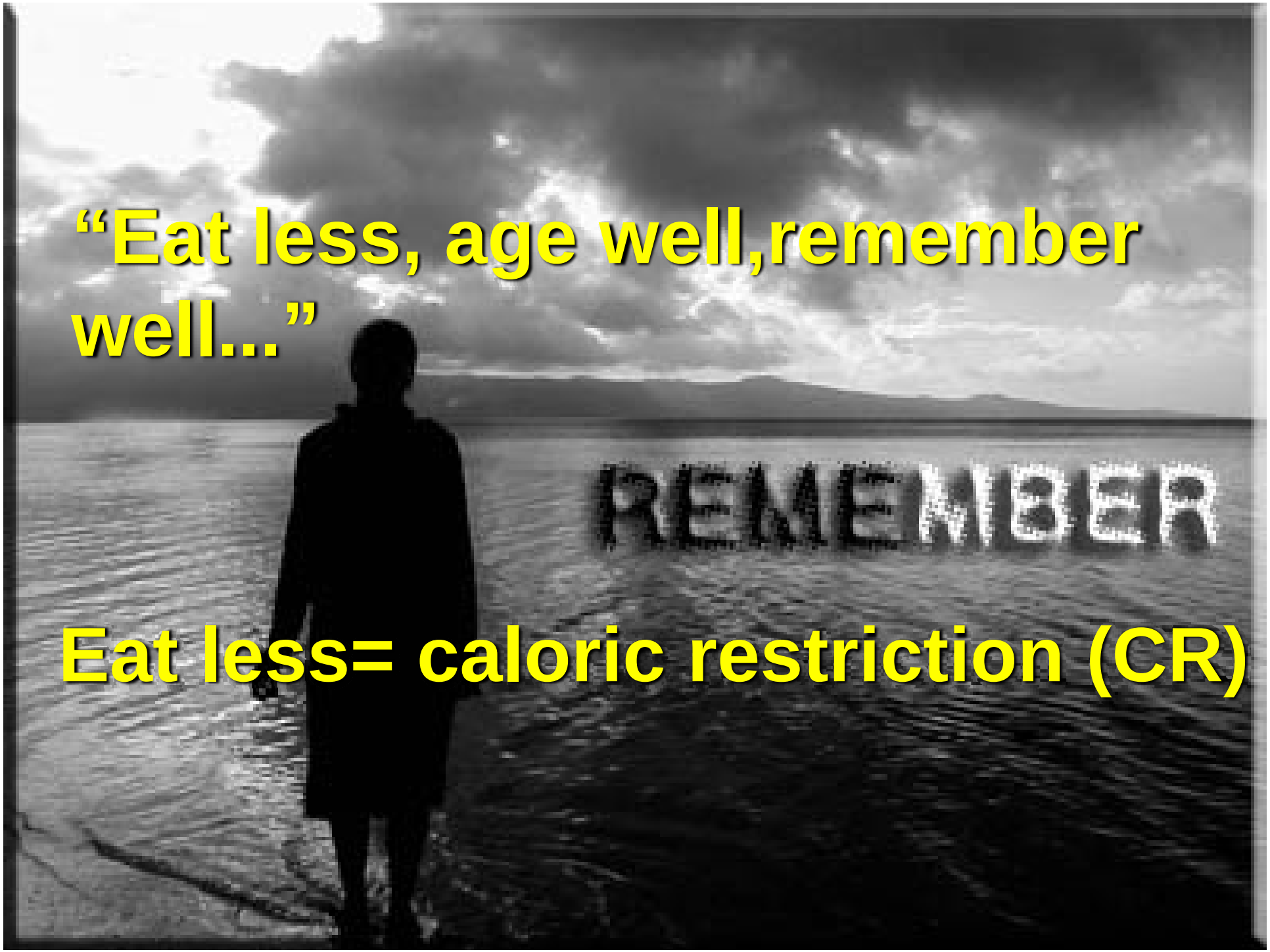
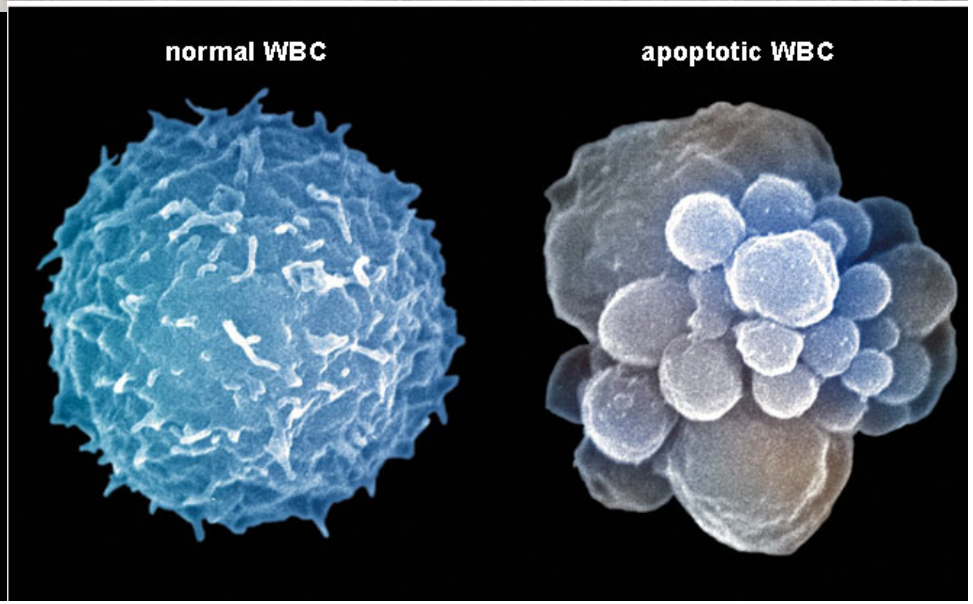
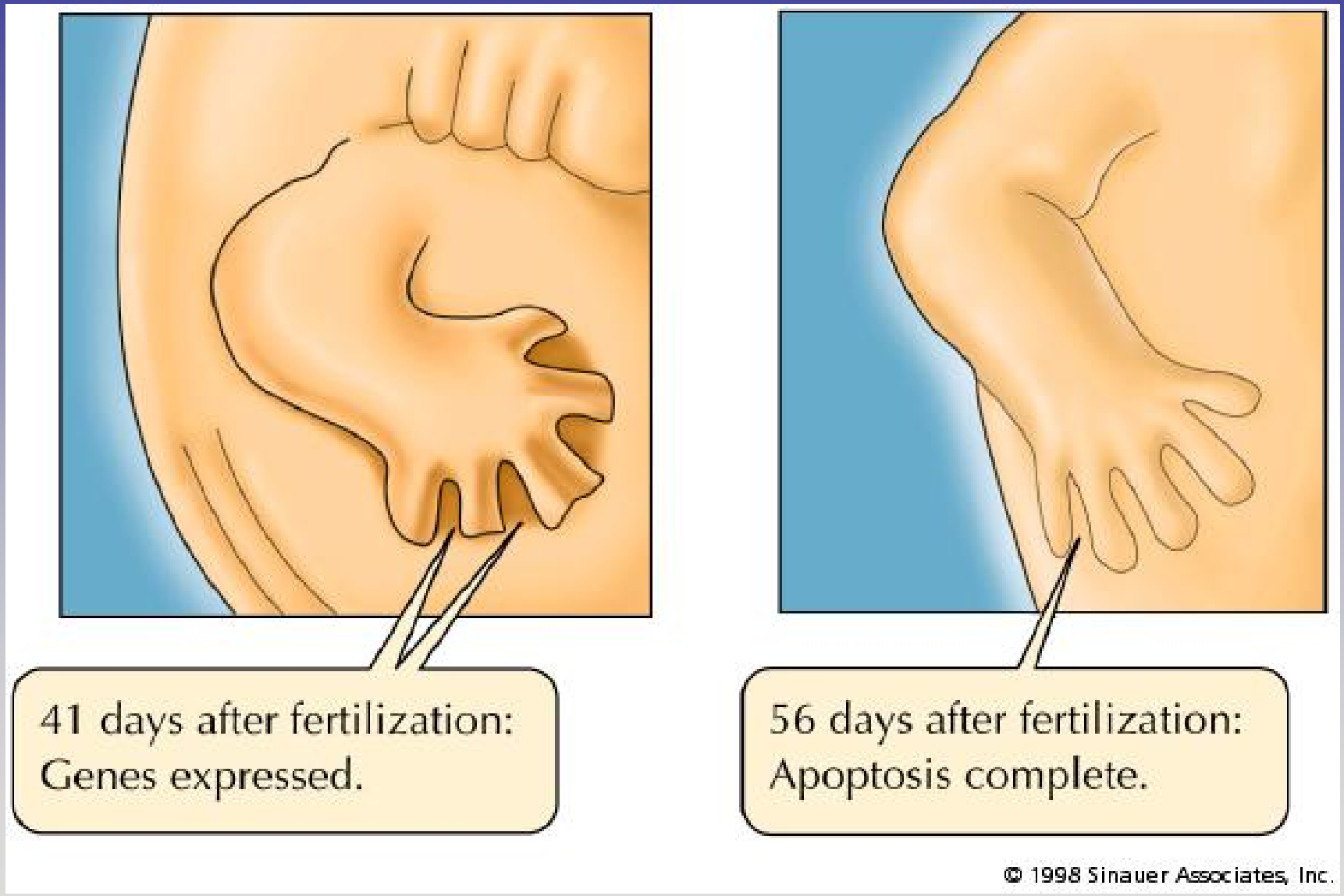


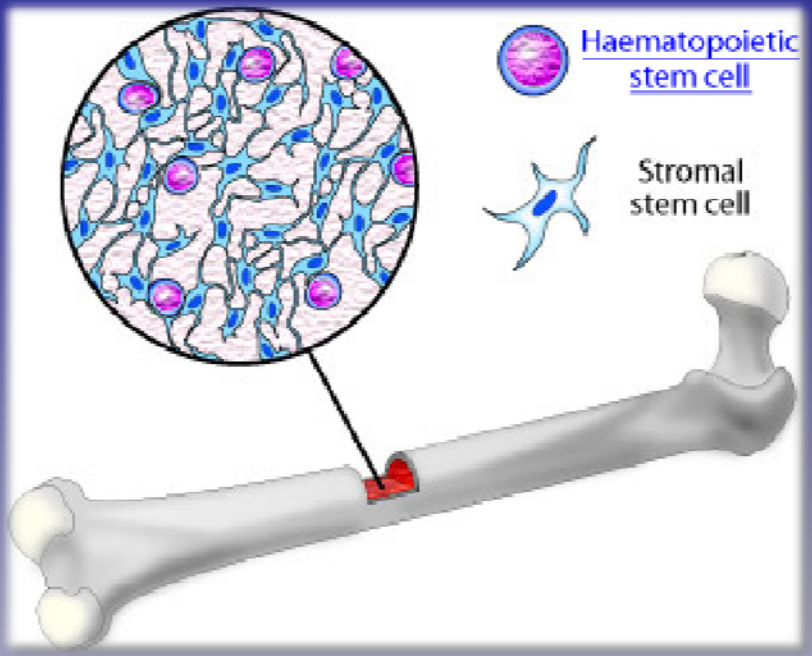
Fig. 1. SIRT1 produces different outputs as a result of different stimuli. Activation of SIRT 1 to the brain causes an increase in the expression of the transcription factor FOXO 3A with antiaging properties. Besides an increase in NF transcription factor may explain, among others, the neuroprotective properties of SIRT1. SIRT1 protects pancreatic cells and muscle cells against stress-induced apoptosis by increasing activity of the forkhead protein FOXO1. In the liver, SIRT1 deacetylases the coactivator PGC-1α, thereby increasing the expression of genes for gluconeogenesis. In the muscles, the effect of SIRT1 on FOXO1 increases mitochondrial biogenesis and insulin secretion.

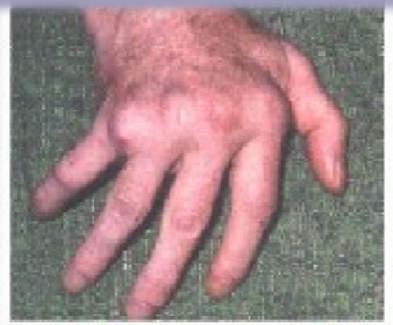

“Eat less, age well,remember well…”
REMEMBER
Eat less= caloric restriction (CR)

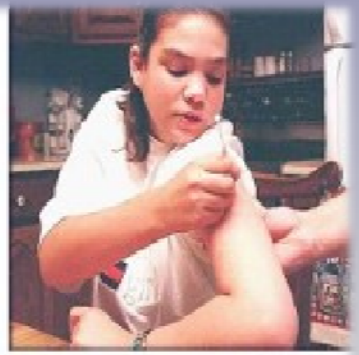

APOPTOSIS

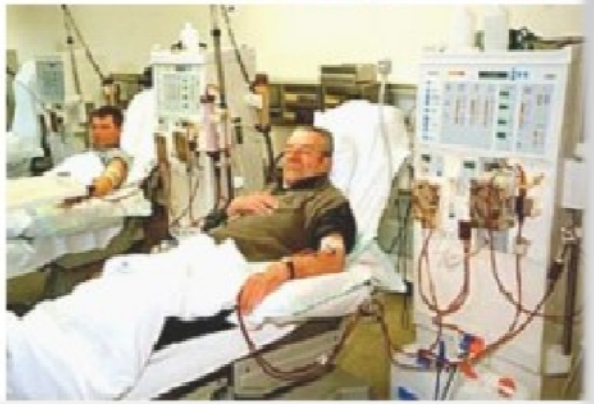

normal WBC
apoptotic WBC

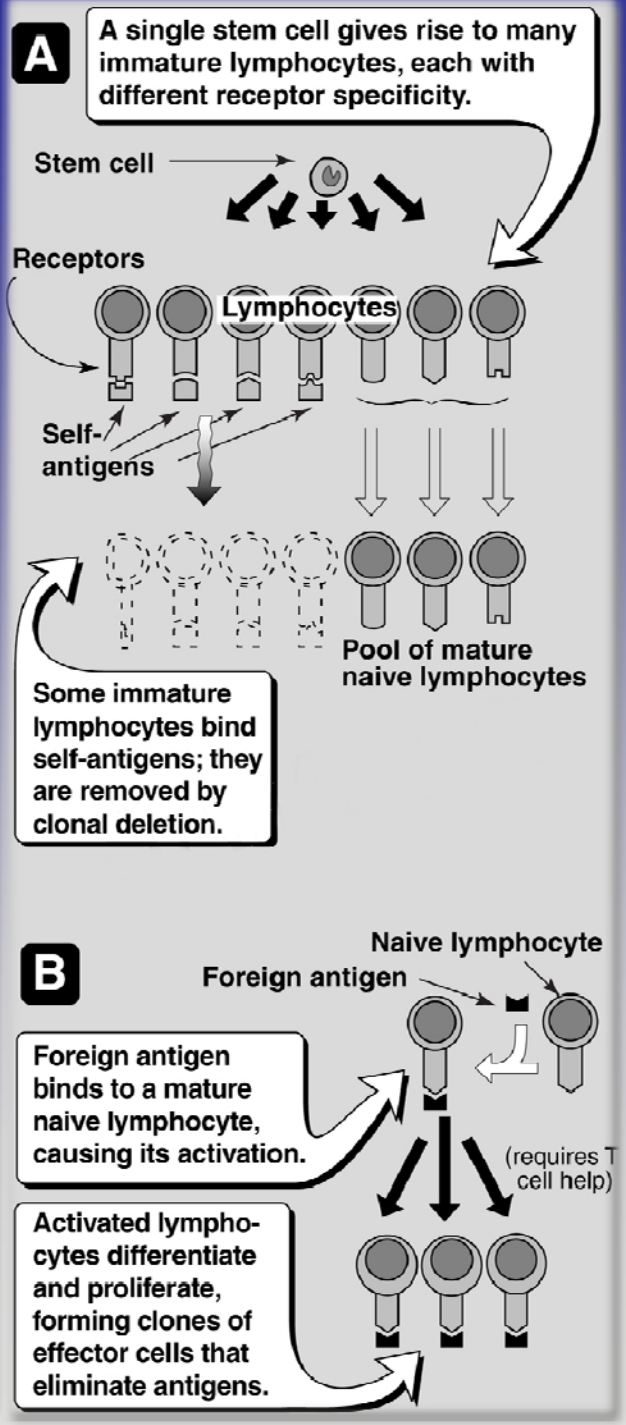


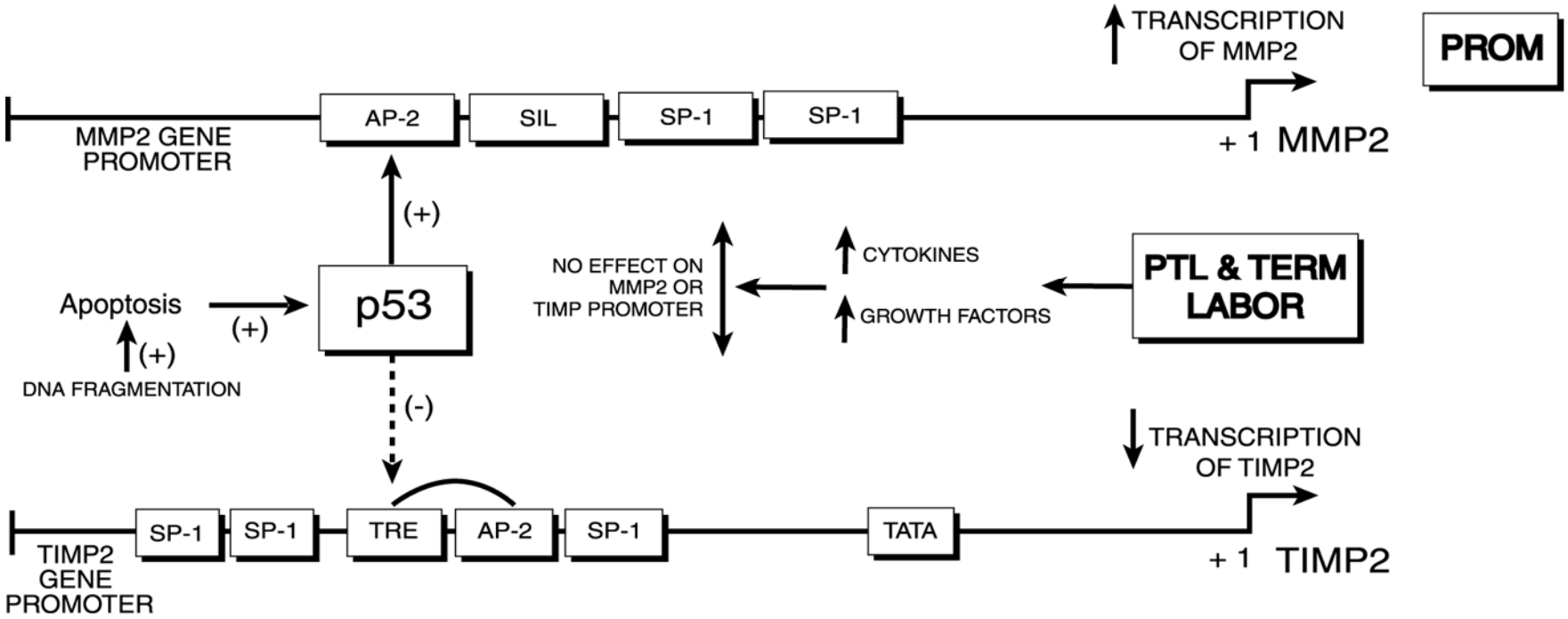

Haematopoietic stem cell
Stromal stem cell

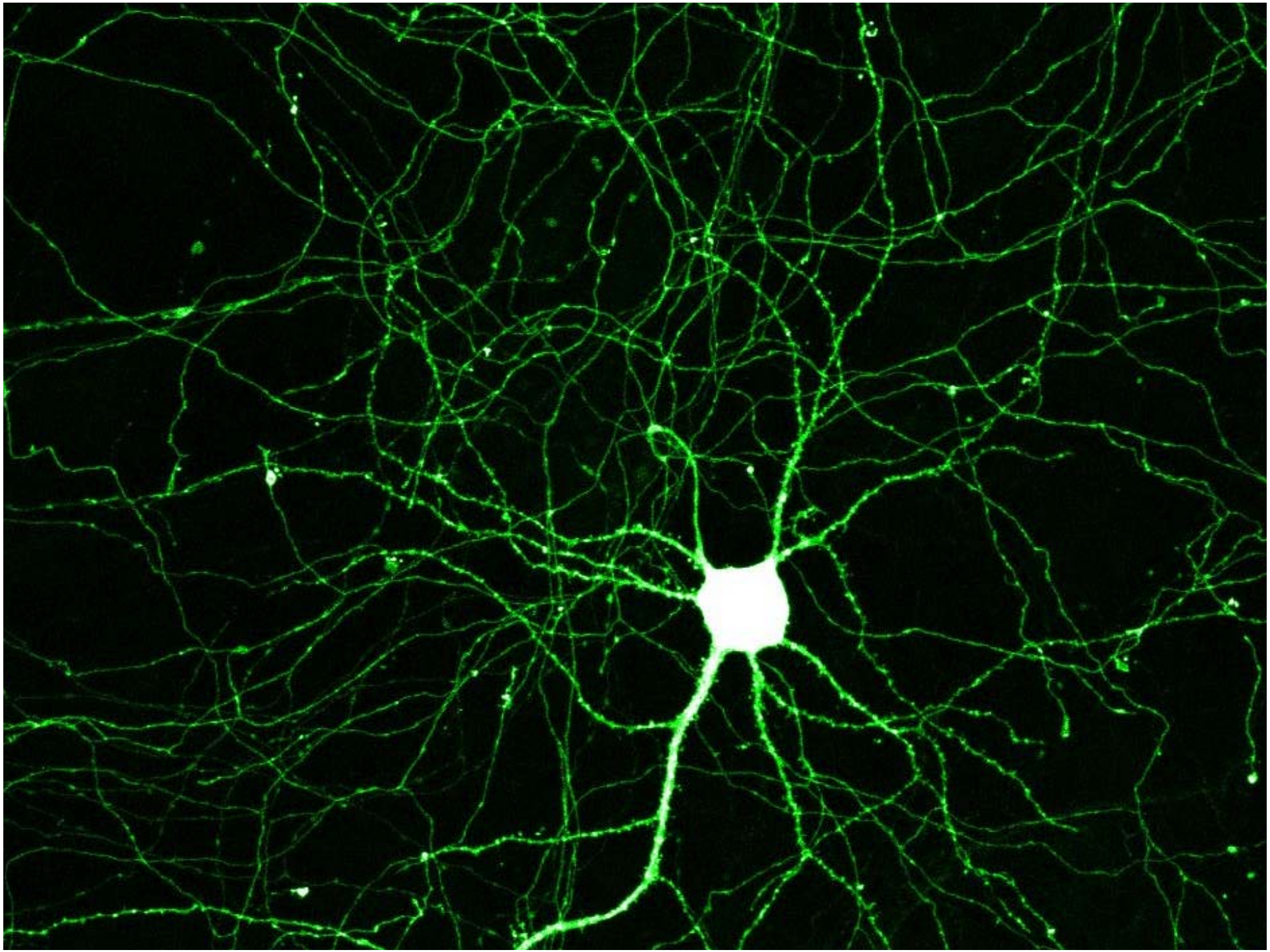


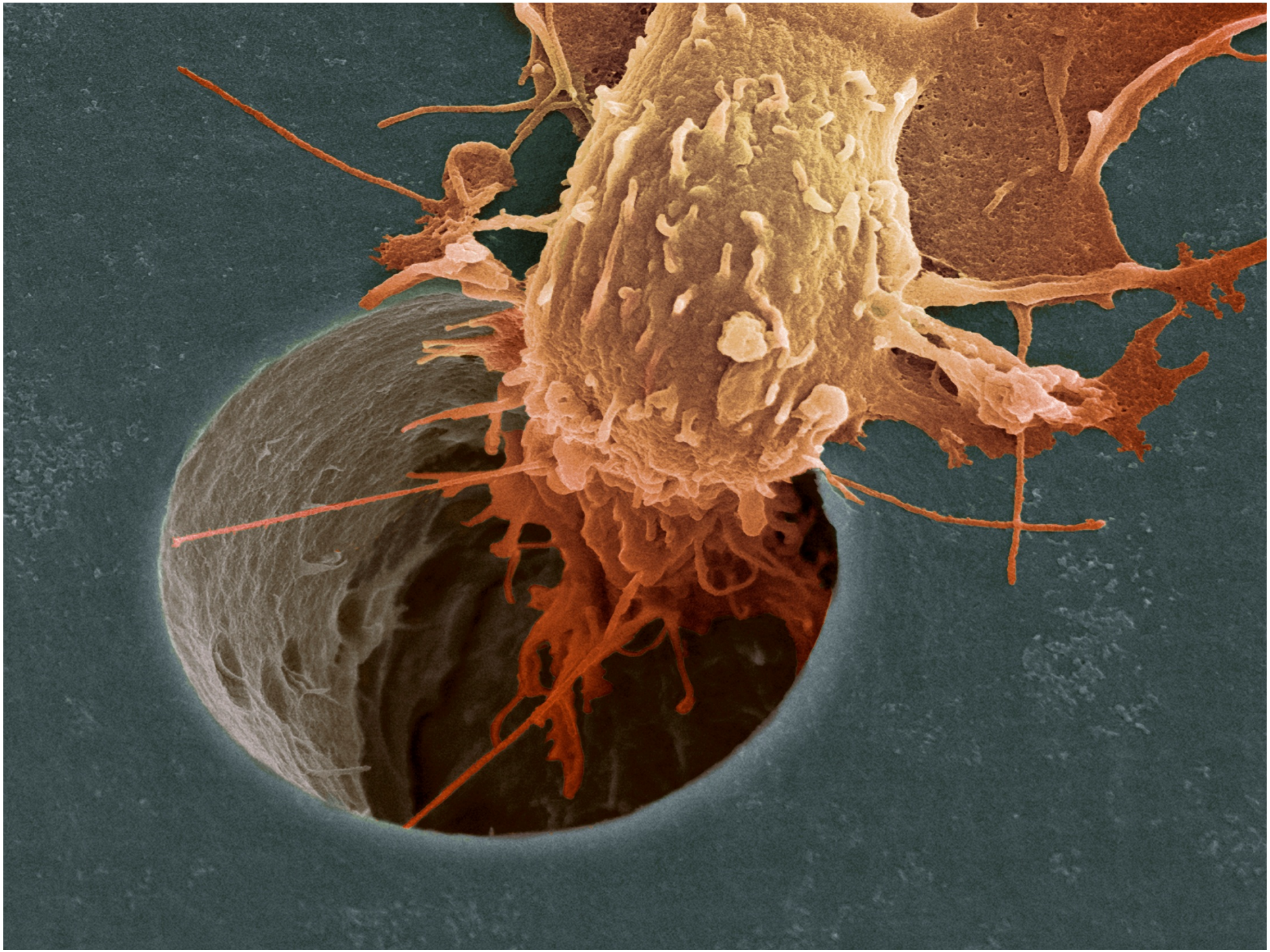


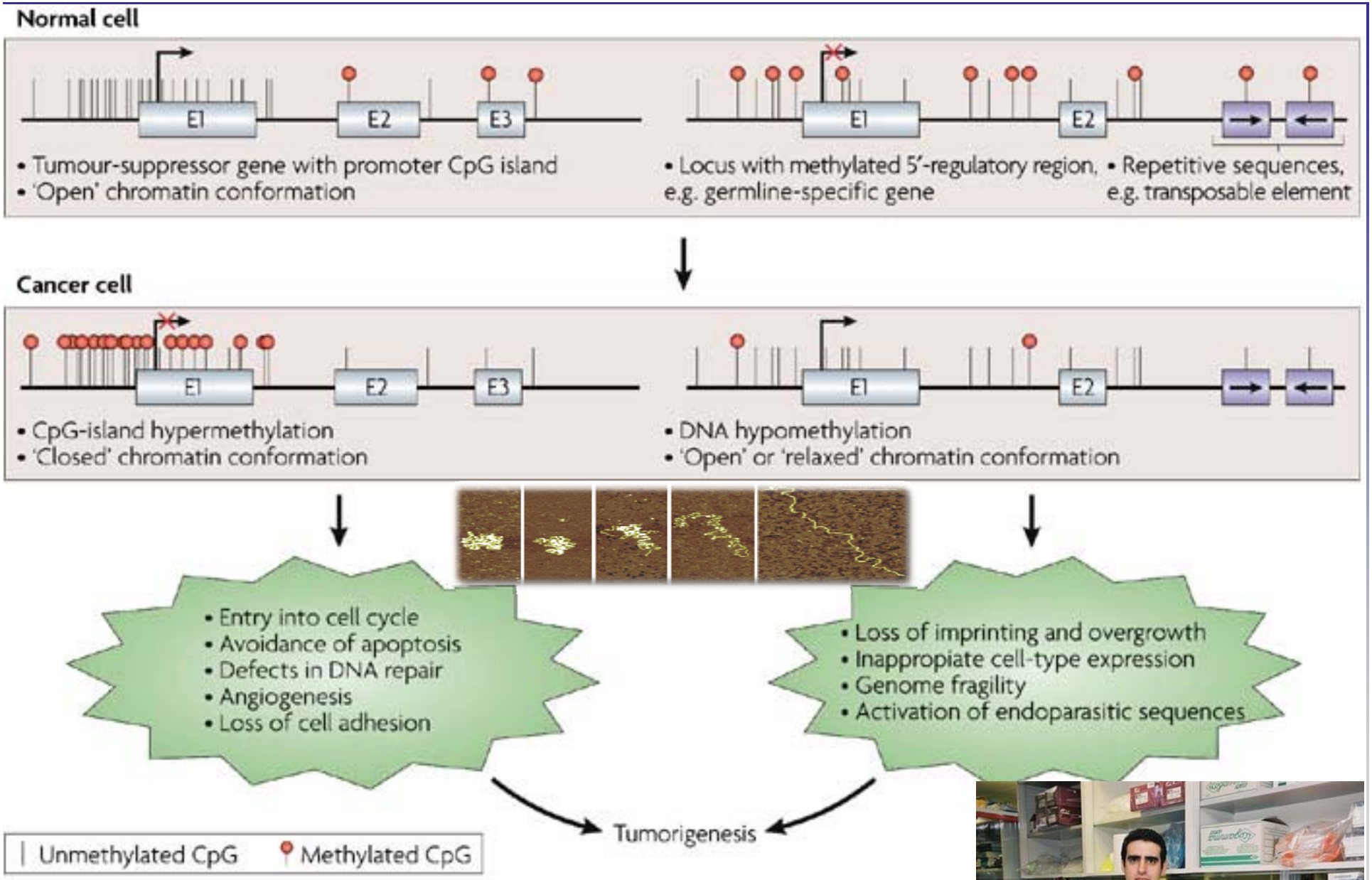



A
A single stem cell gives rise to many immature lymphocytes, each with different receptor specificity.
Stem cell
Receptors
Lymphocytes
Self-antigens
Pool of mature naive lymphocytes
Some immature lymphocytes bind self-antigens; they are removed by clonal deletion.
B
Naive lymphocyte
Foreign antigen
Foreign antigen binds to a mature naive lymphocyte, causing its activation.
(requires T cell help)
Activated lympho-cytes differentiate and proliferate, forming clones of effector cells that eliminate antigens.

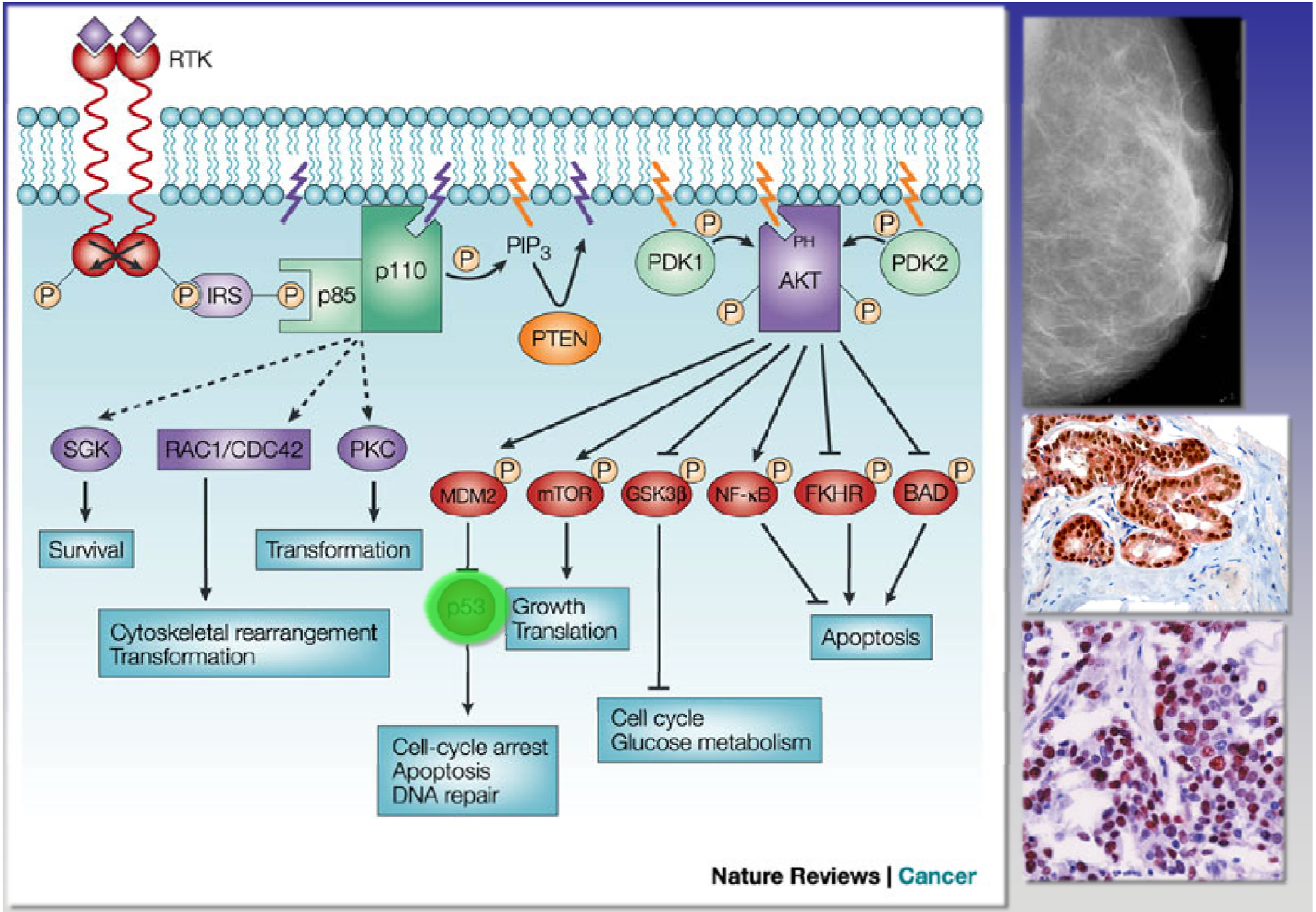

TRANSCRIPTION
OF MMP2
PROM
AP-2
SIL
SP-1
SP-1
MMP2 GENE
PROMOTER
+ 1 MMP2
(+)
Apoptosis
(+)
p53
NO EFFECT ON
MMP2 OR
TIMP PROMOTER
CYTOKINES
GROWTH FACTORS
PTL & TERM
LABOR
(+)
DNA FRAGMENTATION
(-)
TRANSCRIPTION
OF TIMP2
SP-1
SP-1
TRE
AP-2
SP-1
TATA
TIMP2
GENE
PROMOTER
+ 1 TIMP2





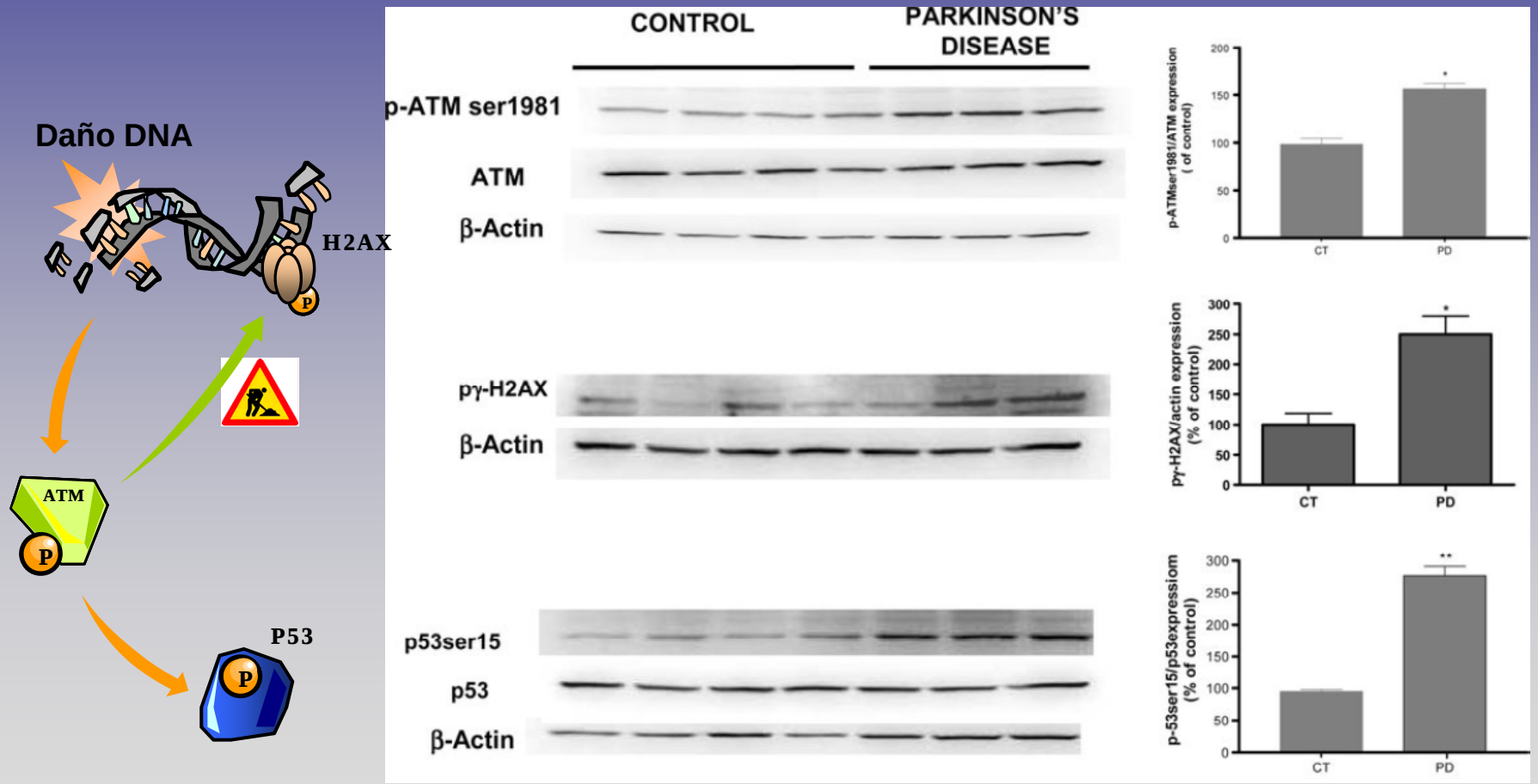


Manel Esteller. ***Nature Reviews Genetics*** **8**, **286-298 (April 2007)**

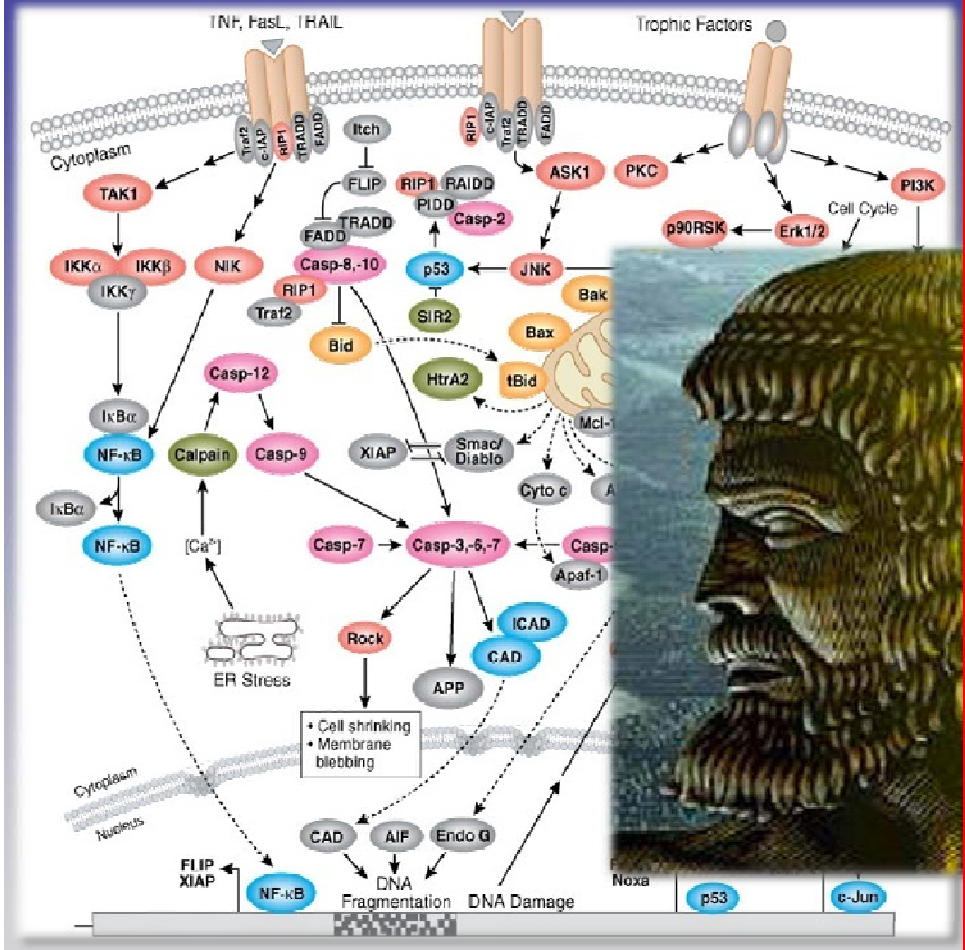


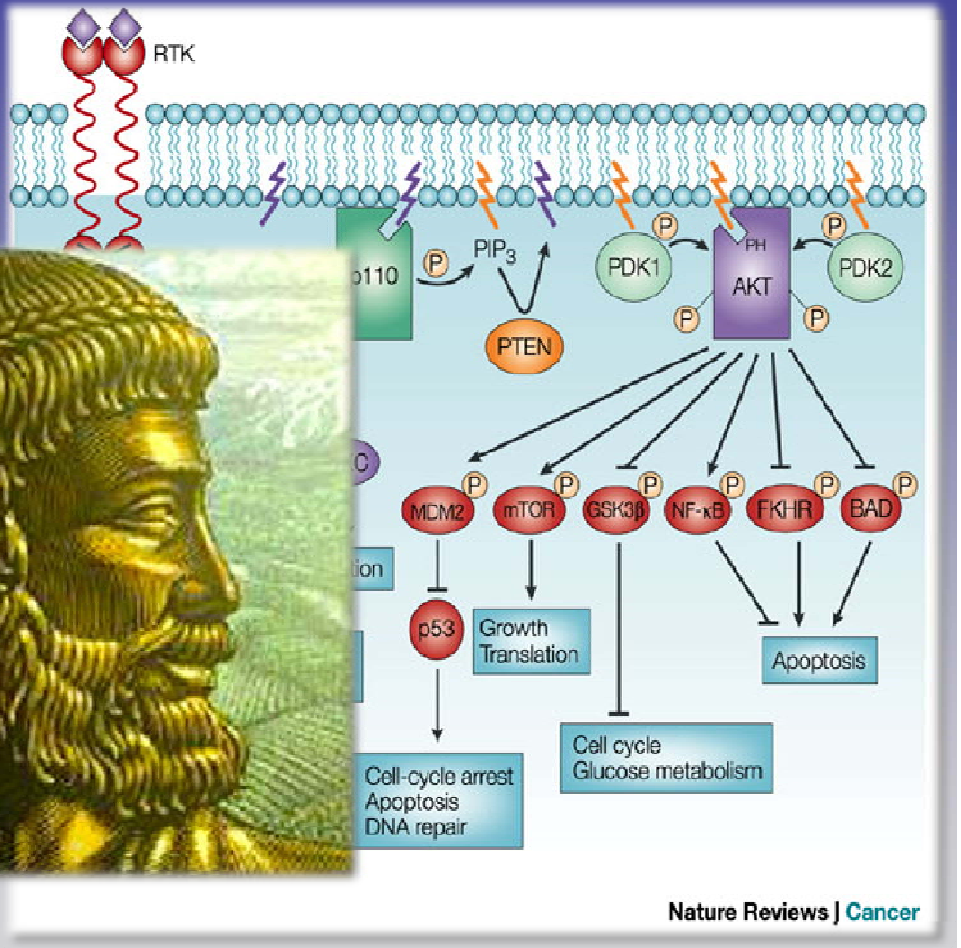
The phosphatidylinositol 3-Kinase–AKT pathway in human cancer. Igor Vivanco & Charles L. Sawyers
Nature Reviews Cancer 2, 489-501 (July 2002)

Muestras humanas *post-mortem* de pacientes con EP



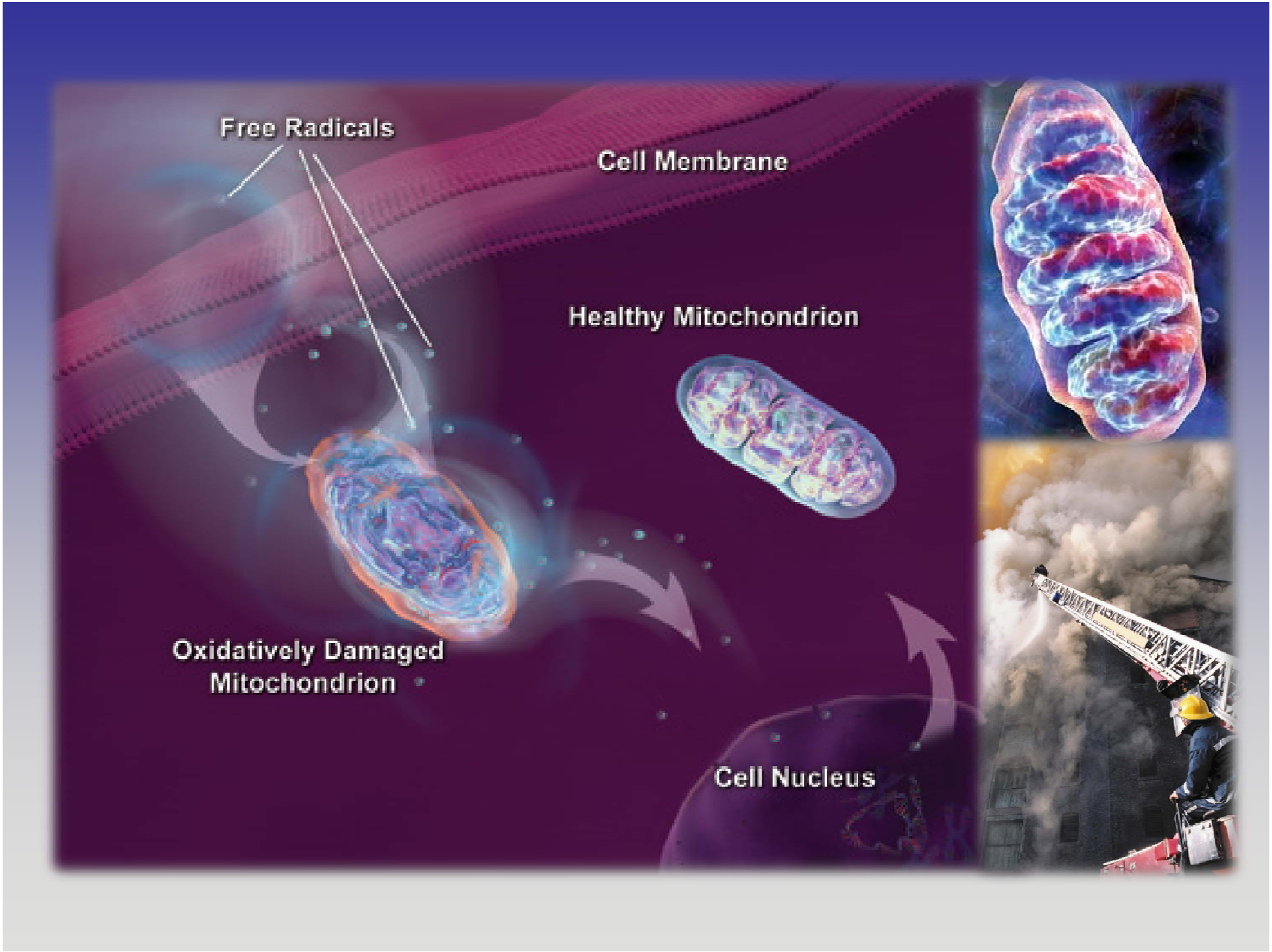
Activation of ataxia telangiectasia muted under experimental models and human Parkinson's disease.
Camins A, Pizarro JG, Alvira D, Gutierrez-Cuesta J, de la Torre AV, Folch J, Sureda FX, Verdaguer E, Junyent F, Jordán J, Ferrer I, Pallàs M. Cell Mol Life Sci. 2010

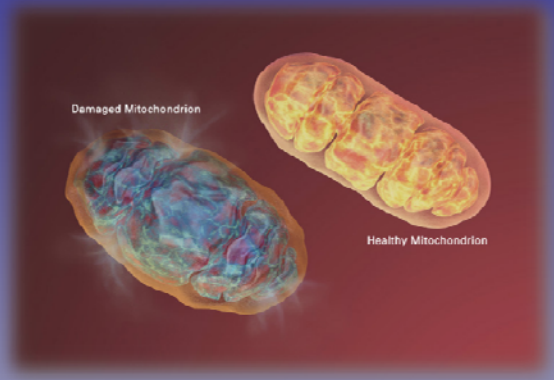




APOPTOSIS
NEURODEGENERACIÓN

APOPTOSIS
CÁNCER


Free Radicals
Cell Membrane
Healthy Mitochondrion
Oxidatively Damaged
Mitochondrion
Cell Nucleus



Reactive Oxygen Free Radical O_2^-

SOD

Hydrogen Peroxide Free Radical H_2O_2

Catalase

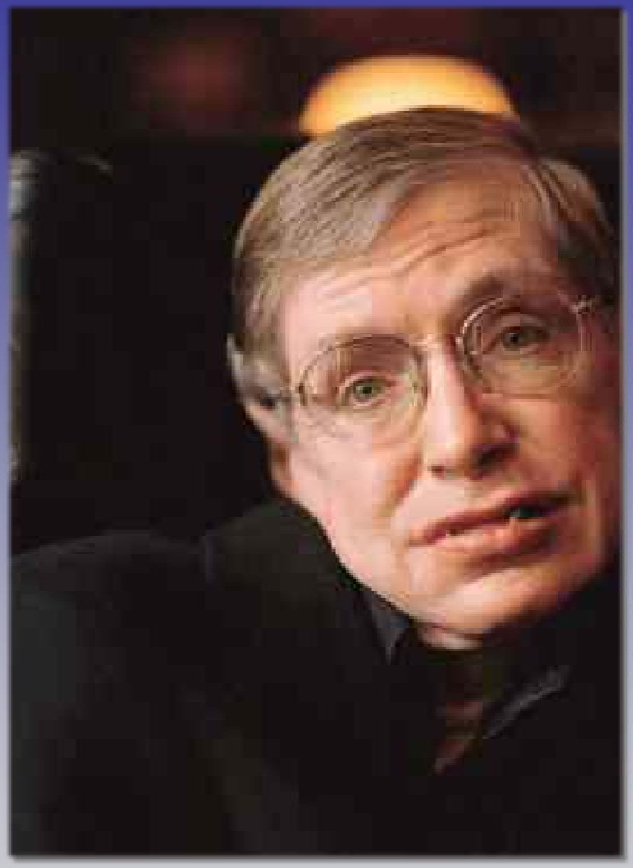
GPx

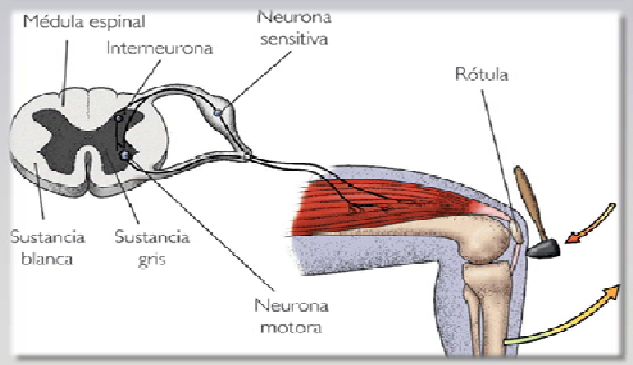
Water H_2O

+

Balanced Oxygen O_2

Esclerosis Lateral Amiotrófica (ALS)





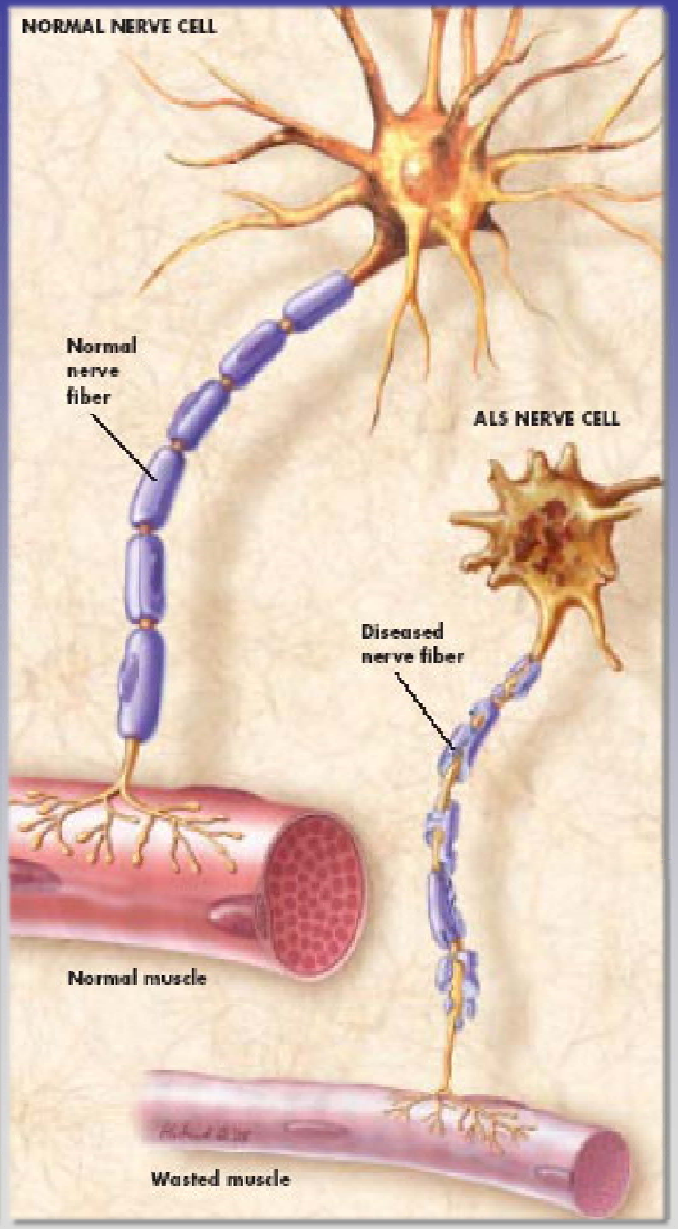


FIGURE 6 | The specificity of the toxic effect of SOD1 mutations on motor neurons arises from the convergence of several risk factors.

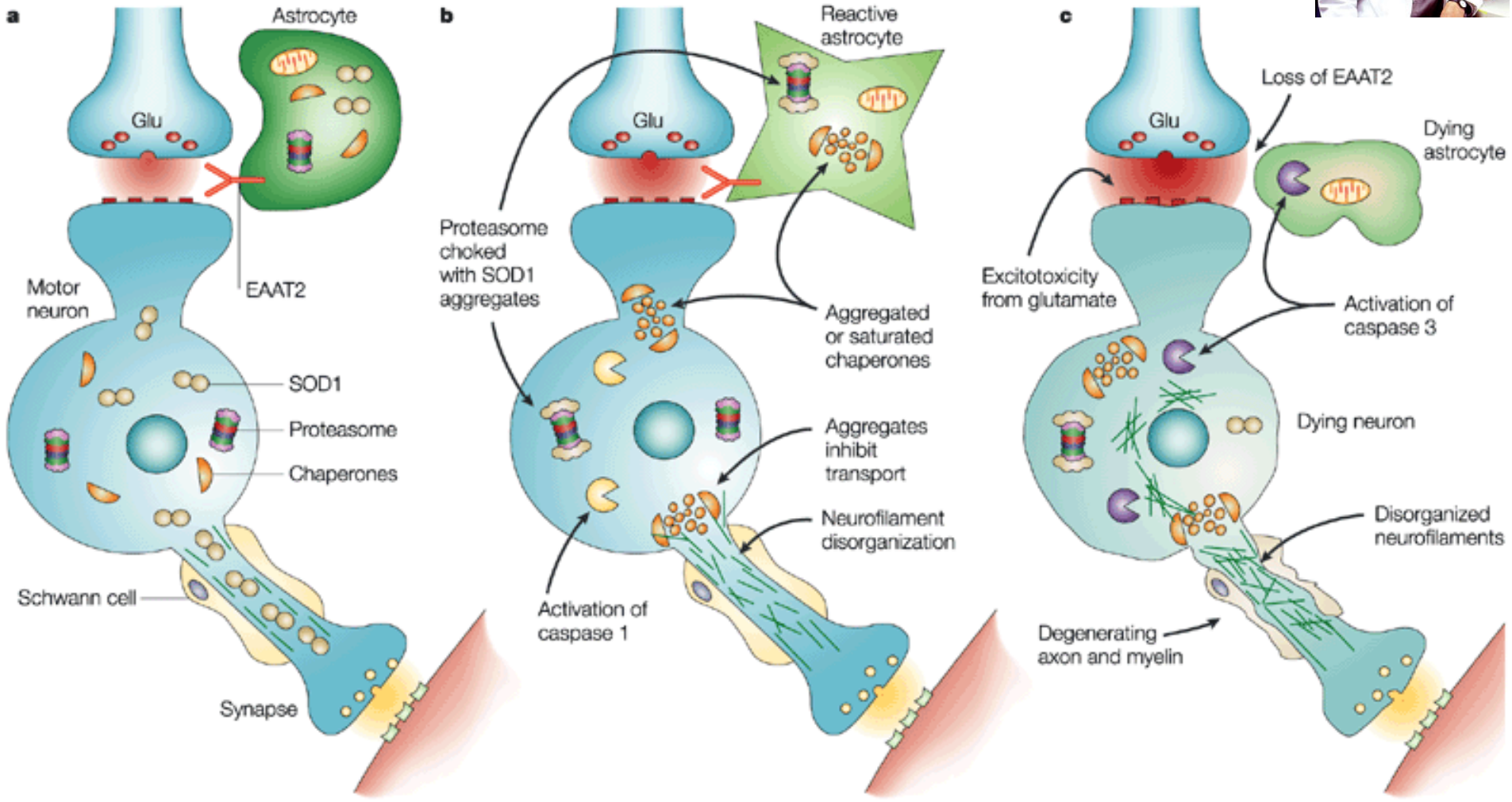
FROM THE FOLLOWING ARTICLE:

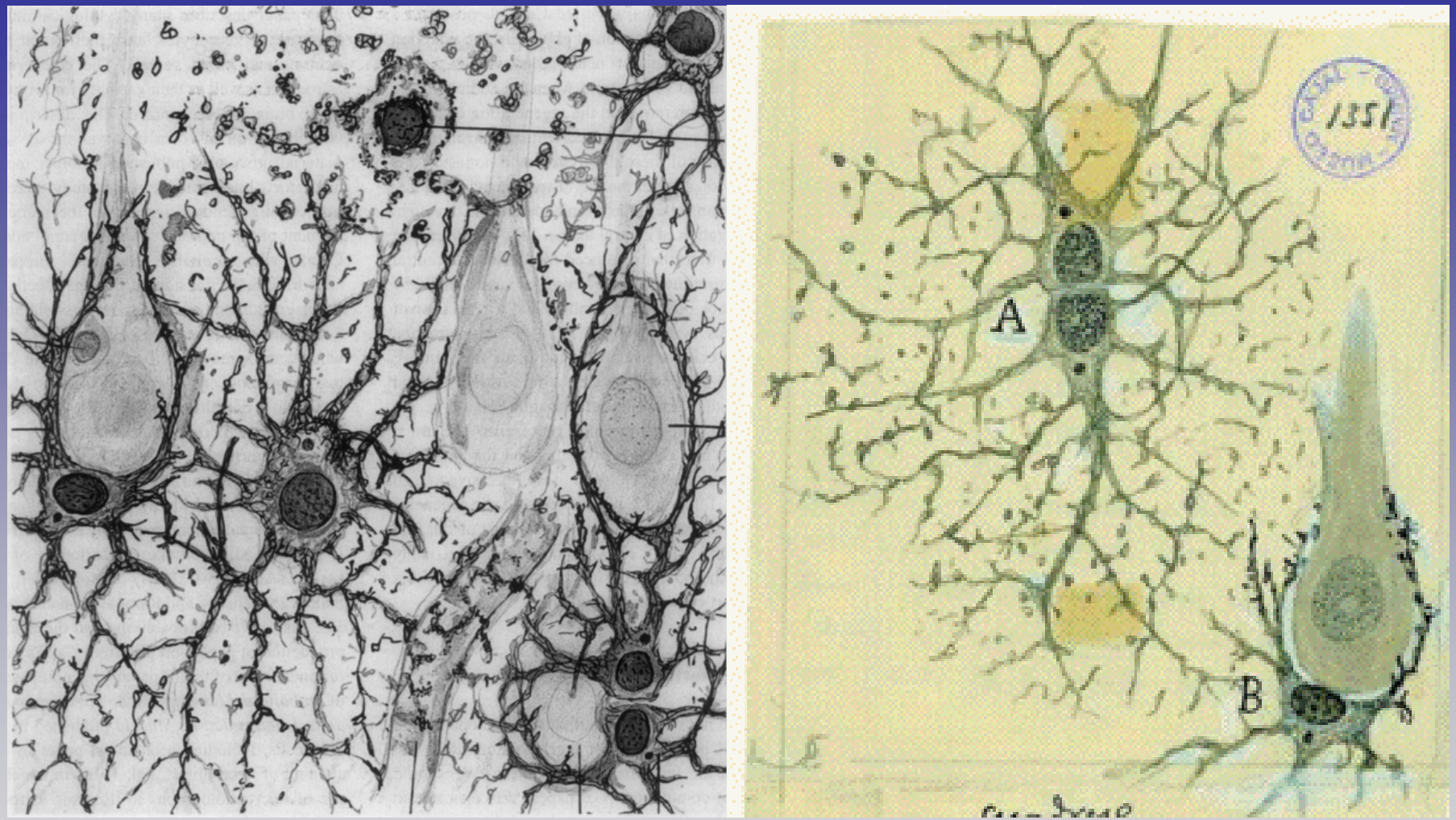
From charcot to lou gehrig: deciphering selective motor neuron death in als

Don W. Cleveland & Jeffrey D. Rothstein

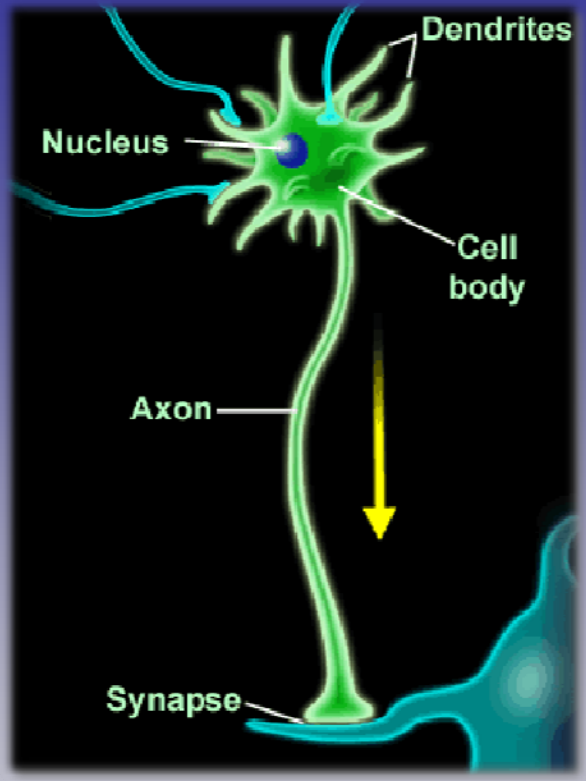
Nature Reviews Neuroscience 2, 806-819 (November 2001)

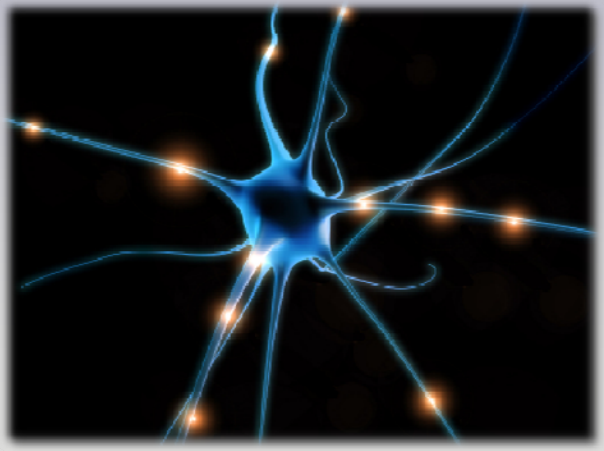
doi:10.1038/35097565

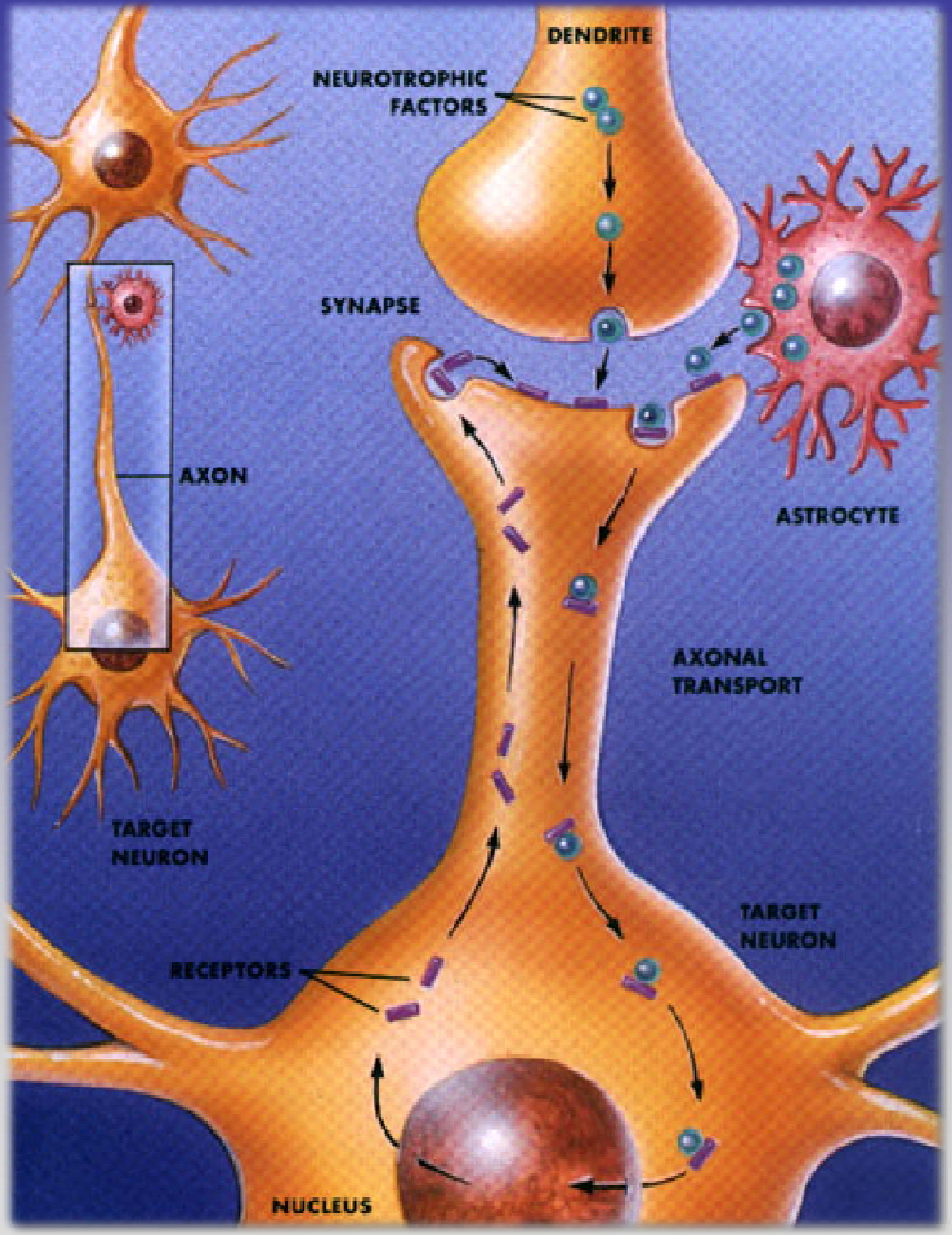


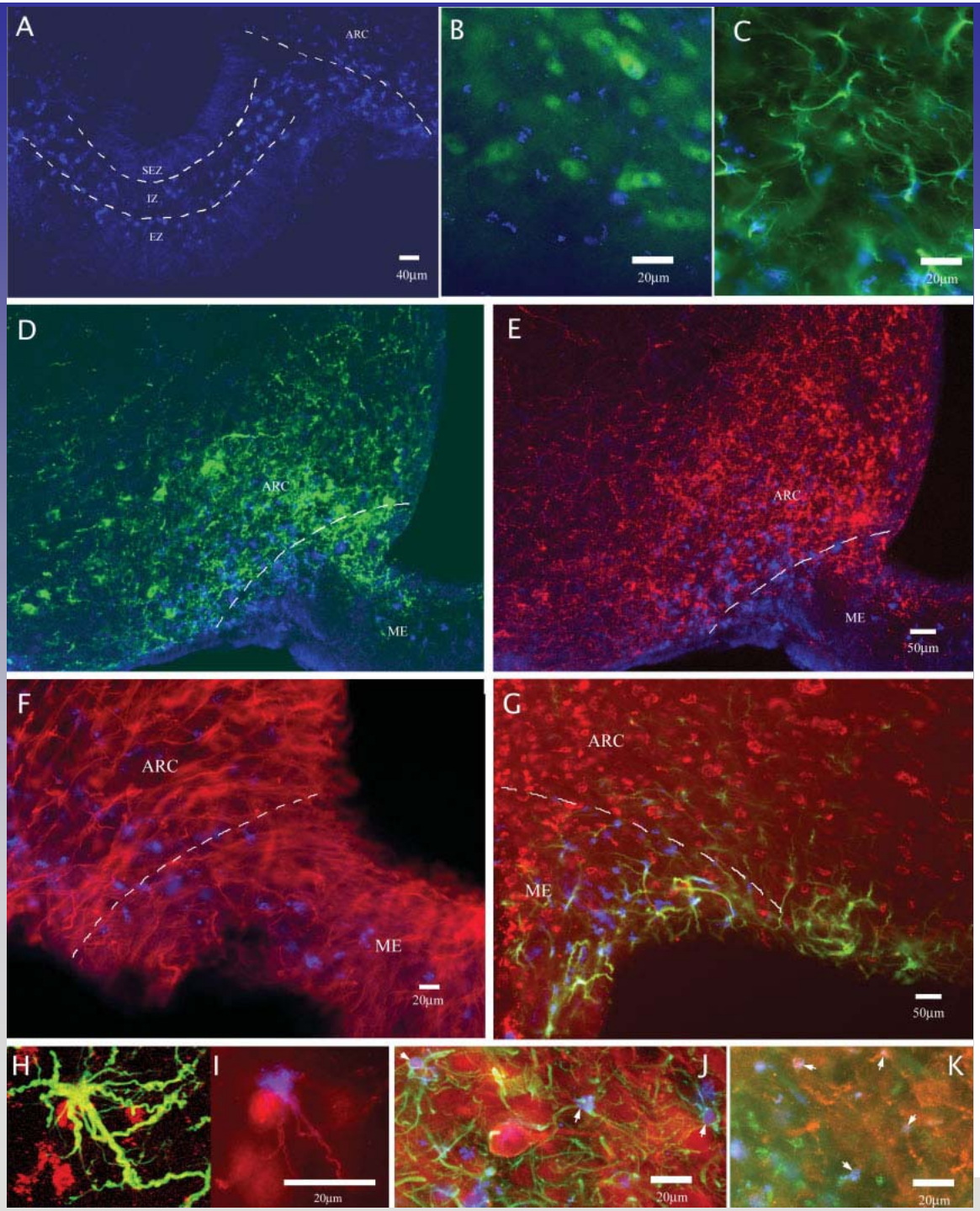


Neuroglia from the hippocampal formation (stratum radiatum of the Ammon horn) of a human brain. In this drawing Cajal shows astrocytic processes embracing pyramidal neurons as well as astrocytic processes in contact with blood vessels.
From Legado Cajal - in: García Segura, 2002.


Dendrites
Nucleus
Cell body
Axon
Synapse



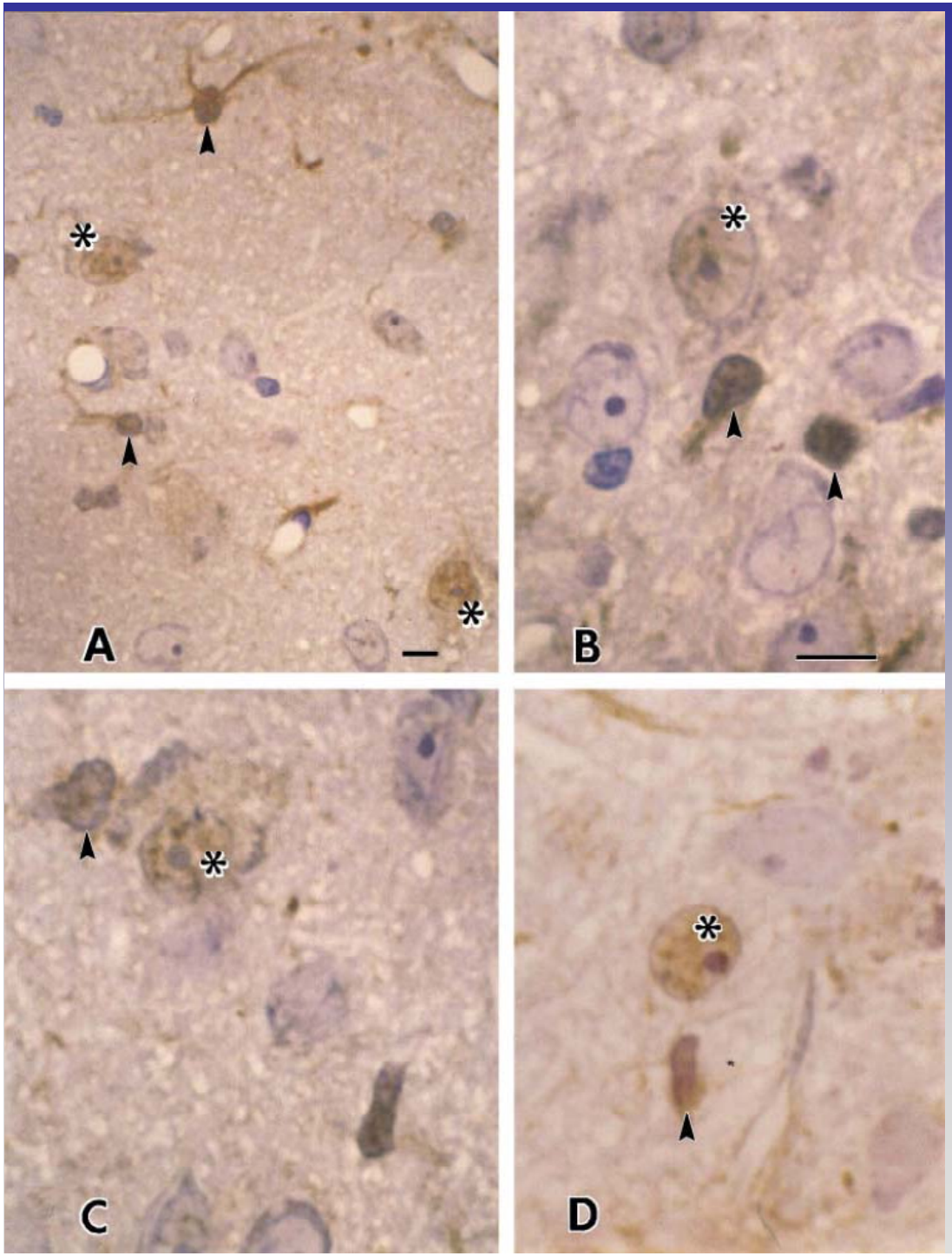

DENDRITE
NEUROTROPHIC FACTORS
SYNAPSE
AXON
ASTROCYTE
AXONAL TRANSPORT
TARGET NEURON
TARGET NEURON
RECEPTORS
NUCLEUS



ORNSIRI CHEUNSUANG AND RICHARD MORRIS
GLIA 52:228–233 (2005)

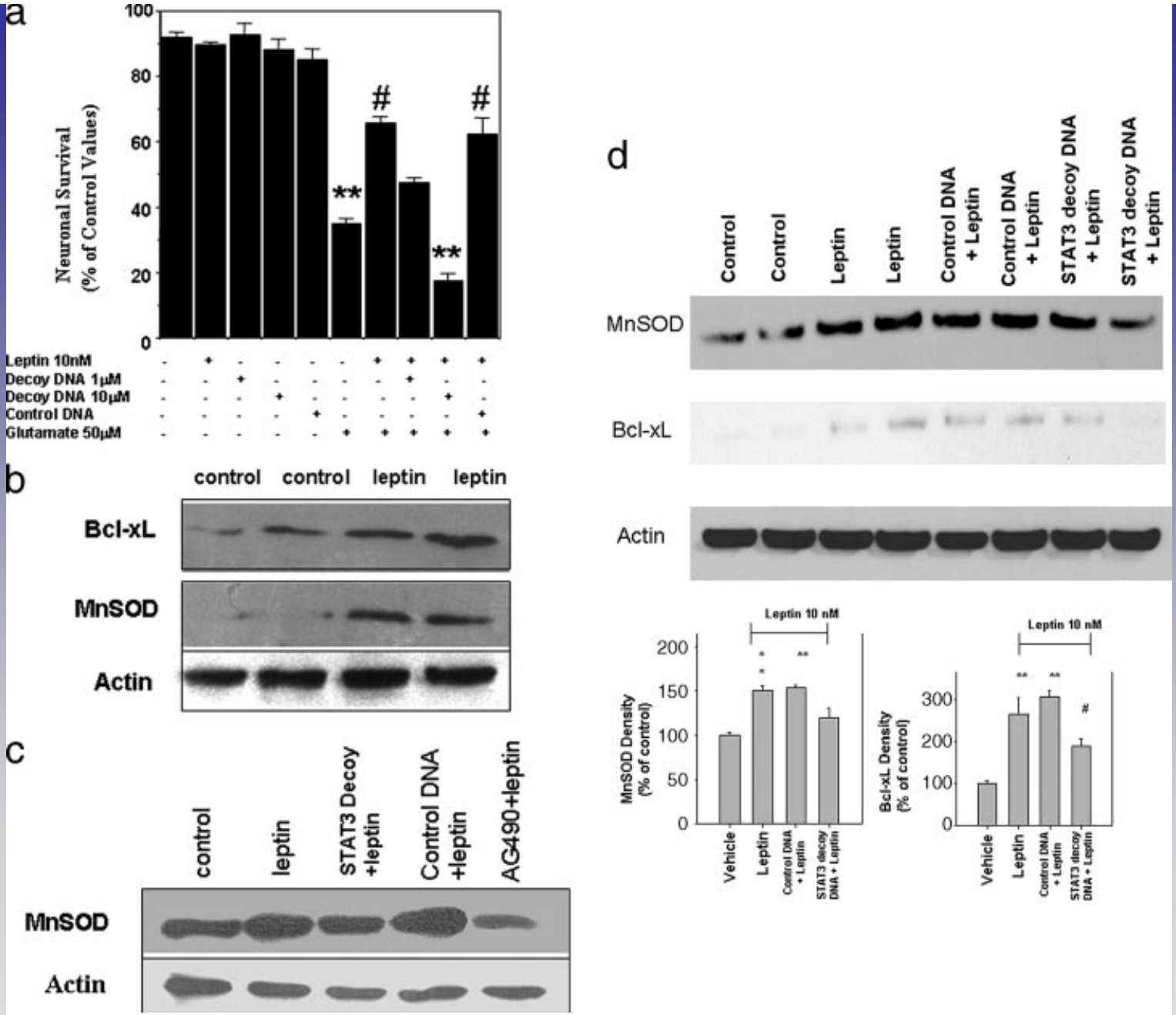
Astrocytes in the Arcuate Nucleus and Median Eminence That Take Up a Fluorescent Dye From the Circulation Express Leptin Receptors and Neuropeptide Y Y1 Receptors

(G). Triple labelling for OHSt (blue), OB-R (red) and GFAP (green) demonstrated the uptake of OHSt by astrocytes expressing OB-R in the ventral part of the arcuate nucleus and median eminence. (H-I) At higher magnification GFAP (green) and OB-R (red) can be clearly seen in the same astrocyte using laser confocal microscopy (H),



Arcuate astrocytes and neurones. Panel A shows that bFABP-immunoreactive astrocytes (arrowheads) occupy the same general area as STAT3-immunoreactive neurones (asterisks).

John K. Young.
Anatomical relationship between specialized astrocytes and leptin-sensitive neurones
J. Anat. (2002) **201**, pp85–90



Zhihong Guo et al., Leptin-mediated Cell Survival Signaling in Hippocampal Neurons Mediated by JAK STAT3 and Mitochondrial Stabilization*. THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 283, NO. 3, pp. 1754–1763, January 18, 2008

oxygen exposure, telomere erosion & cellular senescence

stress & damage

repair

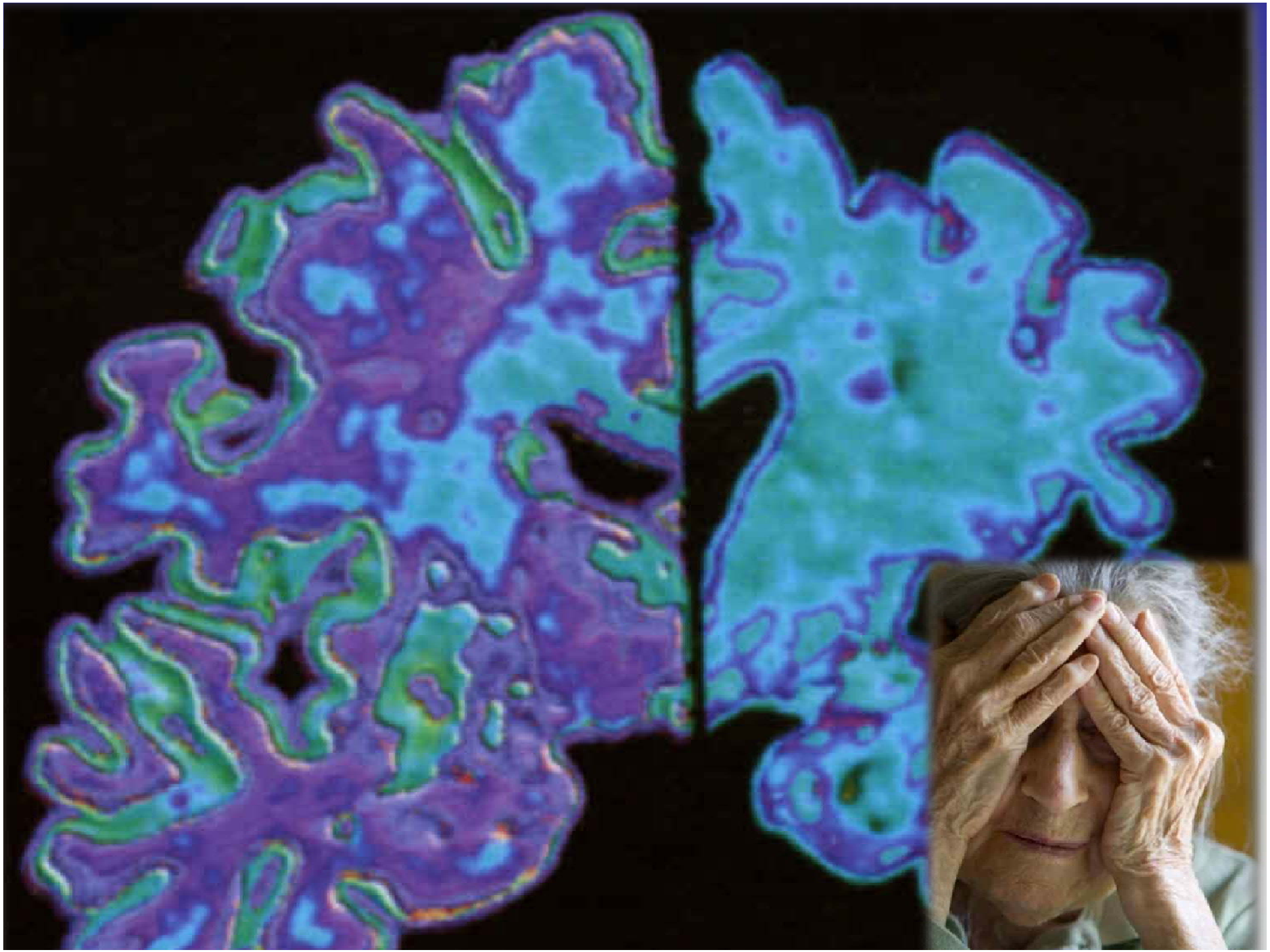
premature aging

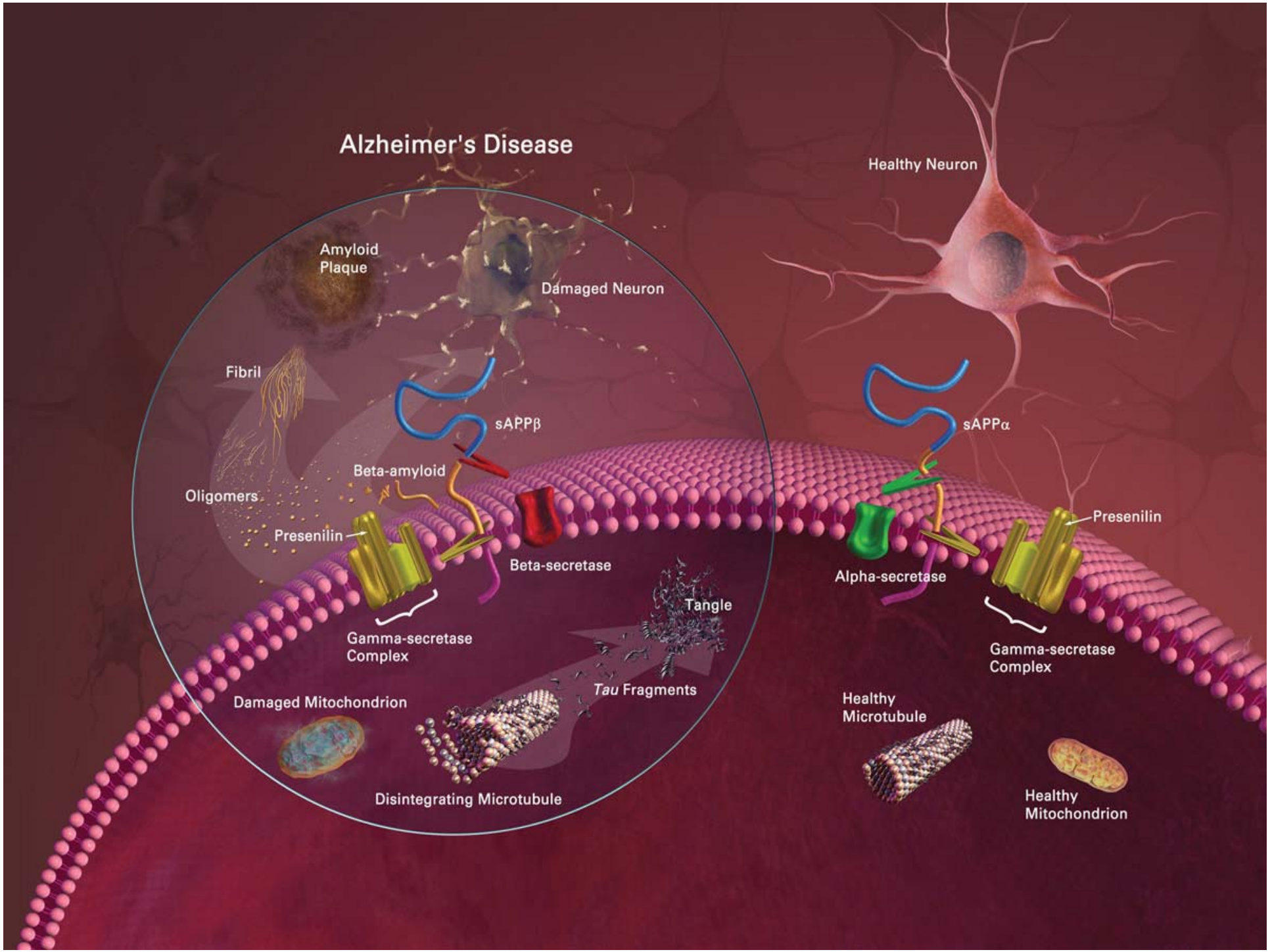
normal lifespan

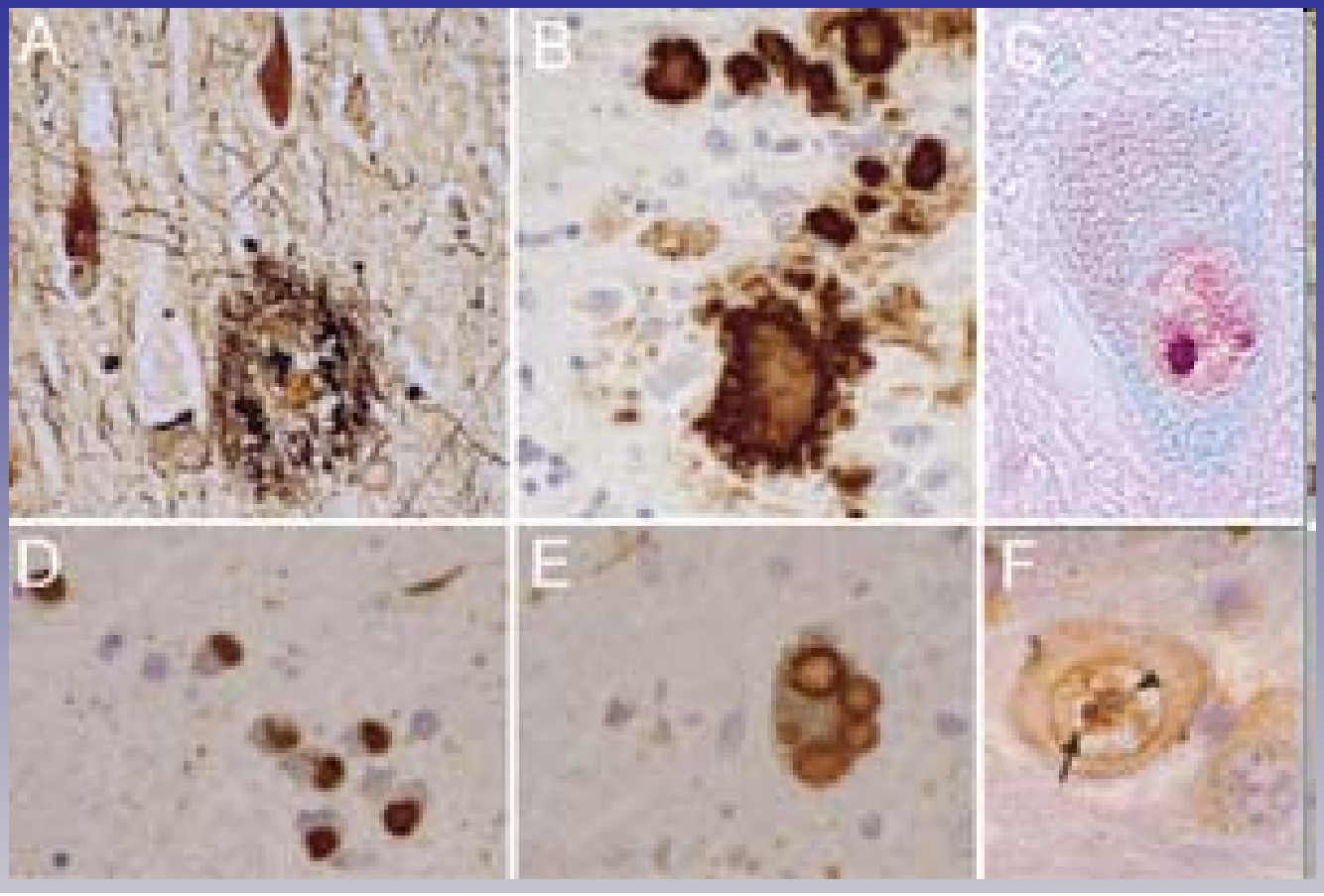
longevity

birth

death




Alzheimer's Disease
Amyloid Plaque
Damaged Neuron
Fibril
sAPPβ
Beta-amyloid
Oligomers
Presenilin
Beta-secretase
Gamma-secretase Complex
Tangle
Tau Fragments
Damaged Mitochondrion
Disintegrating Microtubule
Healthy Neuron
sAPPα
Alpha-secretase
Presenilin
Gamma-secretase Complex
Healthy Microtubule
Healthy Mitochondrion

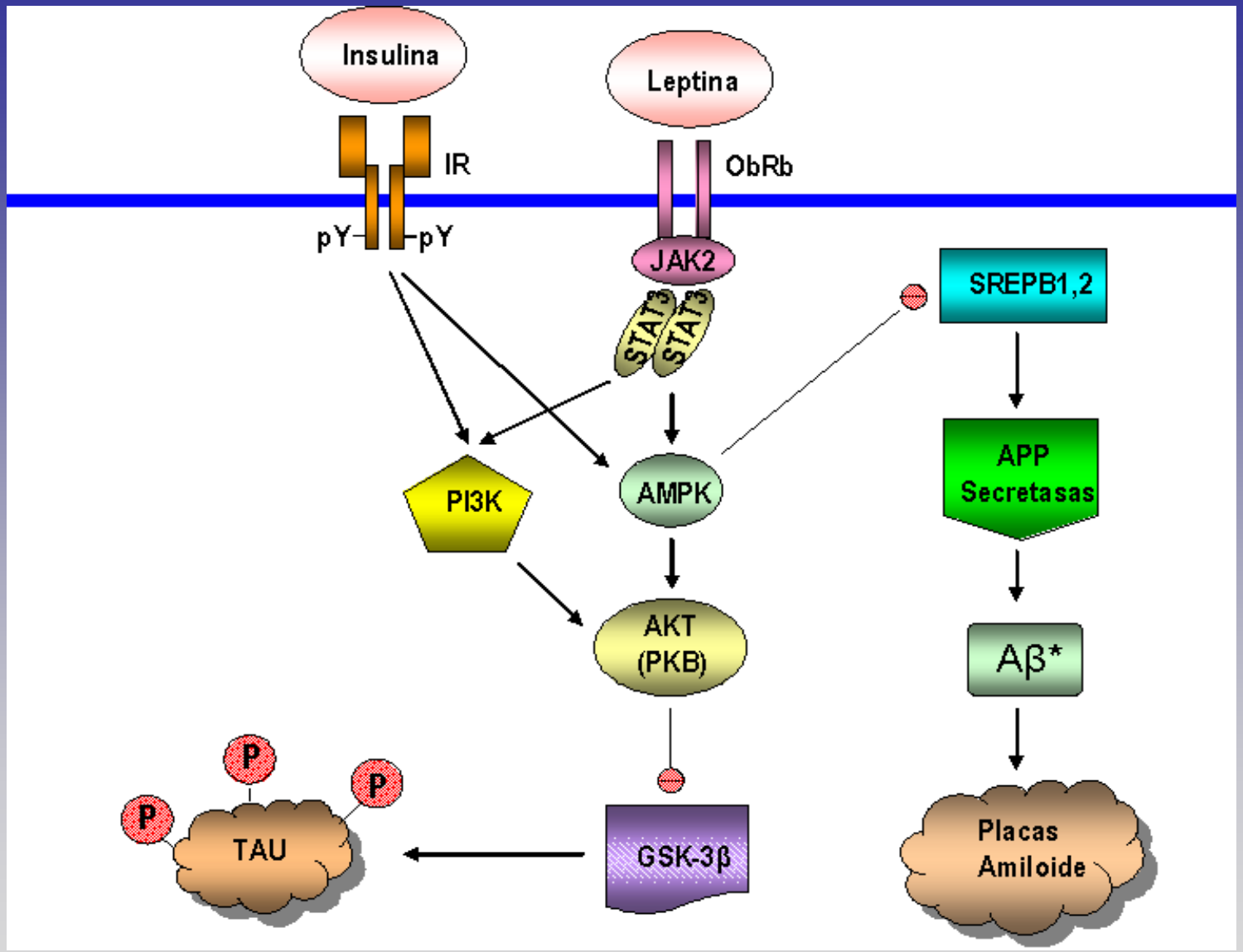


THE USUAL SUSPECTS:

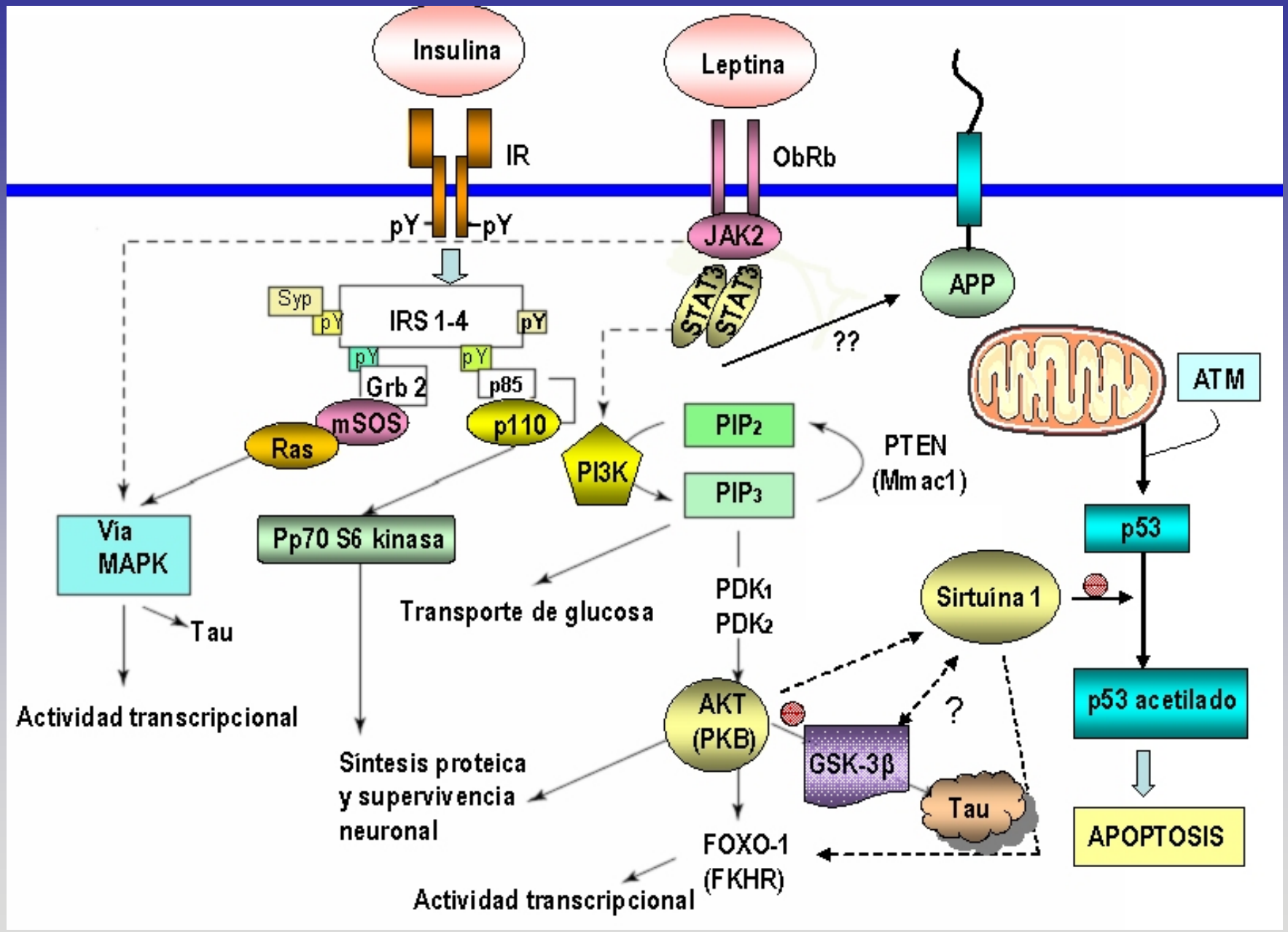
Aggregates of misfolded proteins are implicated in various neurodegenerative diseases:

A. Intracellular neurofibrillary tangles and extracellular amyloid plaque in Alzheimer disease;
B. the PrPSc aggregates in prion diseases;
C. intranuclear inclusions in Kennedy disease;
D. Tau inclusions in Pick disease;
E. Lewy Bodies in Parkinson disease;
F. Intranuclear inclusion of mutant ataxin-3 in Machado-Joseph disease (showing that it is distinct from the nucleolus).

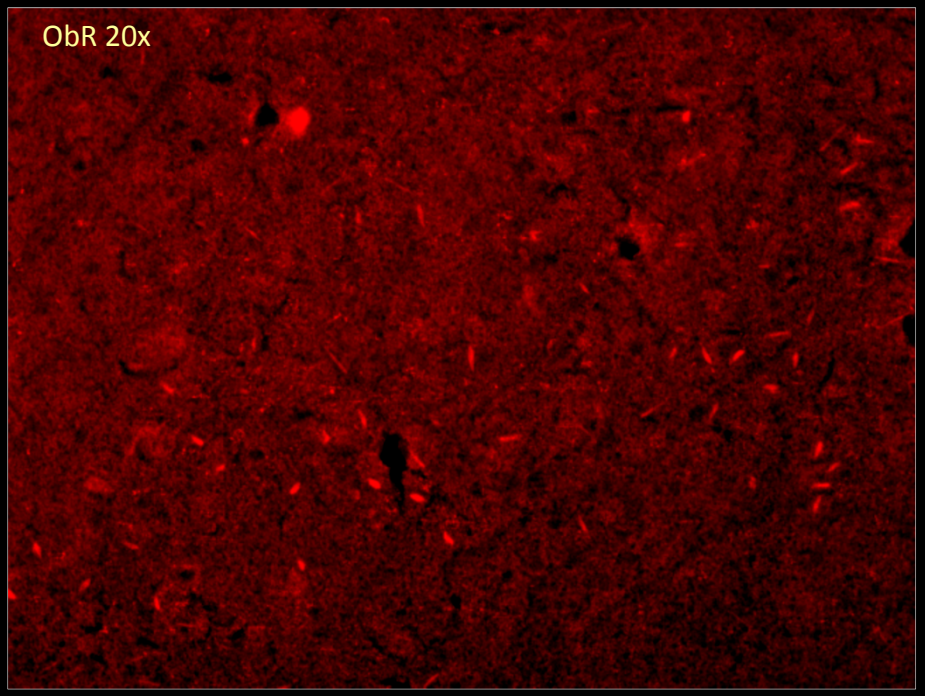
J.P. Taylor et al., Science, 296:1991–5, 2002.)

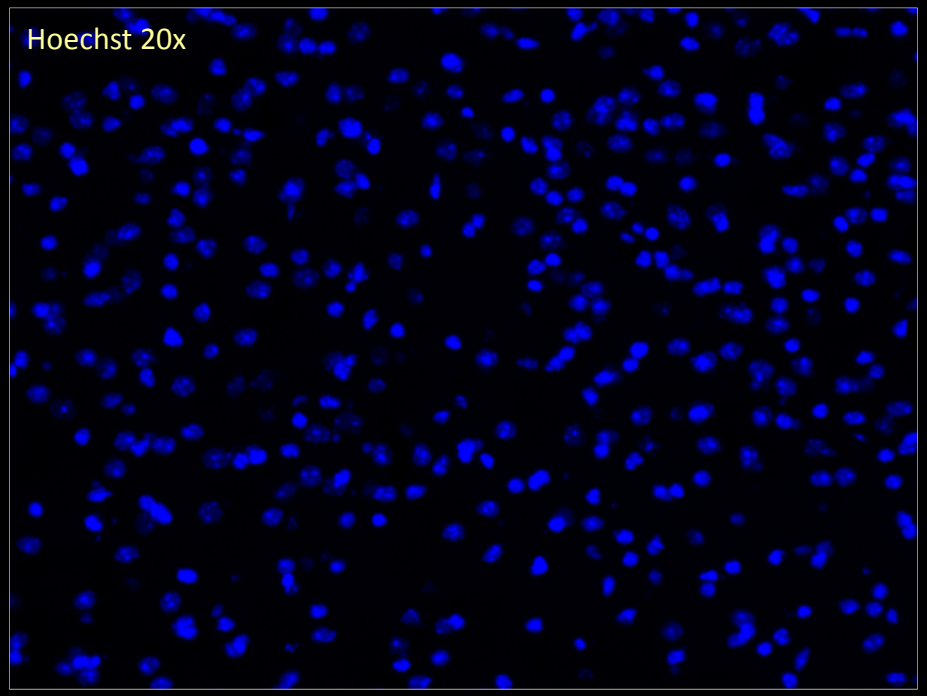


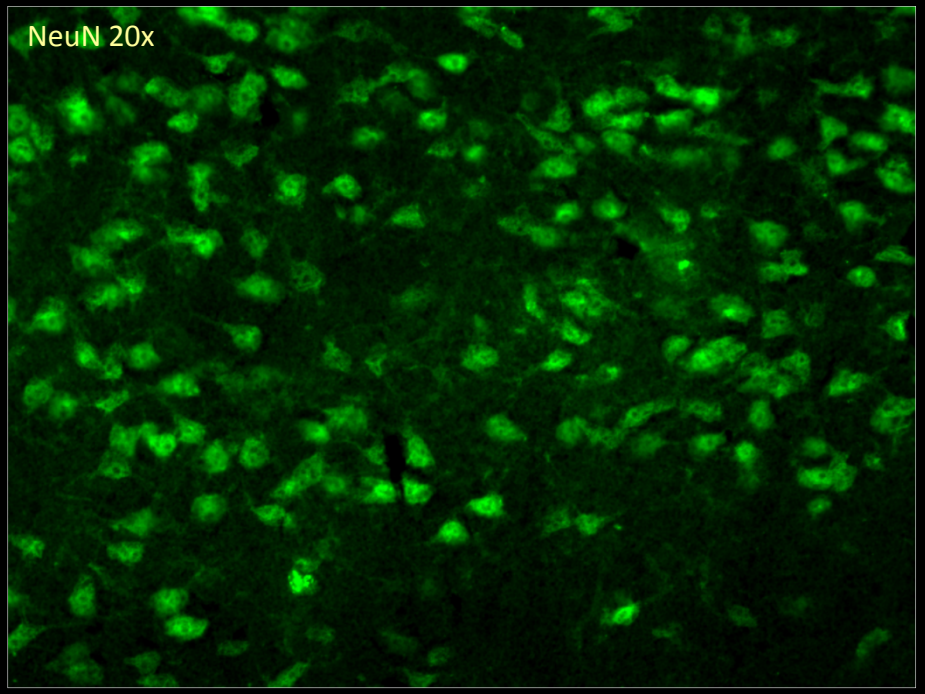
Nikolaos Tezapsidis, Gemma Casadesus, Mark Smith, et al.
Leptin: A Novel Therapeutic Strategy for Alzheimer's Disease
J Alzheimers Dis. 2009 April ; 16(4): 731–740


Insulina
Leptina
IR
ObRb
pY
pY
JAK2
STAT3
STAT3
APP
??
Syp
pY
IRS 1-4
pY
pY
pY
Grb 2
p85
mSOS
p110
Ras
PI3K
PIP2
PIP3
PTEN
(Mmac1)
ATM
Via
MAPK
Pp70 S6 kinasa
p53
Tau
Transporte de glucosa
PDK1
PDK2
Sirtuina 1
Actividad transcripcional
AKT
(PKB)
?
p53 acetilado
GSK-3β
Tau
Síntesis proteica
y supervivencia
neuronal
APOPTOSIS
FOXO-1
(FKHR)
Actividad transcripcional

7.14 p1 SAMP8 12m **Hipotálamo**

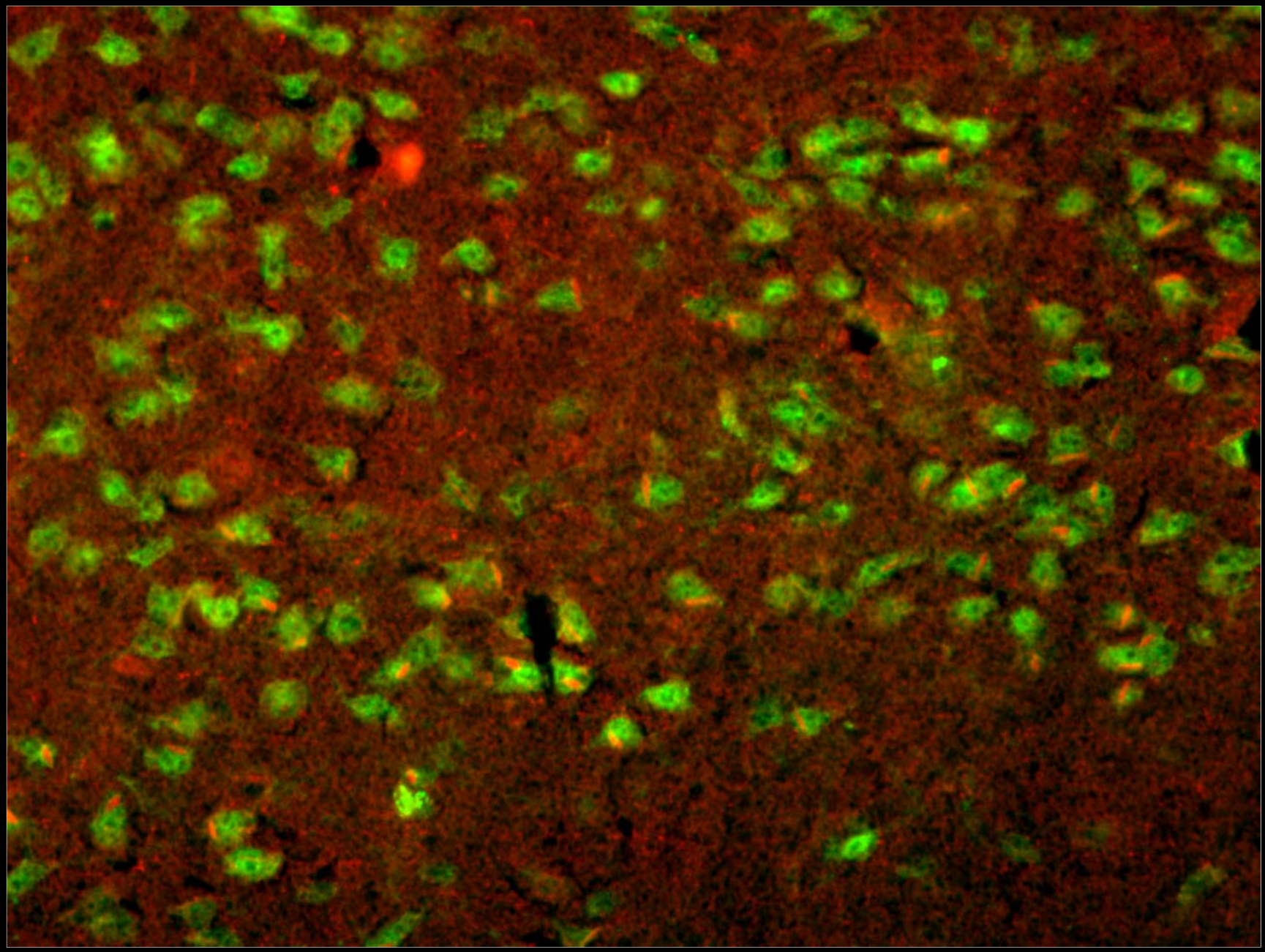






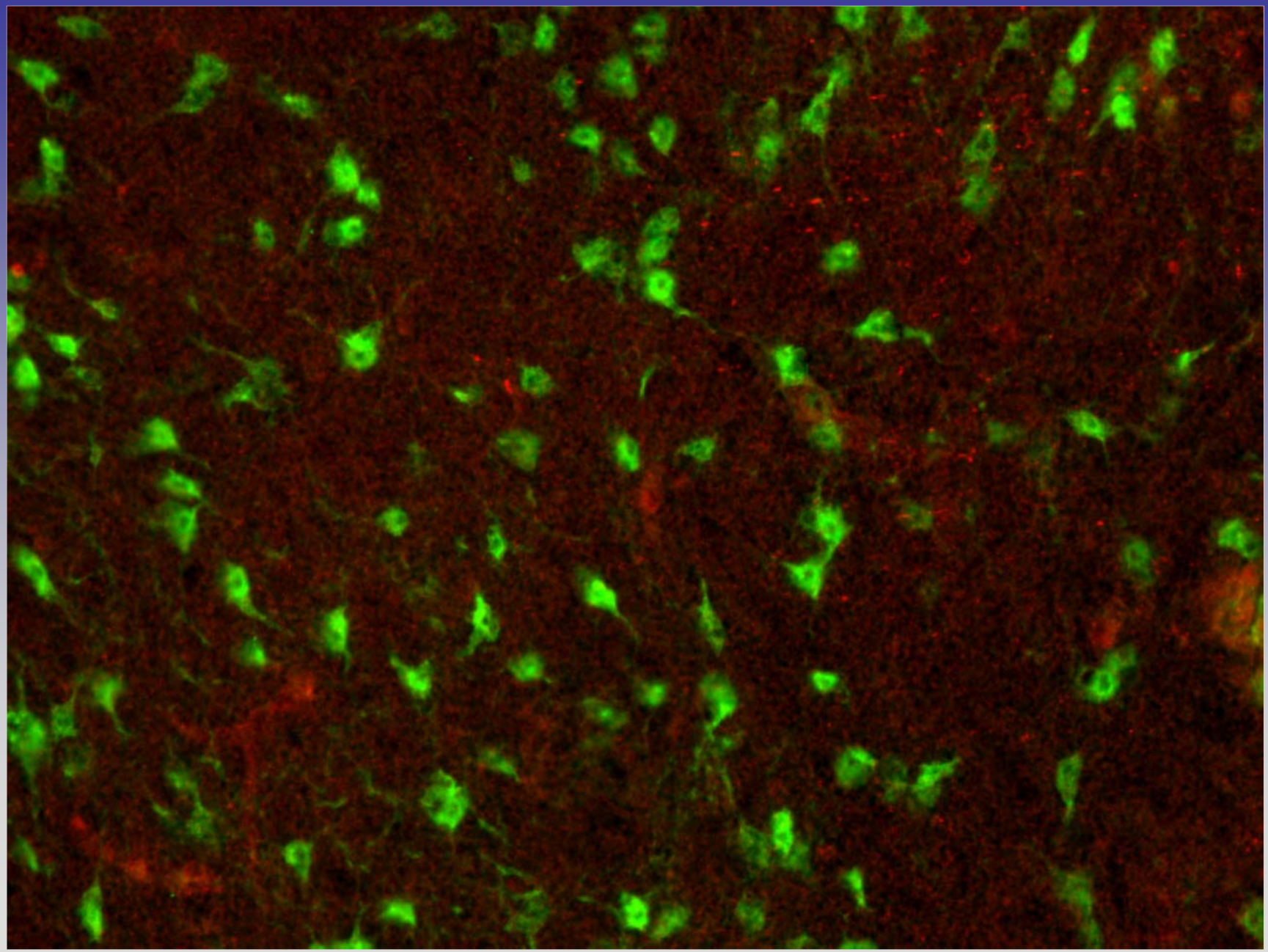
7.14 p1 SAMP8 12m **Hipotálamo**

ObR + NeuN 20x



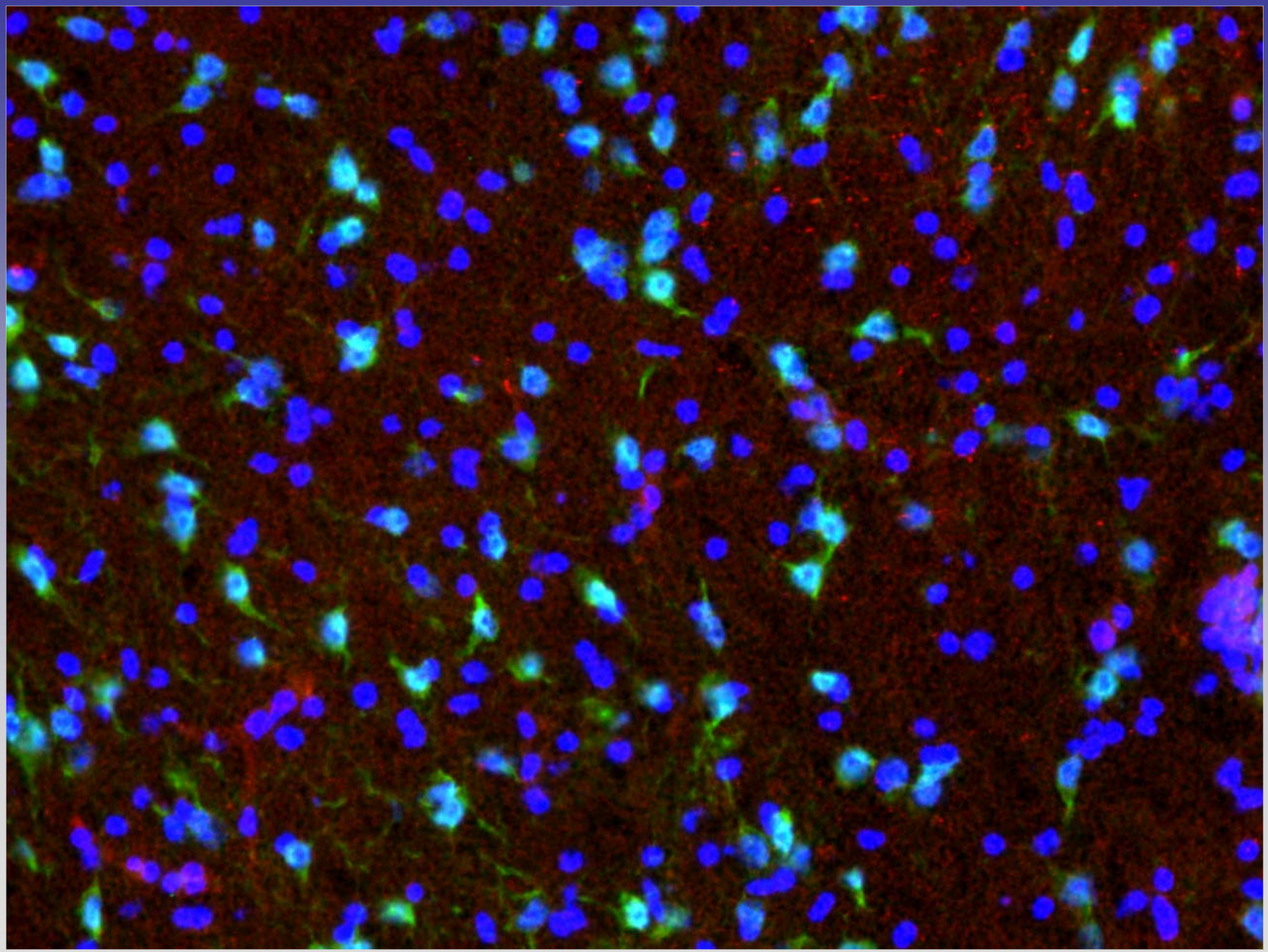
239.9 p2 ICR 12m **Hipotálamo**

ObR + NeuN 20x

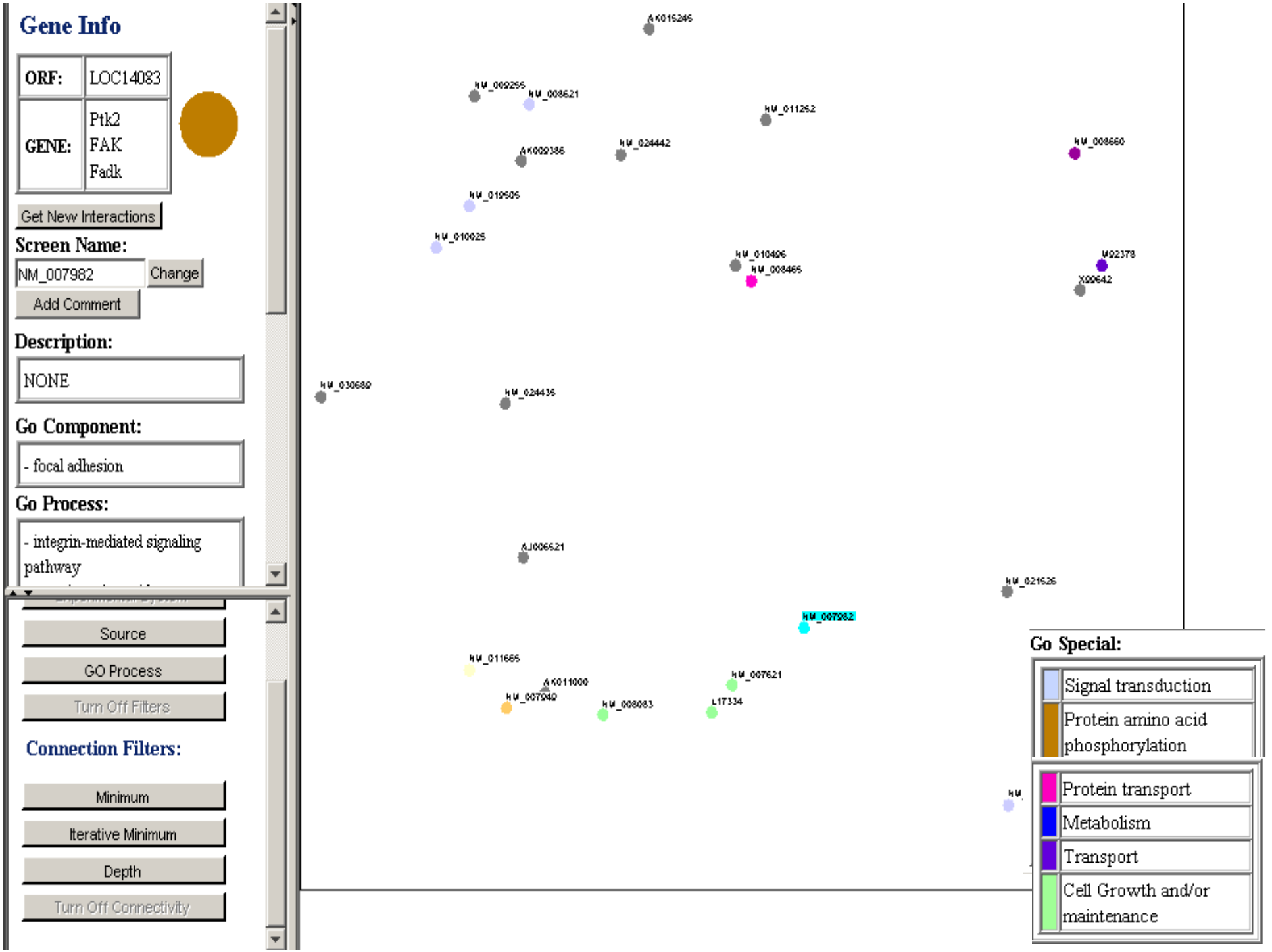


239.9 p2 ICR 12m **Hipotálamo**

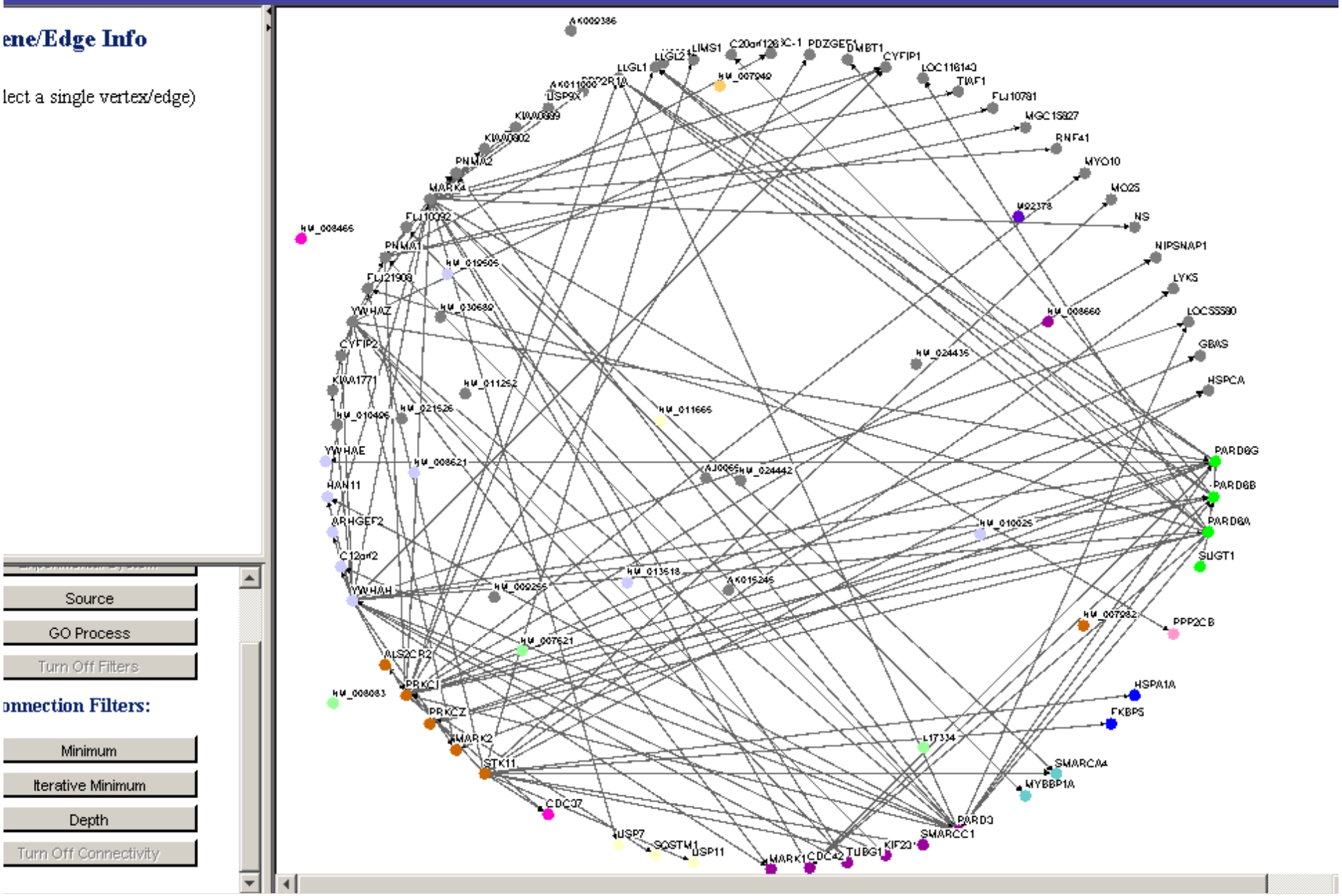
ObR + NeuN + H 40x




RATONES
DOBLES MUTANTES
APP/PS1
MODELO DE ALZHEIMER


Gene Info
ORF:
LOC14083
GENE:
Ptk2
FAK
Fadk
Get New Interactions
Screen Name:
NM_007982
Change
Add Comment
Description:
NONE
Go Component:
- focal adhesion
Go Process:
- integrin-mediated signaling pathway
Source
GO Process
Turn Off Filters
Connection Filters:
Minimum
Iterative Minimum
Depth
Turn Off Connectivity
AK015246
NM_009255
NM_008621
NM_011252
AK009386
NM_024442
NM_008660
NM_010505
NM_010025
NM_010406
NM_008466
M92378
X99642
NM_030680
NM_024435
AJ006621
NM_021526
NM_007982
NM_011665
AK011000
NM_007940
NM_008083
NM_007621
L17334
Go Special:
Signal transduction
Protein amino acid phosphorylation
Protein transport
Metabolism
Transport
Cell Growth and/or maintenance

Malla de interacciones *human grid* (Alzheimer genes)



Genes "*neuron associated*"

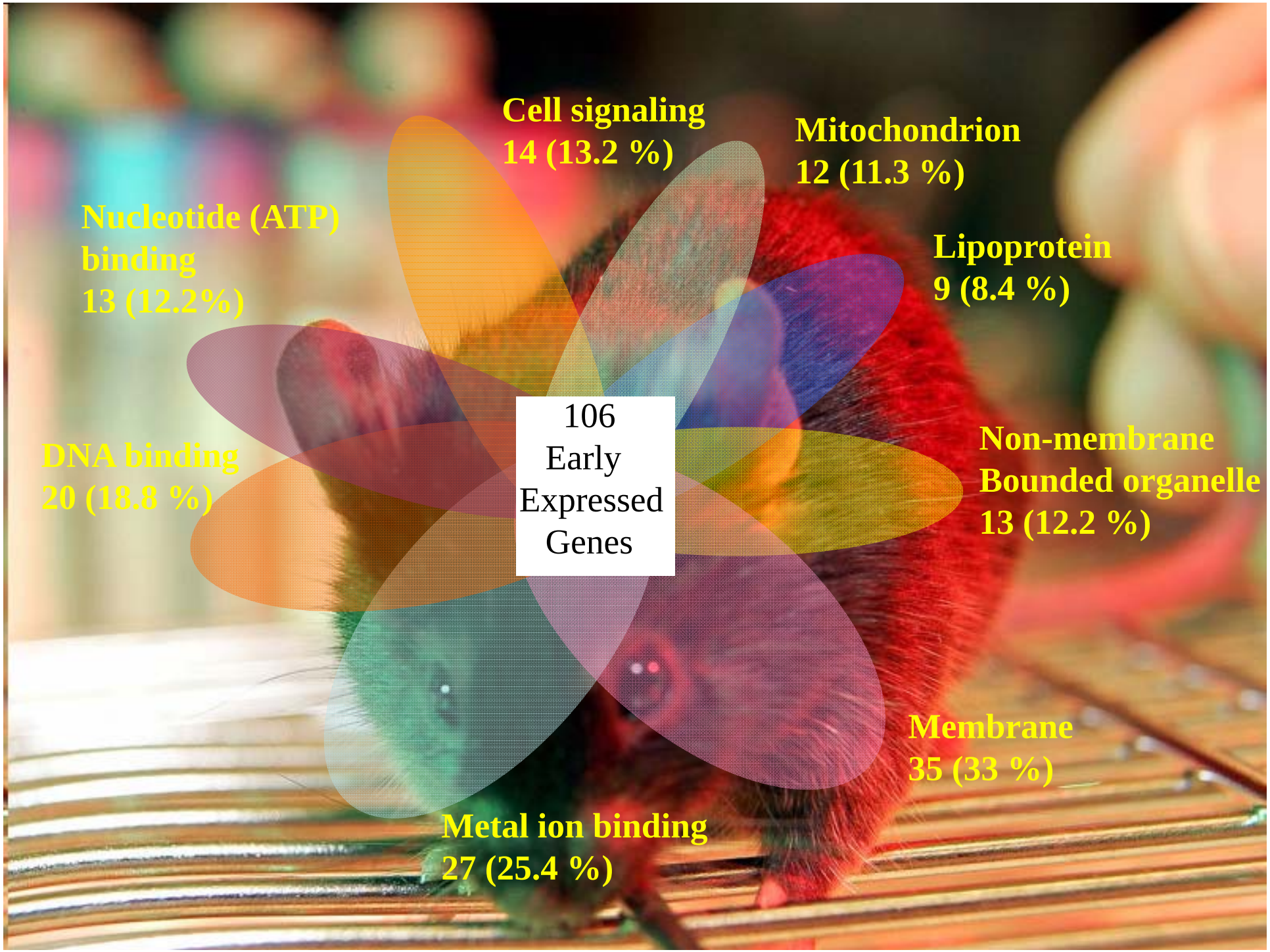
Functional Annotation Chart Help and Manual Current Gene List:

List_1 Current Background: Mus musculus 68 DAVID IDs

60 chart records

Download File

Sublist	Category	Term	RT	Genes	Count	%	P-Value	Benjamin
☐	GOTERM_BP_FAT	B cell activation	RT		5	7,4	2,6E-4	1,2E-1
☐	GOTERM_BP_FAT	B cell differentiation	RT		4	5,9	8,0E-4	1,8E-1
☐	GOTERM_BP_FAT	Wnt receptor signaling pathway, calcium modulating pathway	RT		3	4,4	2,8E-3	3,8E-1
☐	GOTERM_BP_FAT	cell activation	RT		6	8,8	2,9E-3	3,0E-1
☐	KEGG_PATHWAY	Pathways in cancer	RT		6	8,8	5,3E-3	2,8E-1
☐	GOTERM_BP_FAT	lymphocyte activation	RT		5	7,4	6,9E-3	5,0E-1
☐	GOTERM_BP_FAT	lymphocyte differentiation	RT		4	5,9	1,0E-2	5,8E-1
☐	GOTERM_BP_FAT	leukocyte activation	RT		5	7,4	1,1E-2	5,5E-1
☐	INTERPRO	Paralemmin	RT		2	2,9	1,4E-2	9,3E-1
☐	GOTERM_BP_FAT	Wnt receptor signaling pathway	RT		4	5,9	1,5E-2	6,1E-1
☐	GOTERM_BP_FAT	leukocyte differentiation	RT		4	5,9	1,9E-2	6,5E-1
☐	SP_PIR_KEYWORDS	dna-binding	RT		11	16,2	2,2E-2	9,6E-1
☐	SP_PIR_KEYWORDS	developmental protein	RT		8	11,8	2,2E-2	8,1E-1
☐	GOTERM_BP_FAT	hemopoietic or lymphoid organ development	RT		5	7,4	2,5E-2	7,2E-1
☐	SP_PIR_KEYWORDS	acetylation	RT		15	22,1	2,6E-2	7,3E-1
☐	GOTERM_BP_FAT	immune system development	RT		5	7,4	2,9E-2	7,4E-1
☐	GOTERM_BP_FAT	DNA recombination	RT		3	4,4	3,6E-2	7,8E-1
☐	GOTERM_BP_FAT	regulation of nucleotide metabolic process	RT		3	4,4	3,6E-2	7,8E-1
☐	GOTERM_MF_FAT	sequence-specific DNA binding	RT		6	8,8	3,9E-2	1,0E0
☐	GOTERM_BP_FAT	adaptive immune response	RT		3	4,4	4,4E-2	8,2E-1
☐	GOTERM_BP_FAT	adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	RT		3	4,4	4,4E-2	8,2E-1
☐	GOTERM_MF_FAT	transcription factor activity	RT		7	10,3	4,5E-2	9,7E-1
☐	KEGG_PATHWAY	Melanogenesis	RT		3	4,4	5,1E-2	8,0E-1
☐	GOTERM_BP_FAT	death	RT		6	8,8	5,4E-2	8,7E-1
☐	GOTERM_MF_FAT	calmodulin binding	RT		3	4,4	5,7E-2	9,4E-1


Cell signaling
14 (13.2 %)
Mitochondrion
12 (11.3 %)
Nucleotide (ATP) binding
13 (12.2%)
Lipoprotein
9 (8.4 %)
106 Early Expressed Genes
DNA binding
20 (18.8 %)
Non-membrane Bounded organelle
13 (12.2 %)
Membrane
35 (33 %)
Metal ion binding
27 (25.4 %)

DIABETES - INSULIN - GLUCAGON - GASTROINTESTINAL

Disruption of G Protein-Coupled Receptor 39 Impairs Insulin Secretion *in Vivo*

Frédéric Tremblay, Ann-Marie T. Richard, Sarah Will, Jameel Syed, Nancy Stedman, Mylène Perreault and Ruth E. Gimeno

Author Affiliations

Department of Metabolic Diseases (F.T., A.-M.T.R., S.W., M.P., R.E.G.), Wyeth Research, Cambridge, Massachusetts 02140; and Department of Exploratory Drug Safety (J.S., N.S.), Wyeth Research, Andover, Massachusetts 01810

Address all correspondence and requests for reprints to: Ruth E. Gimeno, Cardiovascular and Metabolic Diseases, Wyeth Research, 200 Cambridge Park Drive, Cambridge, Massachusetts 02140. E-mail: rgimeno@wyeth.com.

Abstract

GPR39 is a G protein-coupled receptor expressed in liver, gastrointestinal tract, adipose tissue, and pancreas. We have recently shown that young GPR39$^{-/-}$ mice have normal body weight, food intake, and fasting glucose and insulin levels. In this study, we examined the role of GPR39 in aging and diet-induced obese mice. Body weight and food intake were similar in wild-type and GPR39$^{-/-}$ mice as they aged from 12 to 52 wk or when fed a low-fat/high-sucrose or high-fat/high-sucrose diet. Fifty-two-week-old GPR39$^{-/-}$ mice showed a trend toward decreased insulin levels after oral glucose challenge. When fed either a low-fat/high-sucrose or high-fat/high-sucrose diet, GPR39$^{-/-}$ mice had increased fed glucose levels and showed decreased serum insulin levels during an oral glucose tolerance test in the face of unchanged insulin tolerance. Pancreas morphology and glucose-stimulated insulin secretion in isolated islets from wild-type and GPR39$^{-/-}$ mice were comparable, suggesting that GPR39 is not required for pancreas development or *ex vivo* insulin secretion. Small interfering RNA-mediated knockdown of GPR39 in clonal NIT-1 β-cells revealed that GPR39 regulates the expression of insulin receptor substrate-2 and pancreatic and duodenal homeobox-1 in a cell-autonomous manner; insulin receptor substrate-2 mRNA was also significantly decreased in the pancreas of GPR39$^{-/-}$ mice. Taken together, our data indicate that GPR39 is required for the increased insulin secretion *in vivo* under conditions of increased demand, *i.e.* on development of age-dependent and diet-induced insulin resistance. Thus, GPR39 agonists may have potential for the treatment of type 2 diabetes.

Received August 25, 2008.
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Obestatin acts in brain to inhibit thirst

Willis K. Samson,[1] Meghan M. White,[1] Christopher Price,[2] and Alastair V. Ferguson[2]
[1]*Department of Pharmacological and Physiological Science, Saint Louis University, St. Louis, Missouri; and* [2]*Department of Physiology, Queen's University, Kingston, Ontario, Canada*

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Samson WK, White MM, Price C, Ferguson AV. Obestatin acts in brain to inhibit thirst. *Am J Physiol Regul Integr Comp Physiol* 292: R637–R643, 2007. First published August 24, 2006; doi:10.1152/ajpregu.00395.2006.—Derived from the same prohormone, obestatin has been reported to exert effects on food intake that oppose those of ghrelin. The obestatin receptor GPR39 is present in brain and pituitary gland. Since the gene encoding those two peptides is expressed also in those tissues, we examined further the possible actions of obestatin in vivo and in vitro. Intracerebroventricular administration of obestatin inhibited water drinking in ad libitum-fed and -watered rats, and in food-and water-deprived animals. The effects on water drinking preceded and were more pronounced than any effect on food intake, and did not appear to be the result of altered locomotor/behavioral activity. In addition, obestatin inhibited ANG II-induced water drinking in animals provided free access to water and food. Current-clamp recordings from cultured, subfornical organ neurons revealed significant effects of the peptide on membrane potential, suggesting this as a potential site of action. In pituitary cell cultures, log molar concentrations of obestatin ranging from 1.0 pM to 100 nM failed to alter basal growth hormone (GH) secretion. In addition, 100 nM obestatin failed to interfere with the stimulation of GH secretion by GH-releasing hormone or ghrelin and did not alter the inhibition by somatostatin in vitro. We conclude that obestatin does not act in pituitary gland to regulate GH secretion but may act in brain to alter thirst mechanisms. Importantly, in rats the effects of obestatin on food intake may be secondary to an action of the peptide to inhibit water drinking.

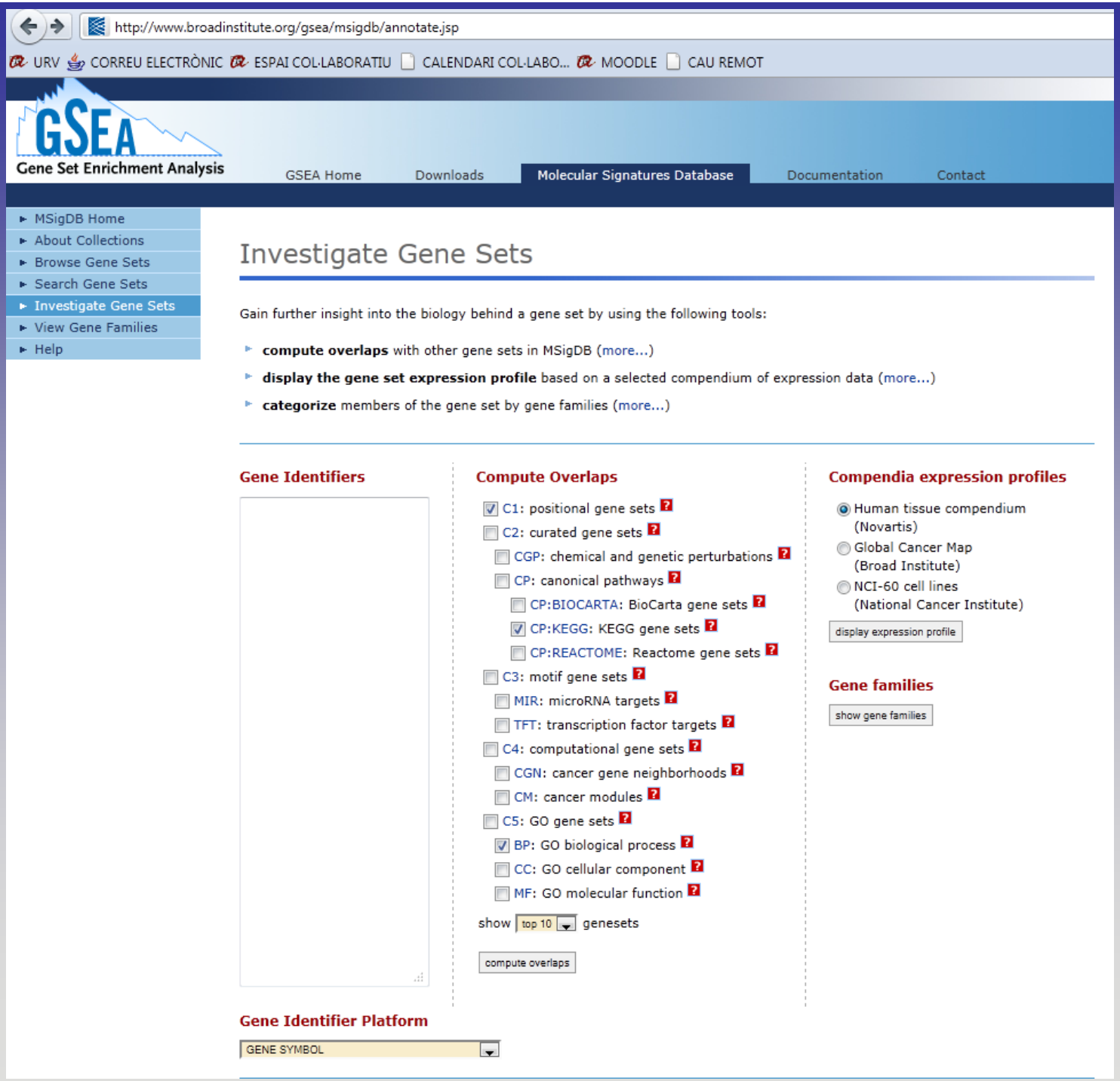
ghrelin; appetite; growth hormone

secretion, although ghrelin, as expected, significantly elevated GH release in their cell cultures (14). We hypothesized that obestatin's action may not, in fact, be on basal, but instead be on releasing-factor stimulated or somatostatin-inhibited GH release in vitro, and we tested a wide range of concentrations of obestatin in rat anterior pituitary cell cultures for these potential actions. To verify the biologic activity of obestatin in rats, as had been described in mice (14), we examined the effects of centrally administered peptide on food intake and water drinking in fed and fasted male rats.

MATERIALS AND METHODS

Animals. All procedures have been approved by the Animal Care Committee of Saint Louis University or Queen's University. Adult male rats (Harlan Sprague Dawley, Indianapolis, IN or Charles River, Quebec, Canada) were employed as tissue donors and for in vivo protocols. They were maintained (12:12-h light-dark cycle, lights on 0600, 23–25°C) with free access to food and water, unless otherwise indicated.

In vitro studies. Dispersed anterior pituitary cell cultures. Rats (250–300 g) were killed by decapitation (9). Anterior pituitary glands were collected into minimum essential medium containing HEPES (20 mM), 1% penicillin-streptomycin (all obtained from Invitrogen, Carlsbad, CA), 0.1% BSA (Sigma, St. Louis, MO), and 0.1% trypsin (1:250, Difco, Detroit, MI) and mechanically dispersed until a single-cell suspension was obtained (37°C). Single-cell suspensions were aliquoted into 12 × 75-mm test tubes (~200,000 cells/tube) and incubated for 72 h at 37°C (room air) in Medium 199 (Sigma) containing 20 mM HEPES and 10% horse serum and 1% penicillin-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Browse Gene Sets
Search Gene Sets
Investigate Gene Sets
View Gene Families
Help
Investigate Gene Sets
Gain further insight into the biology behind a gene set by using the following tools:
compute overlaps with other gene sets in MSigDB (more...)
display the gene set expression profile based on a selected compendium of expression data (more...)
categorize members of the gene set by gene families (more...)
Gene Identifiers
Compute Overlaps
C1: positional gene sets
C2: curated gene sets
CGP: chemical and genetic perturbations
CP: canonical pathways
CP:BIOCARTA: BioCarta gene sets
CP:KEGG: KEGG gene sets
CP:REACTOME: Reactome gene sets
C3: motif gene sets
MIR: microRNA targets
TFT: transcription factor targets
C4: computational gene sets
CGN: cancer gene neighborhoods
CM: cancer modules
C5: GO gene sets
BP: GO biological process
CC: GO cellular component
MF: GO molecular function
show top 10 genesets
compute overlaps
Compendia expression profiles
Human tissue compendium (Novartis)
Global Cancer Map (Broad Institute)
NCI-60 cell lines (National Cancer Institute)
display expression profile
Gene families
show gene families
Gene Identifier Platform
GENE SYMBOL

Expressed at 3m

original id	gene symbol	description
APOL9B	no mapping	
C4BP	no mapping	
CBY3	no mapping	
CX3CL1	CX3CL1	chemokine (C-X3-C motif) ligand 1
CYTH1	no mapping	
DEFCR14	no mapping	
FBP	FBP	emopamil binding protein (sterol isomerase)
EGLYC	no mapping	
ERCC2	ERCC2	excision repair cross-complementing rodent repair deficiency, complementation group 2 (xeroderma pigmentosum D)
FAM53C	FAM53C	family with sequence similarity 53, member C
GM1419	no mapping	
HK1	HK1	hexokinase 1
HK2	HK2	hexokinase 2
HP1BP3	HP1BP3	heterochromatin protein 1, binding protein 3
KIF11	KIF11	kinesin family member 11
NTS	NTS	neurotensin
ULK4	no mapping	
PARK2	PARK2	Parkinson disease (autosomal recessive, juvenile) 2, parkin
PCDHB15	PCDHB15	protocadherin beta 15
PNMAL1	no mapping	
PRNP	PRNP	prion protein (p27-30) (Creutzfeldt-Jakob disease, Gerstmann-Strausler-Scheinker syndrome, fatal familial insomnia)
RBMX	RBMX	RNA binding motif protein, X-linked
RNF113A2	no mapping	
RPUSD4	RPUSD4	RNA pseudouridylate synthase domain containing 4
SNORD23	SNORD23	small nucleolar RNA, C/D box 23
TET1	no mapping	
TMEM63A	TMEM63A	transmembrane protein 63A
TMTM01	TMTM01	transmembrane protein 01
UBE2I	UBE2I	ubiquitin-conjugating enzyme E2I (UBC9 homolog, yeast)
UCP2	UCP2	uncoupling protein 2 (mitochondrial, proton carrier)
V1RD10	no mapping	
VMN2R88	no mapping	
WFS1	WFS1	Wolfram syndrome 1 (wolframin)
ZCCHC24	no mapping	

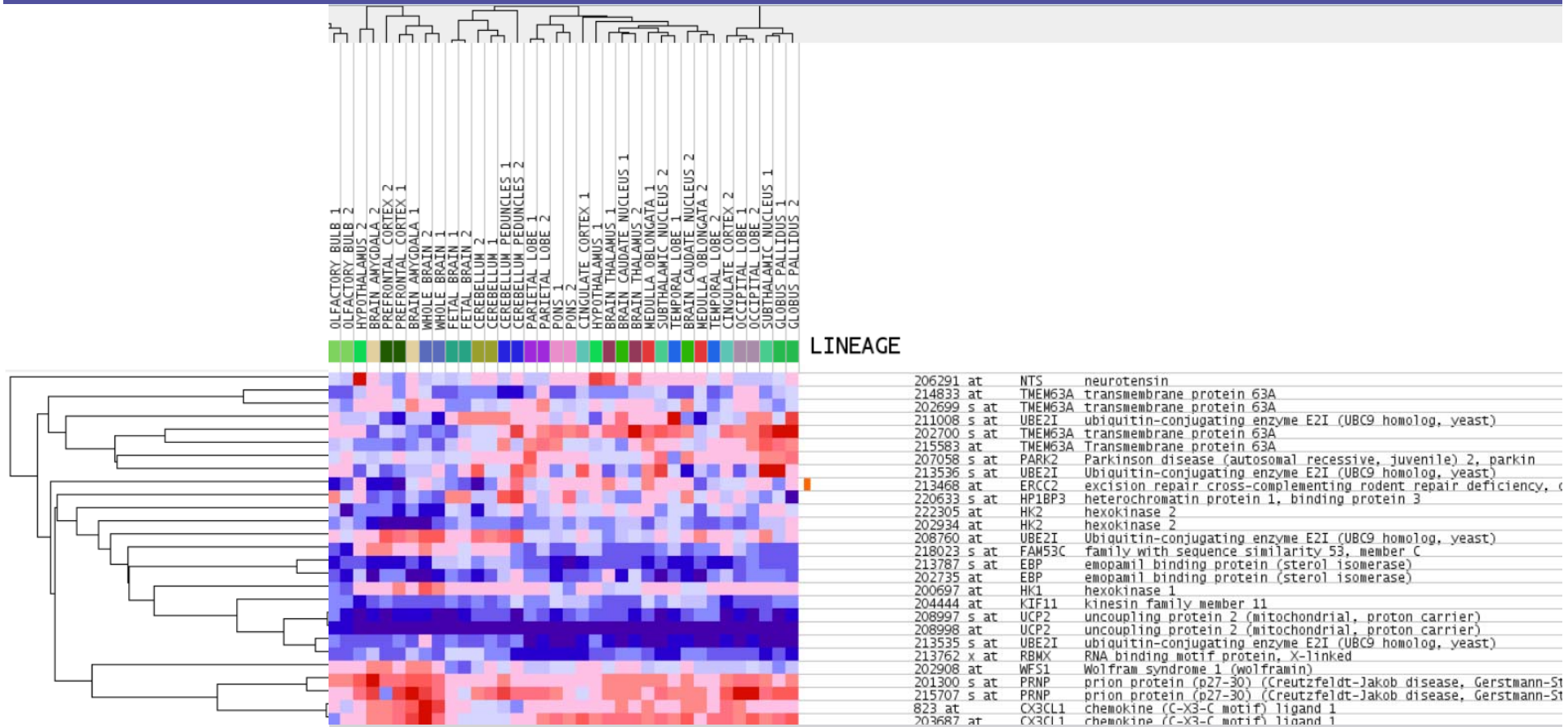
Gene Set Name [# Genes (K)]	Description	# Genes in Overlap (k)	k/K	p value
MACROMOLECULE_CATABOLIC_PROCESS [135]	Genes annotated by the GO term GO:0009057. The chemical reactions and pathways resulting in the breakdown of a macromolecule, any large molecule including proteins, nucleic acids and carbohydrates.	4		3.59 e^{-5}
CELLULAR_CATABOLIC_PROCESS [209]	Genes annotated by the GO term GO:0044248. The chemical reactions and pathways resulting in the breakdown of substances, carried out by individual cells.	4		2.02 e^{-5}
CATABOLIC_PROCESS [221]	Genes annotated by the GO term GO:0009056. The chemical reactions and pathways resulting in the breakdown of substances, including the breakdown of carbon compounds with the liberation of energy for use by the cell or organism.	4		2.51 e^{-5}
CELLULAR_MACROMOLECULE_CATABOLIC_PROCESS [103]	Genes annotated by the GO term GO:0044265. The chemical reactions and pathways resulting in the breakdown of a macromolecule, any large molecule including proteins, nucleic acids and carbohydrates, as carried out by individual cells.	3		7.21 e^{-5}
BIOPOLYMER_CATABOLIC_PROCESS [115]	Genes annotated by the GO term GO:0043285. The chemical reactions and pathways resulting in the breakdown of biopolymers, long, repeating chains of monomers found in nature e.g. polysaccharides and proteins.	3		1 e^{-4}
KEGG_GALACTOSE_METABOLISM [26]	Galactose metabolism	2		1.93 e^{-4}
KEGG_FRUCTOSE_AND_MANNOSE_METABOLISM [34]	Fructose and mannose metabolism	2		3.31 e^{-4}
SYSTEM_DEVELOPMENT [855]	Genes annotated by the GO term GO:0048731. The process whose specific outcome is the progression of an organismal system over time, from its formation to the mature structure. A system is a regularly interacting or interdependent group of organs or tissues that work together to carry out a given biological process.	5		4.53 e^{-4}
KEGG_AMINO_SUGAR_AND_NUCLEOTIDE_SUGAR_METABOLISM [44]	Amino sugar and nucleotide sugar metabolism	2		5.56 e^{-4}
RESPONSE_TO_OXIDATIVE_STRESS [45]	Genes annotated by the GO term GO:0006979. A change in state or	2		5.82 e^{-4}

Expressed at 3m

Gene/geneset overlap matrix

overlap matrix by gene and geneset	MACROMOLECULE_CATABOLIC_PROCESS	CELLULAR_CATABOLIC_PROCESS	CATABOLIC_PROCESS	CELLULAR_MACROMOLECULE_CATABOLIC_PROCESS	BIOPOLYMER_CATABOLIC_PROCESS	KEGG_GALACTOSE_METABOLISM	KEGG_FRUCTOSE_AND_MANNOSE_METABOLISM	SYSTEM_DEVELOPMENT	KEGG_AMINO_SUGAR_AND_NUCLEOTIDE_SUGAR_METABOLISM	RESPONSE_TO_OXIDATIVE_STRESS	Entrez	Source	description
PARK2	■	■	■	■	■			■				S	Parkinson disease (autosomal recessive, juvenile) 2, parkin
UBE2I	■	■	■	■	■							S	ubiquitin-conjugating enzyme E2I (UBC9 homolog, yeast)
HK1	■	■	■	■		■	■		■			S	hexokinase 1
ERCC2	■	■	■		■			■		■		S	excision repair cross-complementing rodent repair deficiency, complementation group 2 (xeroderma
HK2						■	■		■			S	hexokinase 2
PCDHB15								■				S	protocadherin beta 15
WFS1								■				S	Wolfram syndrome 1 (wolframin)
EBP								■				S	emopamil binding protein (sterol isomerase)
PRNP										■		S	prion protein (p27-30) (Creutzfeldt-Jakob disease, Gerstmann-Strausler-Scheinker syndrome, fatal f
CX3CL1												S	chemokine (C-X3-C motif) ligand 1
FAM53C												S	family with sequence similarity 53, member C
KIF11												S	kinesin family member 11
SNORD23												S	small nucleolar RNA, C/D box 23
UCP2												S	uncoupling protein 2 (mitochondrial, proton carrier)
HP1BP3												S	heterochromatin protein 1, binding protein 3
TMEM81												S	transmembrane protein 81
RBMX												S	RNA binding motif protein, X-linked
TMEM63A												S	transmembrane protein 63A
RPUSD4												S	RNA pseudouridylate synthase domain containing 4
NTS												S	neurotensin

Expressed at 3m



Expressed at 6m

Converted 19 submitted identifiers into 17 gene symbols. click here for details.

Conversion Details

Converted from "GENE_SYMBOL" to "GENE_SYMBOL"

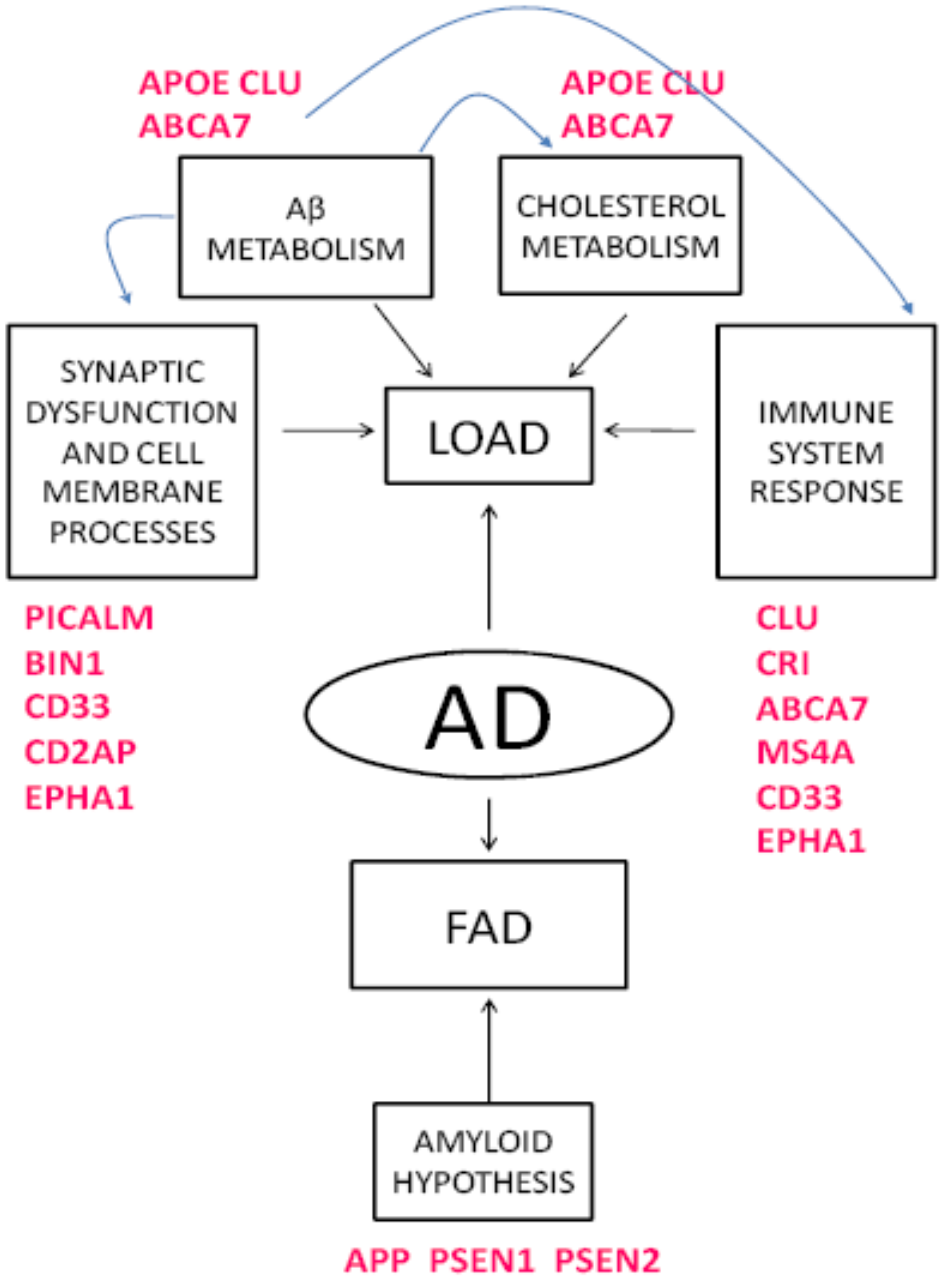
original id	gene symbol	description
AFP	AFP	alpha-fetoprotein
APP	APP	amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer disease)
CCDC105	CCDC105	coiled-coil domain containing 105
CHRNA6	CHRNA6	cholinergic receptor, nicotinic, alpha 6
CNOT10	CNOT10	CCR4-NOT transcription complex, subunit 10
DMRTC1C1	no mapping	
IL2RA	IL2RA	interleukin 2 receptor, alpha
MCART6	MCART6	mitochondrial carrier triple repeat 6
NGB	NGB	neuroglobin
POU2F1	POU2F1	POU domain, class 2, transcription factor 1
PRNP	*PRNP*	prion protein (p27-30) (Creutzfeldt-Jakob disease, Gerstmann-Strausler-Scheinker syndrome, fatal familial insomnia)
PTK2	PTK2	PTK2 protein tyrosine kinase 2
RPUSD1	RPUSD1	RNA pseudouridylate synthase domain containing 1
SMAD4	SMAD4	SMAD, mothers against DPP homolog 4 (Drosophila)
SOD1	*SOD1*	superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))
SSSCA1	SSSCA1	Sjogren's syndrome/scleroderma autoantigen 1
SUMO2	SUMO2	SMT3 suppressor of mif two 3 homolog 2 (S. cerevisiae)
USMG5	USMG5	upregulated during skeletal muscle growth 5 homolog (mouse)
ZFP84	no mapping	

Gene Set Name [# Genes (K)]	Description	In Overlap (k)	k/K	p value
REGULATION_OF_CYTOKINE_PRODUCTION [25]	Genes annotated by the GO term GO:0001817. Any process that modulates the frequency, rate, or extent of production of a cytokine.	2		1.28 e^{-4}
KEGG_PRION_DISEASES [35]	Prion diseases	2		2.52 e^{-4}
RESPONSE_TO_OXIDATIVE_STRESS [45]	Genes annotated by the GO term GO:0006979. A change in state or activity of a cell or an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of oxidative stress, a state often resulting from exposure to high levels of reactive oxygen species, e.g. superoxide anions, hydrogen peroxide (H2O2), and hydroxyl radicals.	2		4.18 e^{-4}
REGULATION_OF_GROWTH [54]	Genes annotated by the GO term GO:0040008. Any process that modulates the frequency, rate or extent of the growth of all or part of an organism so that it occurs at its proper speed, either globally or in a specific part of the organism's development.	2		6.02 e^{-4}
NEGATIVE_REGULATION_OF_CELLULAR_METABOLIC_PROCESS [252]	Genes annotated by the GO term GO:0031324. Any process that stops, prevents or reduces the frequency, rate or extent of the chemical reactions and pathways by which individual cells transform chemical substances.	3		6.08 e^{-4}
NEGATIVE_REGULATION_OF_METABOLIC_PROCESS [255]	Genes annotated by the GO term GO:0009892. Any process that stops, prevents or reduces the frequency, rate or extent of the chemical reactions and pathways within a cell or an organism.	3		6.29 e^{-4}
GROWTH [71]	Genes annotated by the GO term GO:0040007. The increase in size or mass of an entire organism, a part of an organism or a cell.	2		1.04 e^{-3}
CYTOKINE_PRODUCTION [72]	Genes annotated by the GO term GO:0001816. The appearance of a cytokine due to biosynthesis or secretion following a cellular stimulus, resulting in an increase in its intracellular or extracellular levels.	2		1.07 e^{-3}
CELLULAR_CATION_HOMEOSTASIS [101]	Genes annotated by the GO term GO:0030003. The regulation of the levels, transport, and metabolism of cations within a cell or between a cell and its external environment.	2		2.09 e^{-3}
CATION_HOMEOSTASIS [104]	Genes annotated by the GO term GO:0055080. The regulation of the levels,	2		2.21 e^{-3}

Expressed at 6m

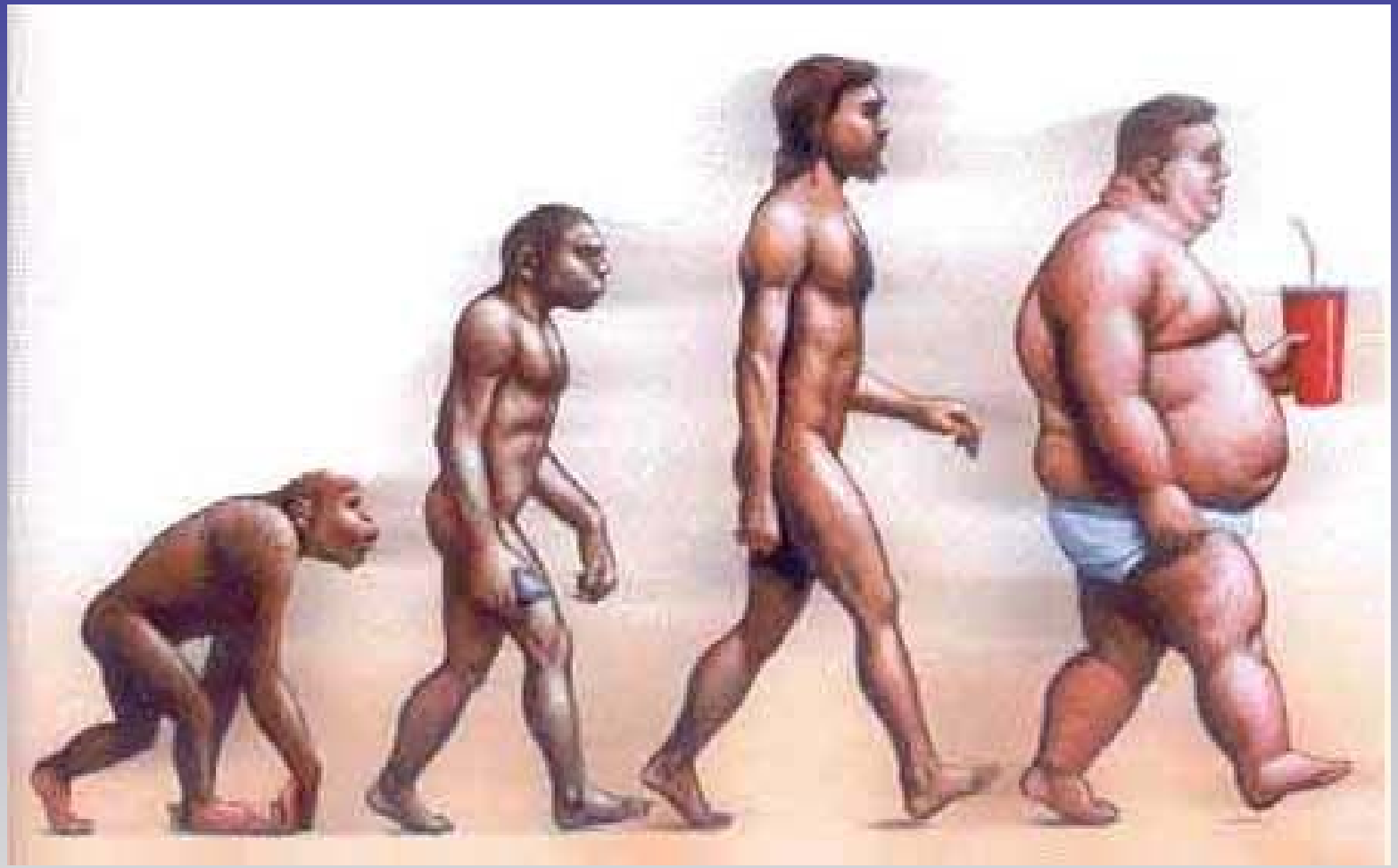
Gene/geneset overlap matrix

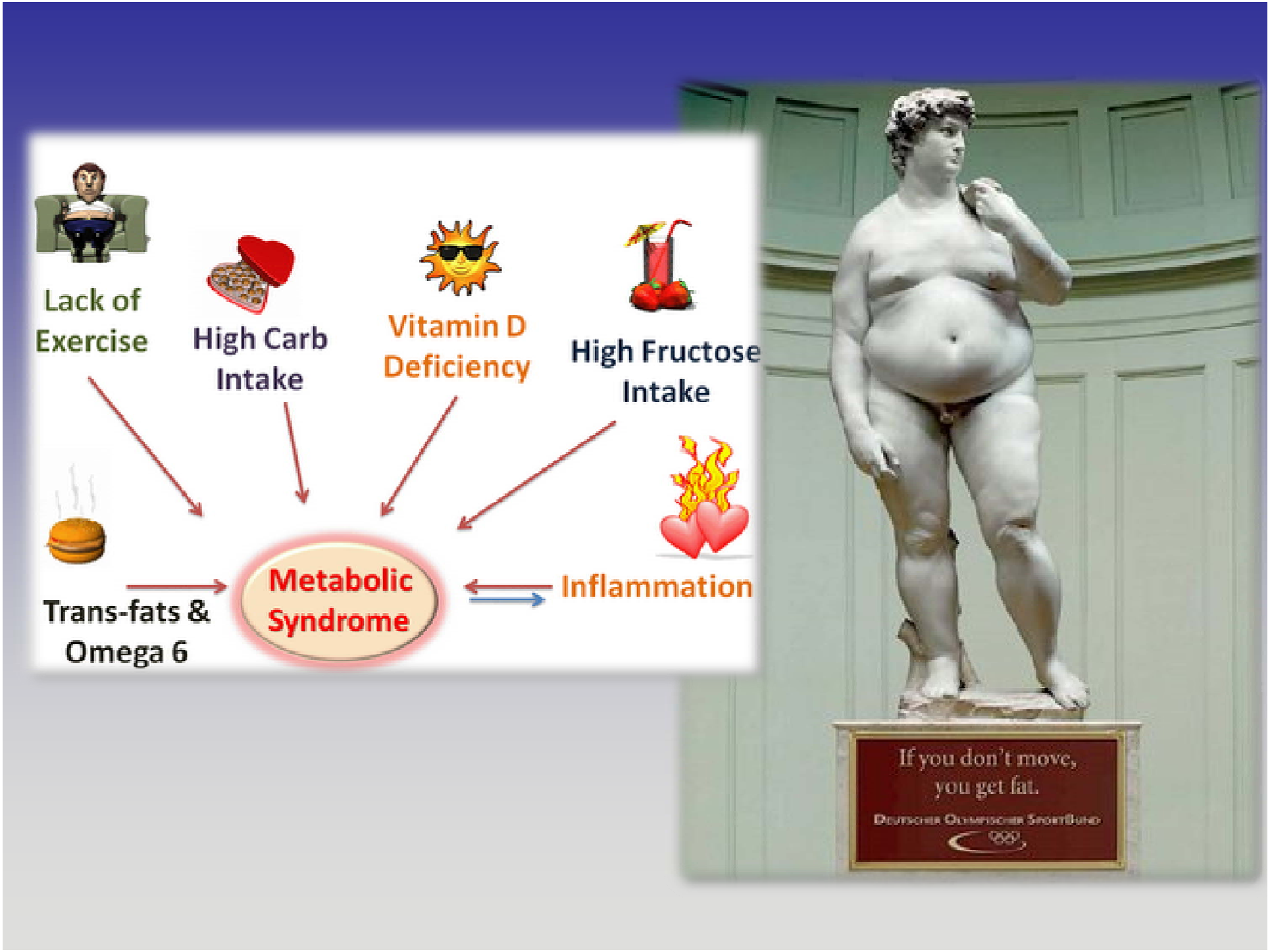
overlap matrix by gene and geneset	REGULATION_OF_CYTOKINE_PRODUCTION	KEGG_PRION_DISEASES	RESPONSE_TO_OXIDATIVE_STRESS	REGULATION_OF_GROWTH	NEGATIVE_REGULATION_OF_CELLULAR_METABOLIC_PROCESS	NEGATIVE_REGULATION_OF_METABOLIC_PROCESS	GROWTH	CYTOKINE_PRODUCTION	CELLULAR_CATION_HOMEOSTASIS	CATION_HOMEOSTASIS	Entrez	Source	description
SOD1	■	■	■	■	■	■	■	■	■	■		S	superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))
SMAD4	■			■	■	■	■	■				S	SMAD, mothers against DPP homolog 4 (Drosophila)
PRNP		■	■									S	prion protein (p27-30) (Creutzfeldt-Jakob disease, Gerstmann-Strausler-Scheinker
POU2F1					■	■						S	POU domain, class 2, transcription factor 1
APP									■	■		S	amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer disease)
CHRNA6												S	cholinergic receptor, nicotinic, alpha 6
IL2RA												S	interleukin 2 receptor, alpha
PTK2												S	PTK2 protein tyrosine kinase 2
CCDC105												S	coiled-coil domain containing 105
SSSCA1												S	Sjogren's syndrome/scleroderma autoantigen 1
RPUSD1												S	RNA pseudouridylate synthase domain containing 1
SUMO2												S	SMT3 suppressor of mif two 3 homolog 2 (S. cerevisiae)
NGB												S	neuroglobin
USMG5												S	upregulated during skeletal muscle growth 5 homolog (mouse)
MCART6												S	mitochondrial carrier triple repeat 6
CNOT10												S	CCR4-NOT transcription complex, subunit 10
AFP												S	alpha-fetoprotein

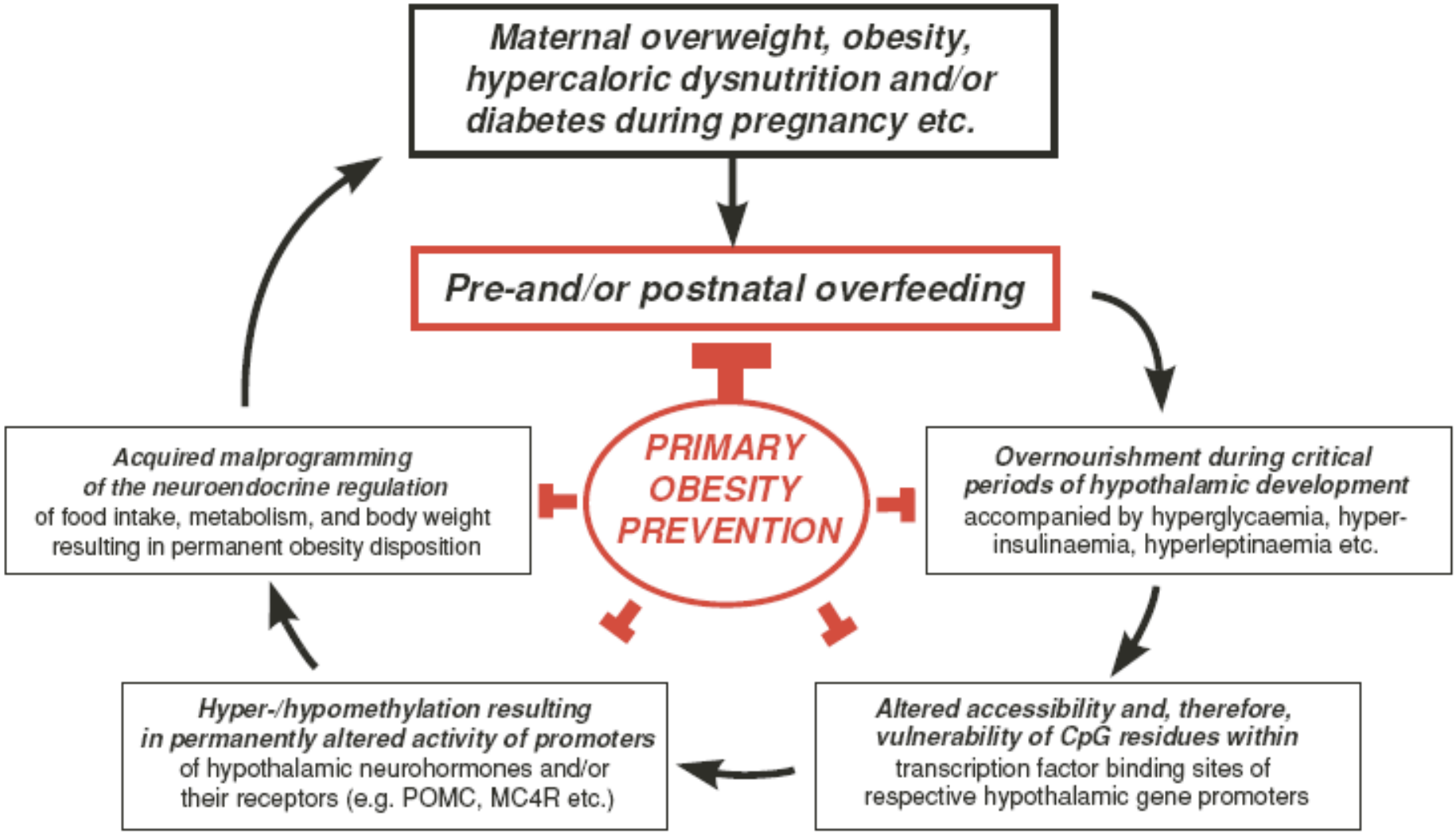


New genes and disease pathways in Alzheimer's disease implicated from recent genome-wide association studies (GWAS). Aβ may have a modulatory effect on these new pathways as indicated by the blue arrows.

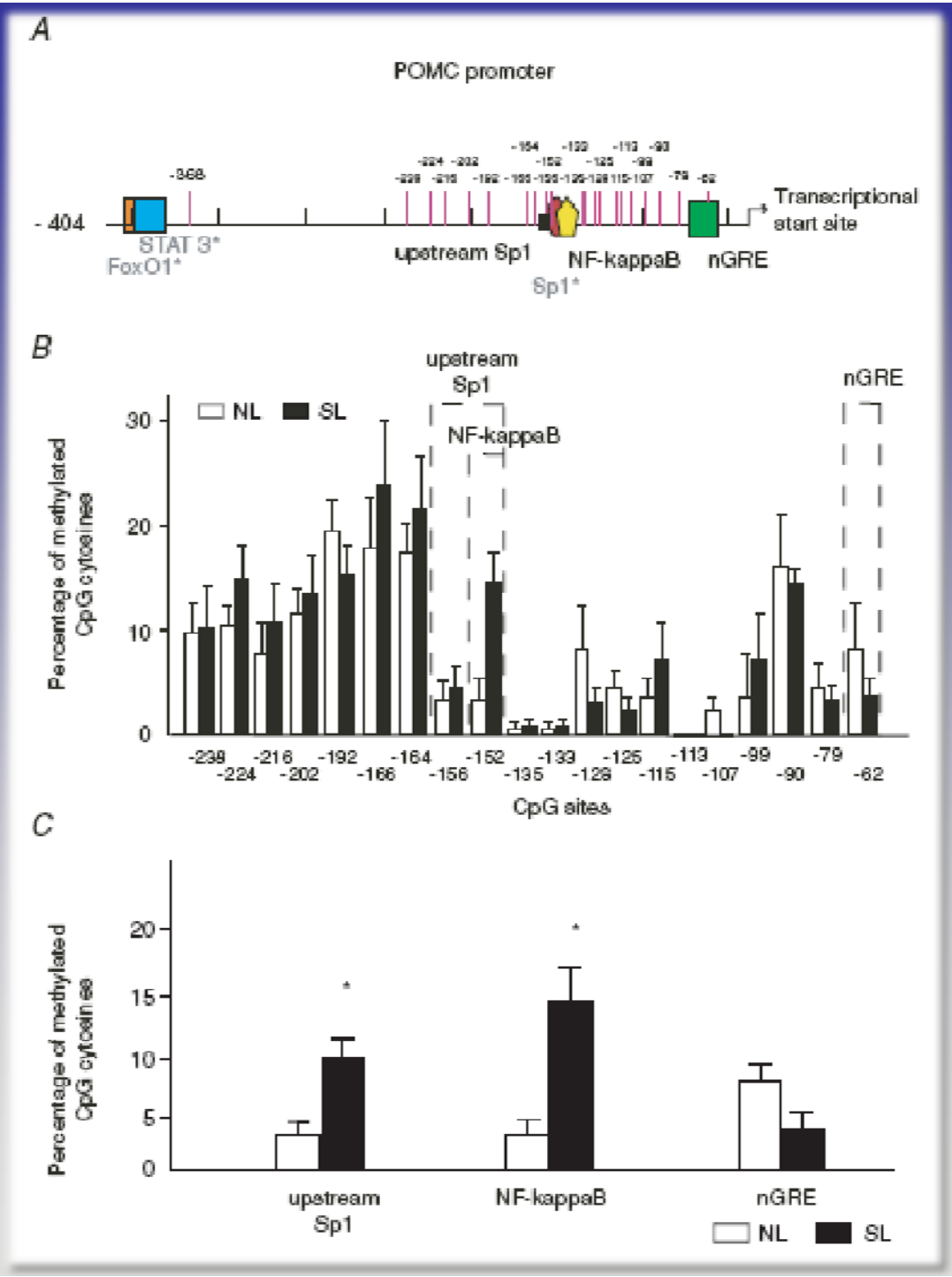
Kevin Morgan
The three new pathways leading to Alzheimer's disease.*
Neuropathology and Applied Neurobiology

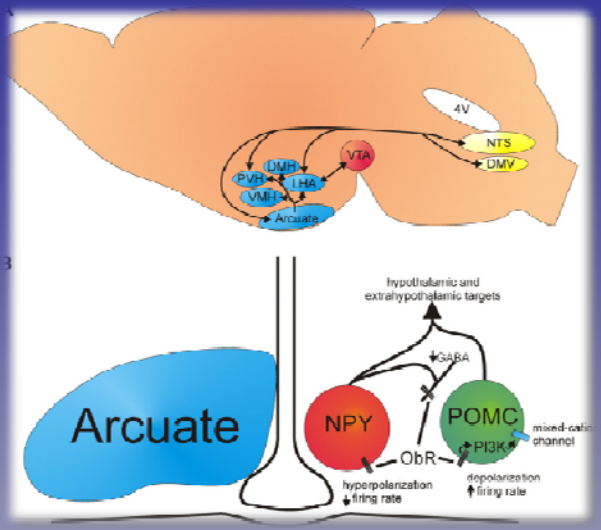



Lack of Exercise
High Carb Intake
Vitamin D Deficiency
High Fructose Intake
Trans-fats & Omega 6
Metabolic Syndrome
Inflammation
If you don't move, you get fat.
Deutscher Olympischer Sportbund



Andreas Plagemann et al., **Hypothalamic proopiomelanocortin promoter methylation becomes altered by early overfeeding: an epigenetic model of obesity and the metabolic syndrome.** *J Physiol* 587.20 (2009) pp 4963–4976





Andreas Plagemann et al., **Hypothalamic proopiomelanocortin promoter methylation becomes altered by early overfeeding: an epigenetic model of obesity and the metabolic syndrome.** *J Physiol* 587.20 (2009) pp 4963–4976

British Journal of Nutrition

British Journal of Nutrition, *FirstView* Article

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Published online: 04 May 2011

Protective effects of leptin during the suckling period against later obesity may be associated with changes in promoter methylation of the hypothalamic pro-opiomelanocortin gene

M. Palou[a1a2], Catalina Picó[a1a2 c1], J. A. McKay[a3], J. Sánchez[a1a2], T. Priego[a1a2], J. C. Mathers[a3] and A. Palou[a1a2]

Abstract

Leptin supplementation of neonatal rats during the suckling period protects against being overweight in adulthood and ameliorates the control of food intake. This was associated with changes in the expression of hypothalamic genes involved in the central action of leptin: pro-opiomelanocortin (*Pomc*), leptin receptor (*Lepr*) and suppressor of cytokine signalling (*Socs3*). The purpose of the present study was to determine the methylation status within the promoter regions of these genes and to assess whether the observed changes in the expression levels of these genes could be explained by changes in their methylation status. Male rats were treated daily with an oral physiological dose of leptin or vehicle during the suckling period. After weaning, animals were fed with a normal-fat or a high-fat (HF) diet until aged 6 months. DNA was extracted from the hypothalamus and methylation within the promoter regions of the gene panel was measured by pyrosequencing. *Pomc* promoter methylation increased in control animals fed the HF diet but decreased in leptin-treated animals. In addition, there was a weak negative correlation between DNA methylation and POMC mRNA levels ($P = 0{\cdot}075$). There were no changes in the methylation status of the CpG sites studied within the promoter regions of *Lepr* and *Socs3* in response to leptin or HF treatments. This is the first demonstration that leptin treatment during lactation may programme methylation of an appetite-related gene in the hypothalamus of animals fed HF diets, with possible implications for gene expression and protection against the development of obesity.

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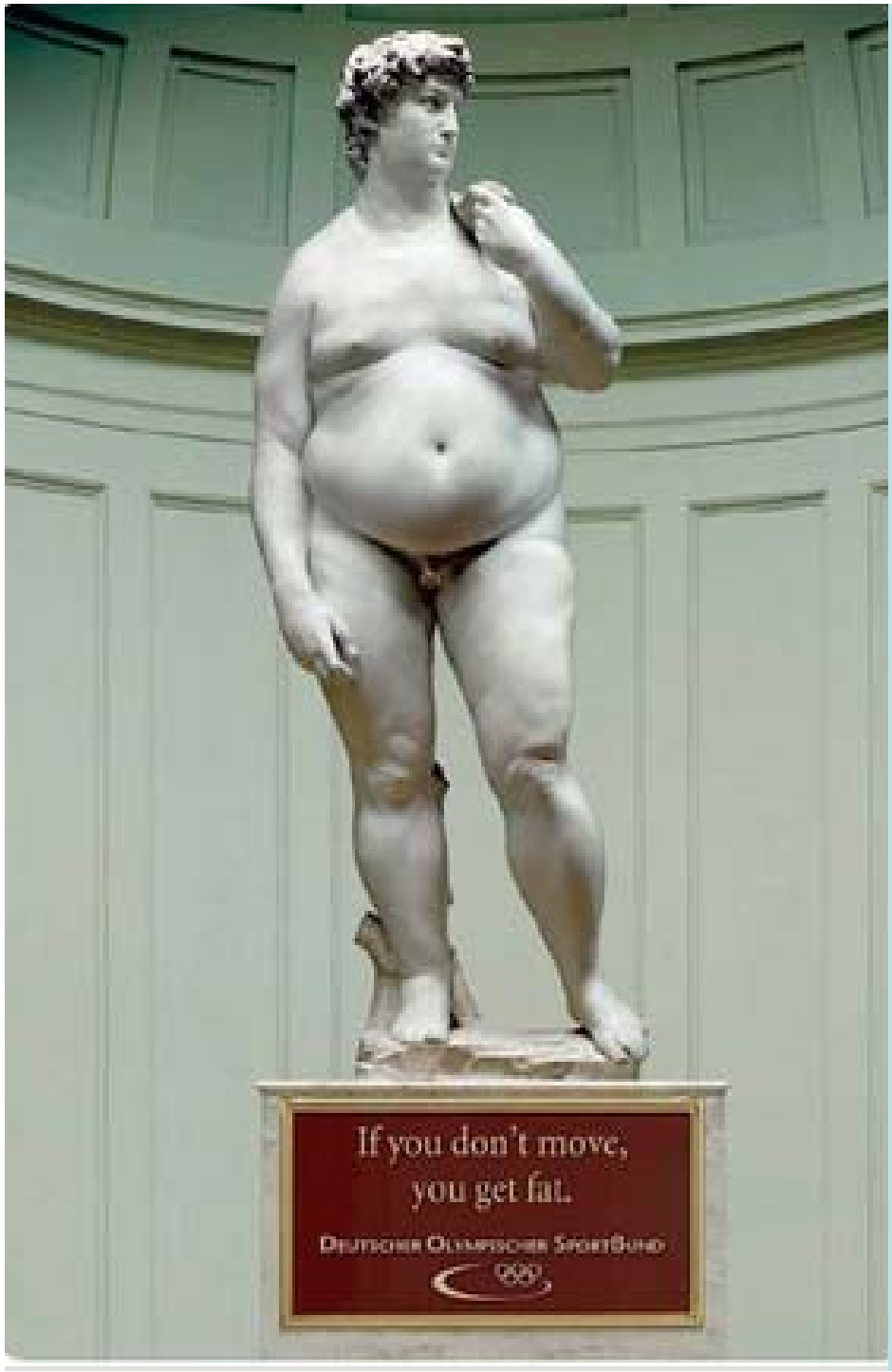
(Revised January 19 2011)
(Accepted February 02 2011)

Key Words:

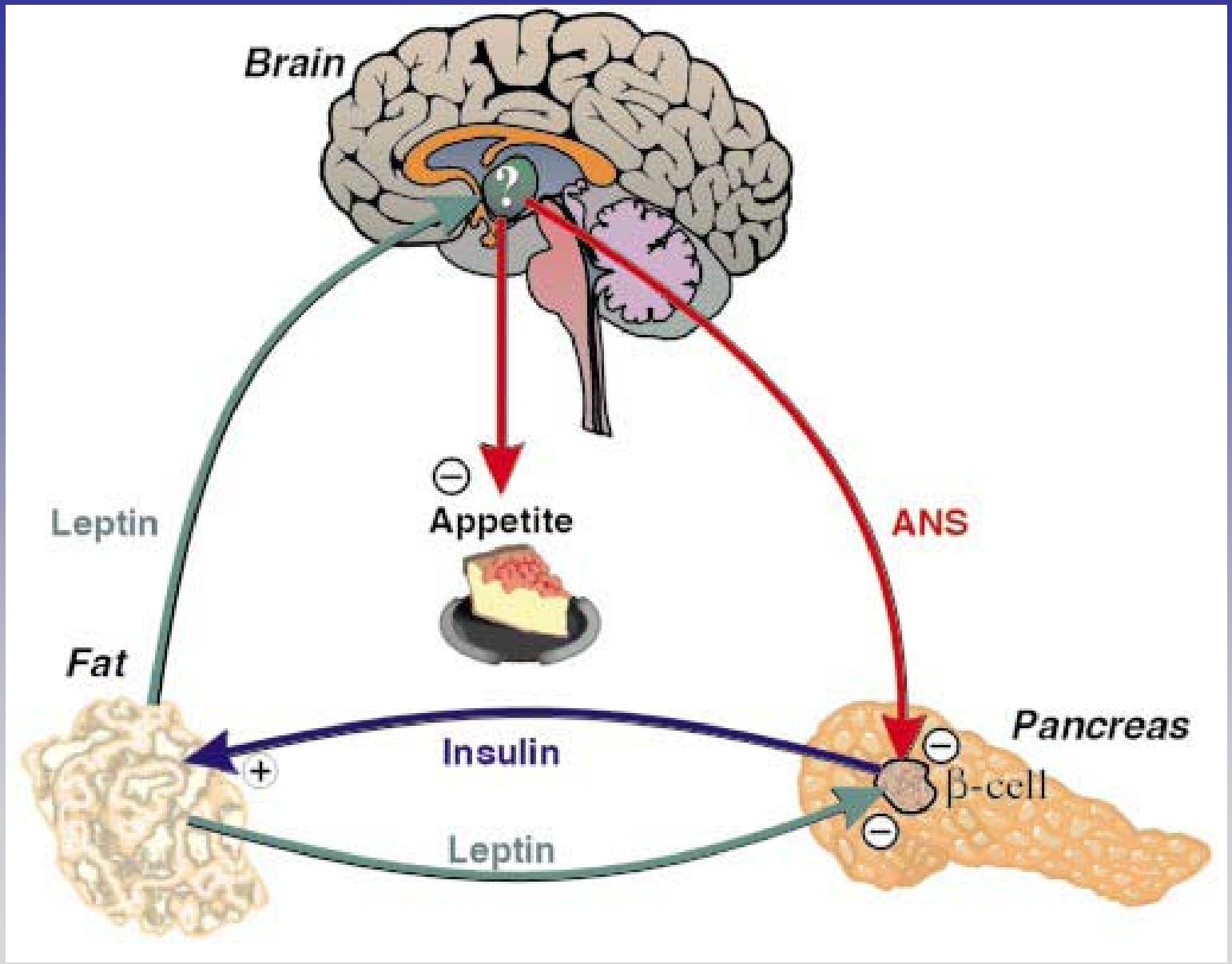


SÍNDROME METABÓLICO

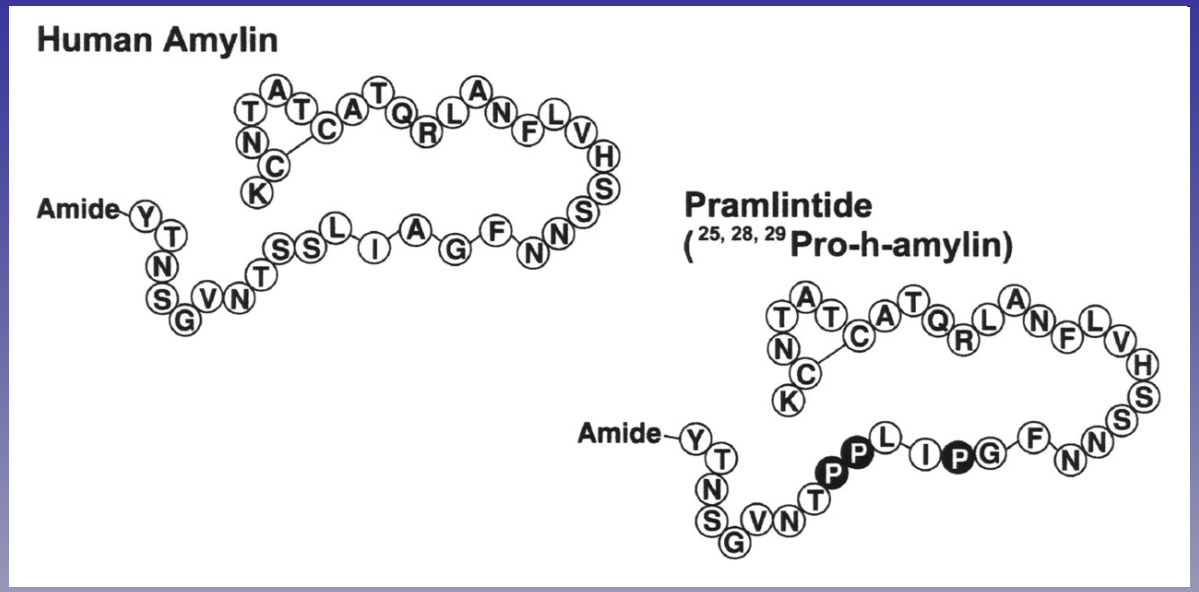
DIABETES II

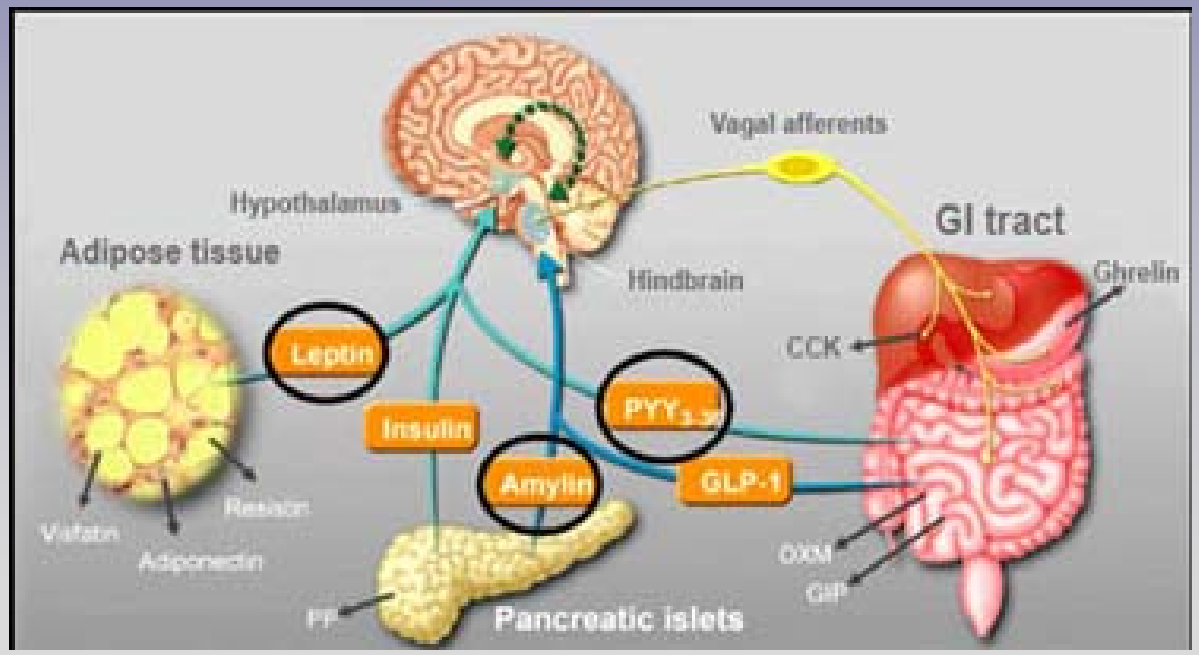
RESISTENCIA INSULINA
RESISTENCIA LEPTINA

NEURODEGENERACIÓN
ISQUEMIA

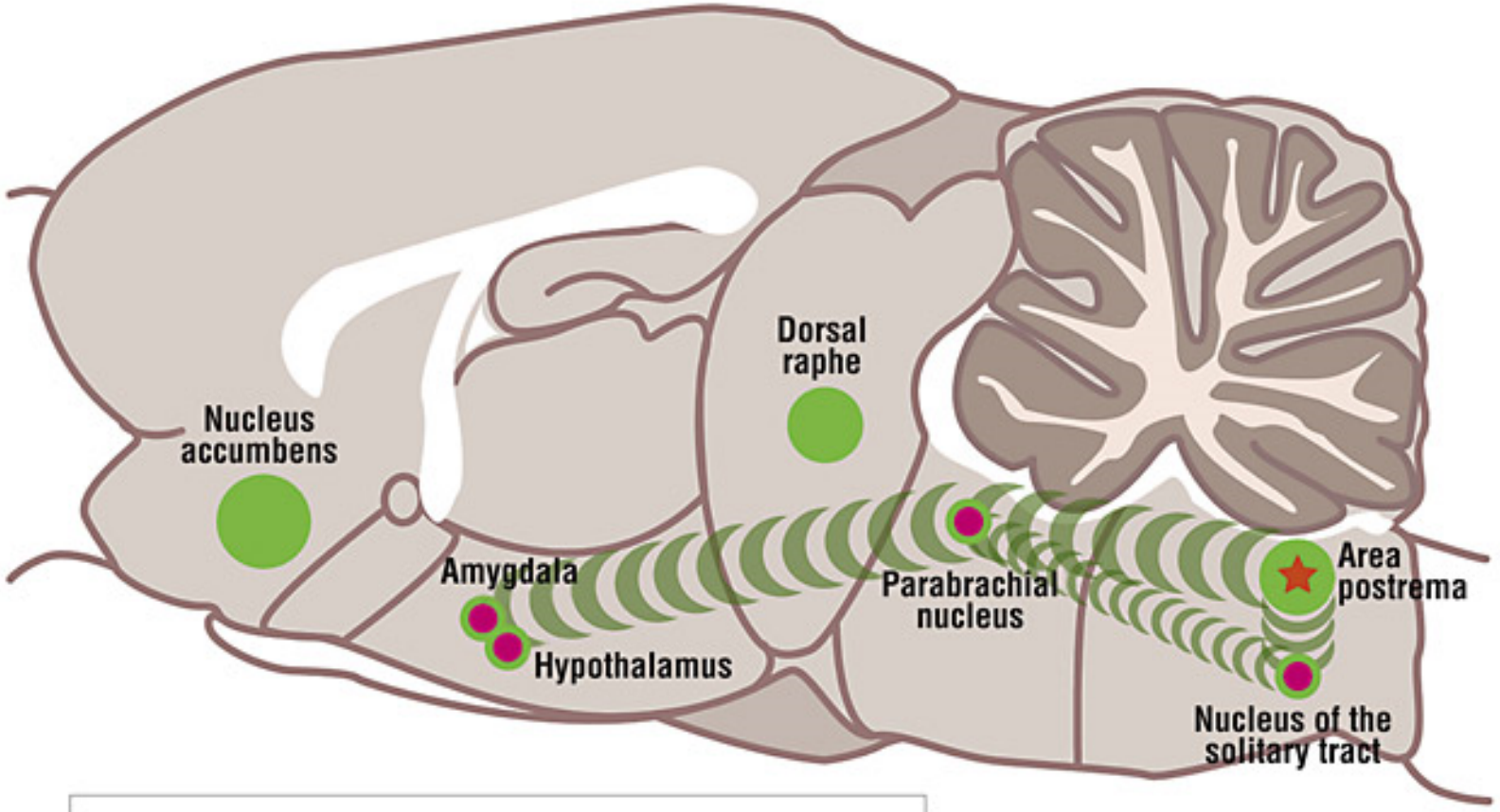


The adipoinsular axis.

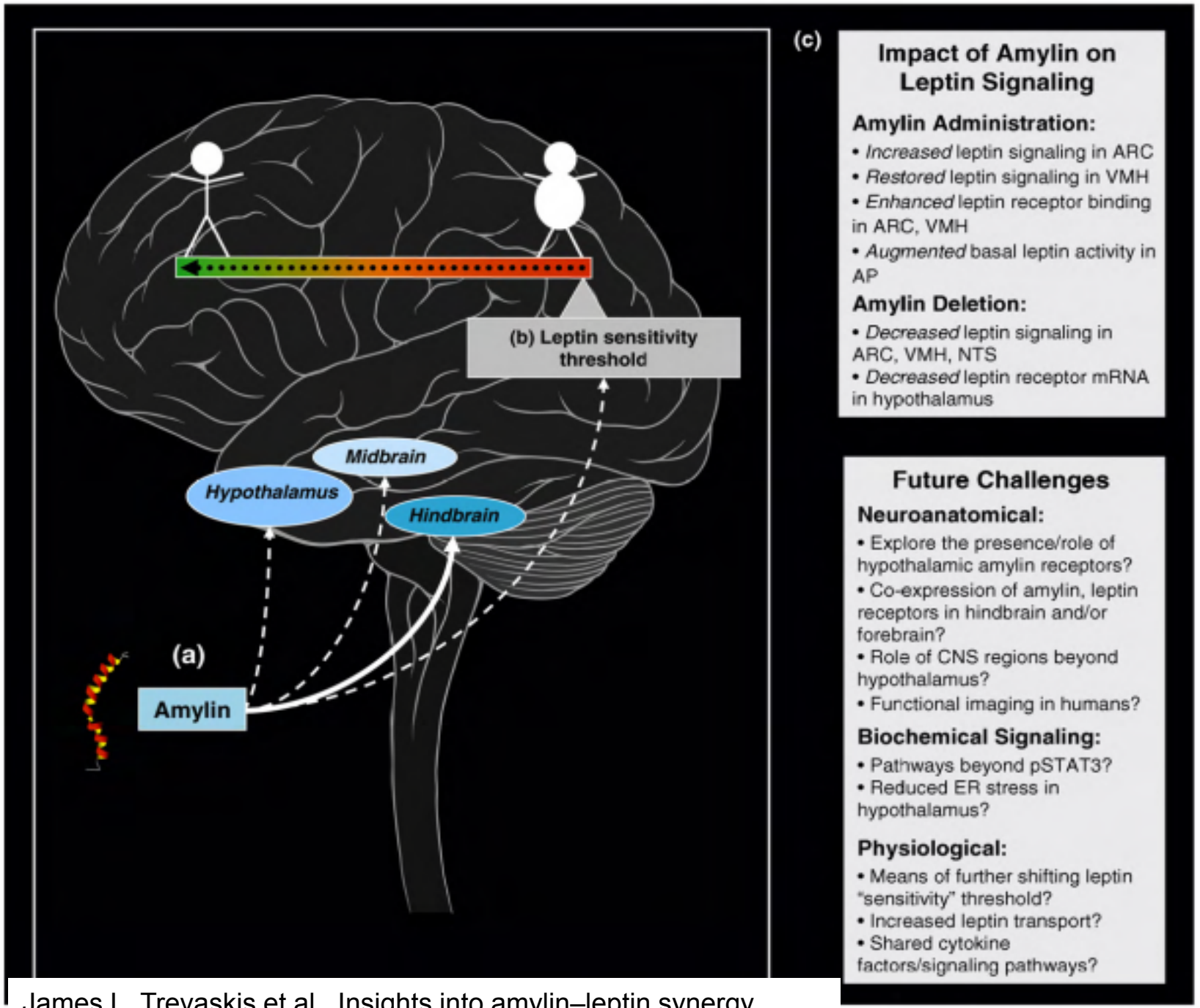




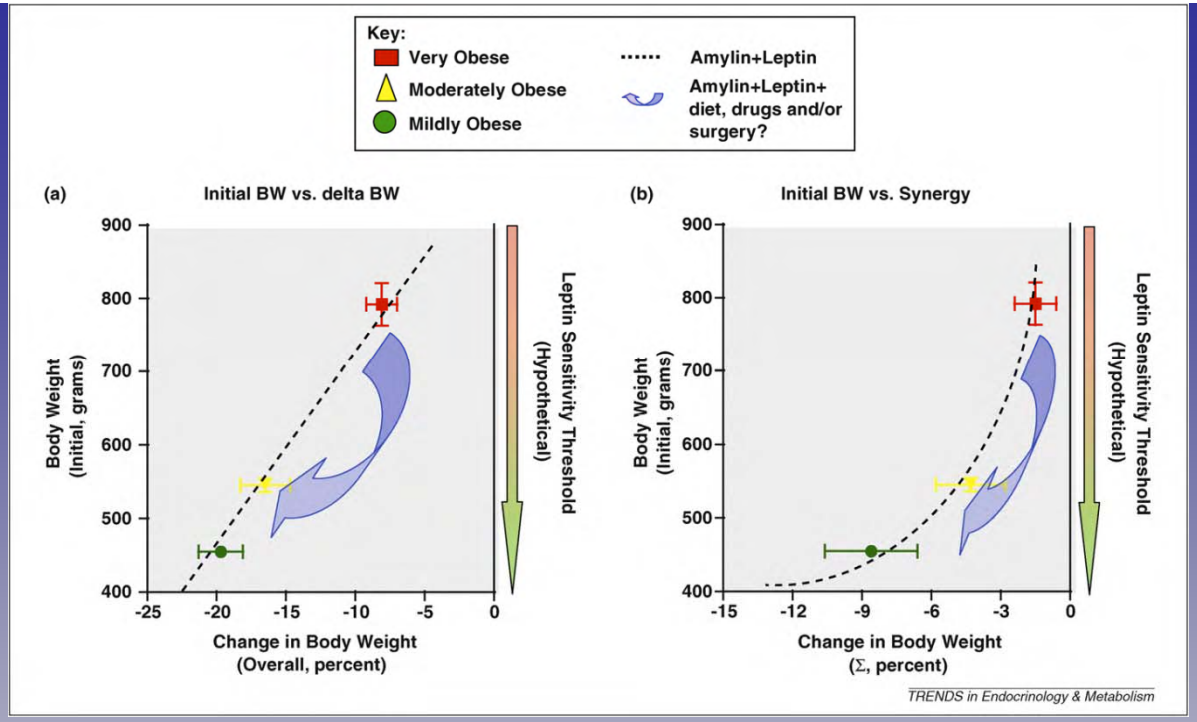
Trends in Endocrinology and Metabolism Vol.21 No.8



Jonathan D. Roth et al.,
Implications of Amylin Receptor Agonism Integrated Neurohormonal Mechanisms and Therapeutic Applications
Arch Neurol. 2009;66(3):306-310.



James L. Trevaskis et al., Insights into amylin–leptin synergy. 2010, in Endocrinology and Metabolism Vol.21 No.8



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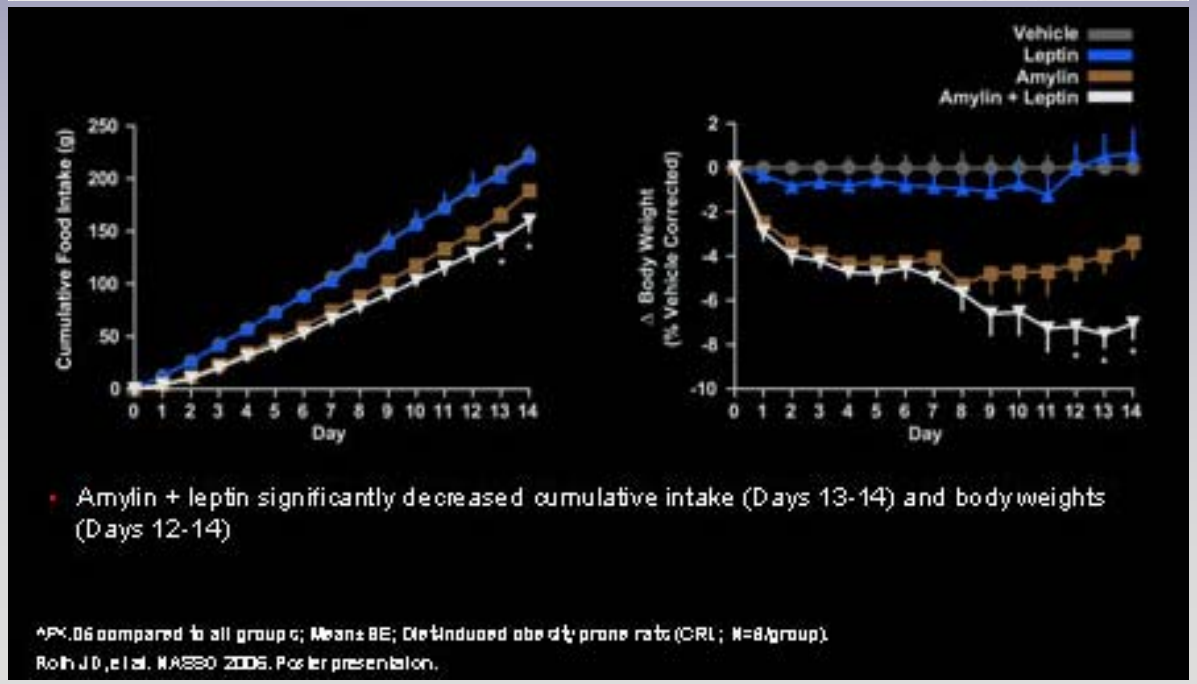

Trends in Endocrinology and Metabolism Vol.21 No.8

Am J Pathol. 2011 Jan;178(1):140-9. Epub 2010 Dec 23.

Actions of β-amyloid protein on human neurons are expressed through the amylin receptor.

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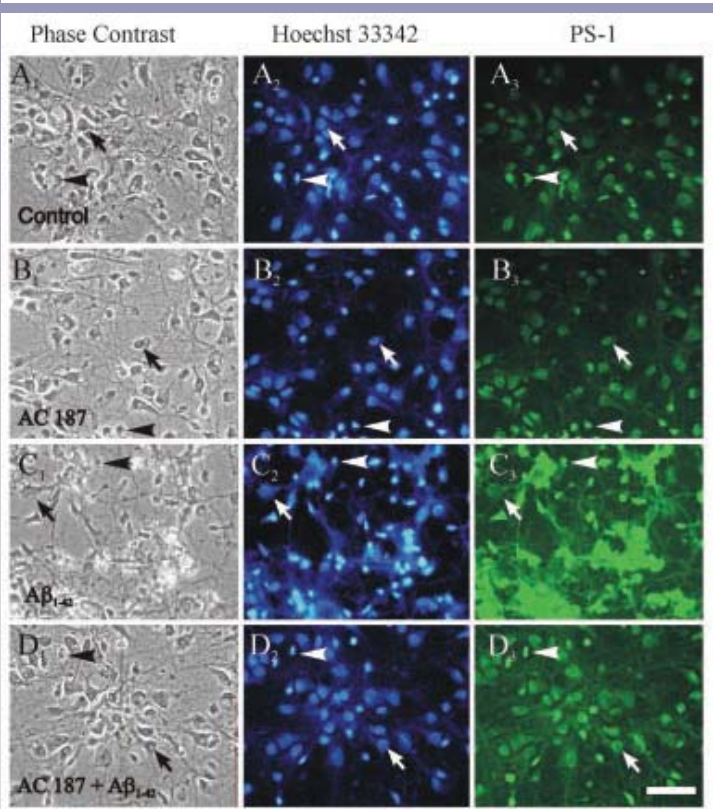
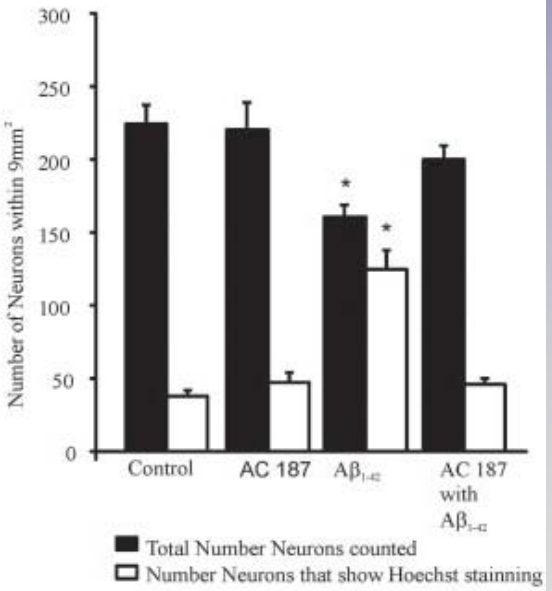
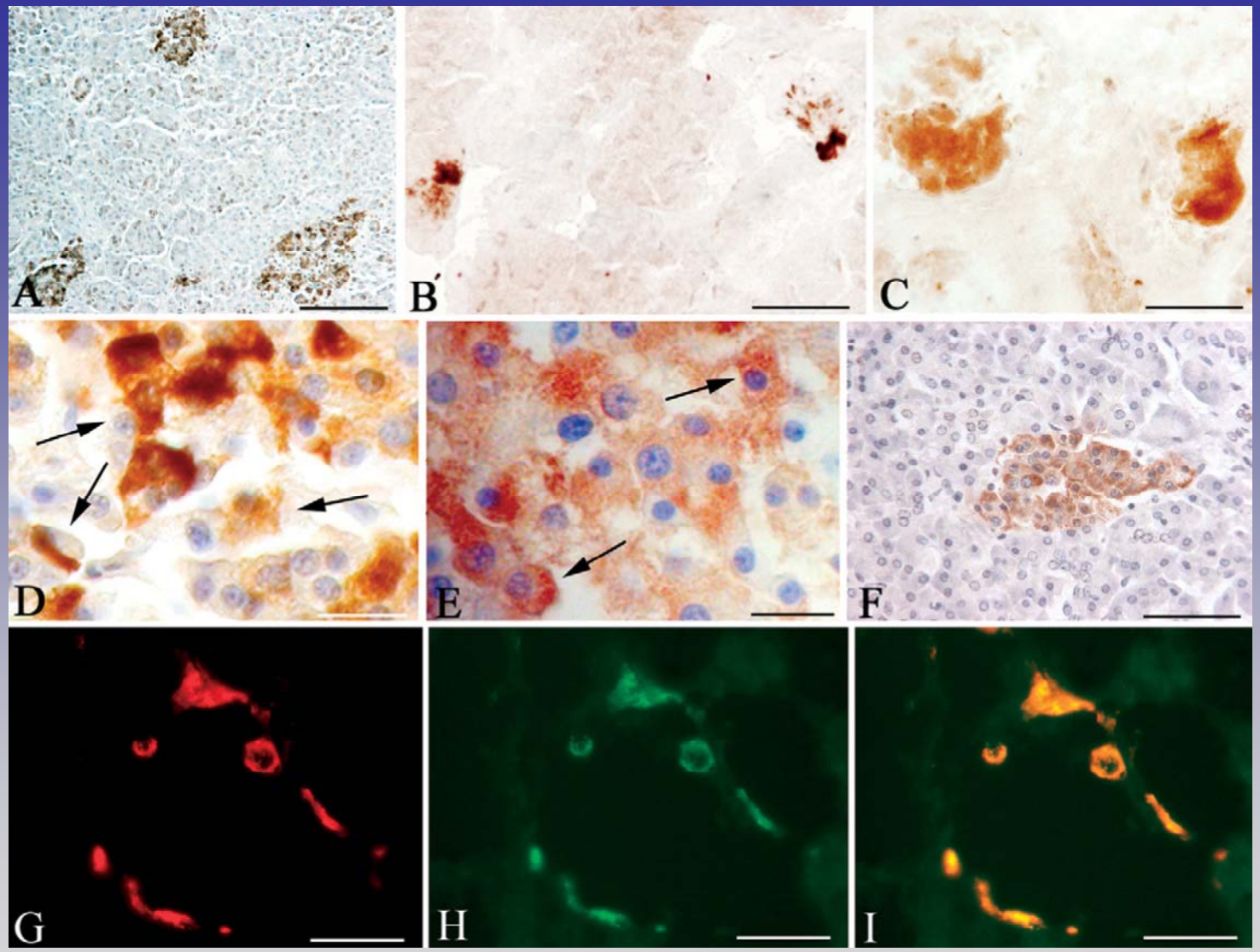
Abstract

Disruption of neurotoxic effects of amyloid β protein (Aβ) is one of the major, but as yet elusive, goals in the treatment of Alzheimer's disease (AD). The amylin receptor, activated by a pancreatic polypeptide isolated from diabetic patients, is a putative target for the actions of Aβ in the brain. Here we show that in primary cultures of human fetal neurons (HFNs), AC253, an amylin receptor antagonist, blocks electrophysiological effects of Aβ. Pharmacological blockade of the amylin receptor or its down-regulation using siRNA in HFNs confers neuroprotection against oligomeric Aβ-induced caspase-dependent and caspase-independent apoptotic cell death. In transgenic mice (TgCRND8) that overexpress amyloid precursor protein, amylin receptor is up-regulated in specific brain regions that also demonstrate an elevated amyloid burden. The expression of Aβ actions through the amylin receptor in human neurons and temporospatial interrelationship of Aβ and the amylin receptor in an in vivo model of AD together provide a persuasive rationale for this receptor as a novel therapeutic target in the treatment of AD.







Judith Miklossy et al., **Beta amyloid and hyperphosphorylated tau deposits in the pancreas in type 2 diabetes.** Neurobiology of Aging 31 (2010) 1503-1515

A in islet amyloid deposits in type 2 diabetes. (A) Islet amyloid deposits showing positive A immunoreaction with anti-A antibodies 21F12 (A), 2F9AF (B) and 4G8 (C) which recognize different epitopes of the molecule (see Table 1). (D and E) Sections of the pancreas from a diabetic patient immunostained with rabbit anti-amylin antibody (D, IAPP 1-37, Dr. A. Clark) and with the 4G8 monoclonal anti-A antibody (E) showing their intracellular localization (arrows). (F) Small group of affected acinar cells showing A immunoreaction demonstrated with the anti-A monoclonal antibody 21F12. (G–I) Pancreas section of a patient with type 2 diabetes doubly immunostained with an anti-amylin monoclonal antibody (GTX 74673, GeneTex, Inc.) labeled with TRITC-tagged secondary anti-mouse antibody (which gives a red fluorescence for amylin) (G) and with a polyclonal antibody to the C terminus of A 40) (Dr. H. Mori) which was labeled with a FITC-tagged anti-rabbit secondary antibody shows a green fluorescence. The orange color of the merged image shows the co-localization of amylin and A in islet amyloid deposits. Bars: (A and C) 250m, (B) 70m, (D and E) 50m, (F) 200m, (G–I) 120m.

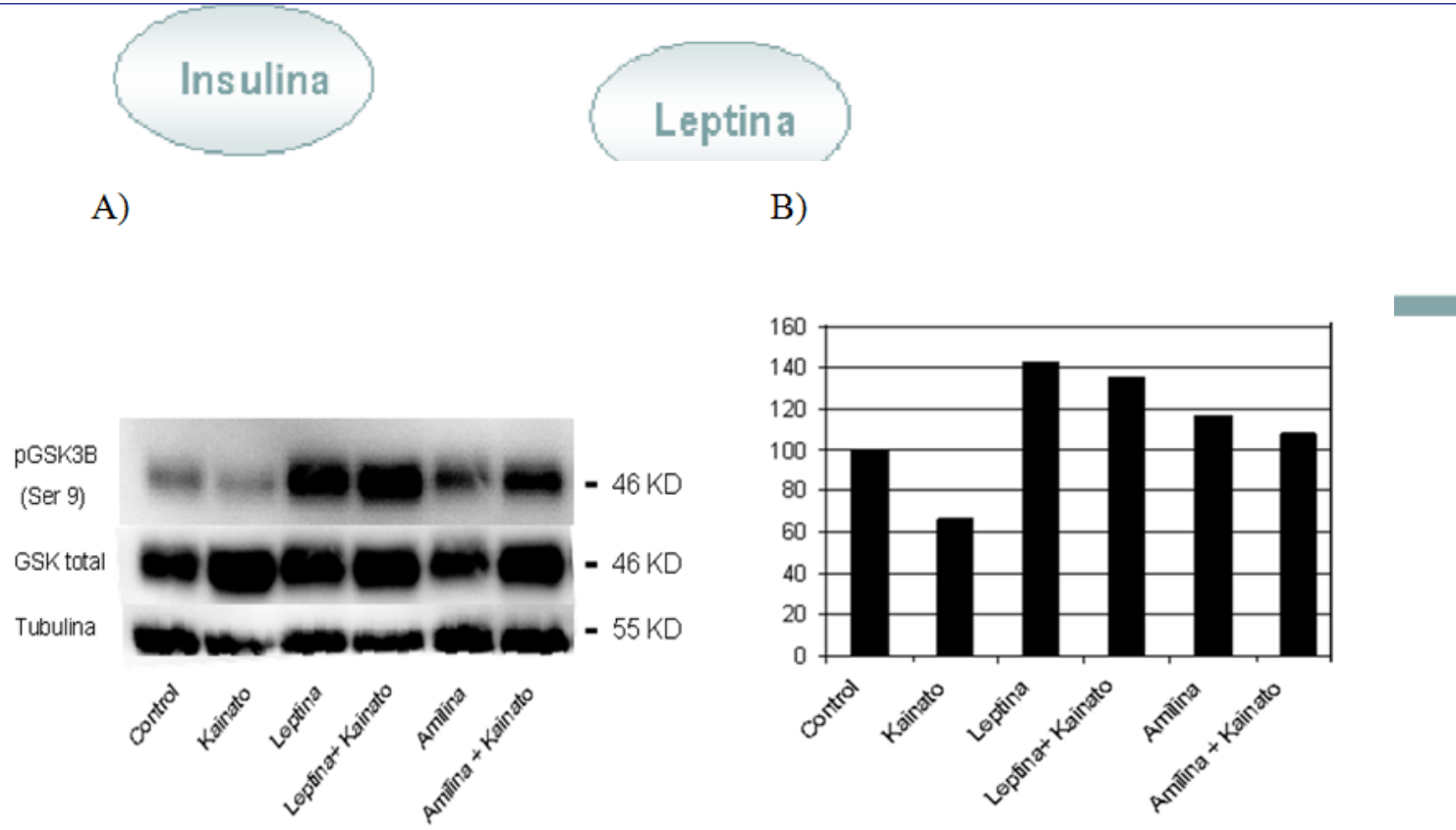
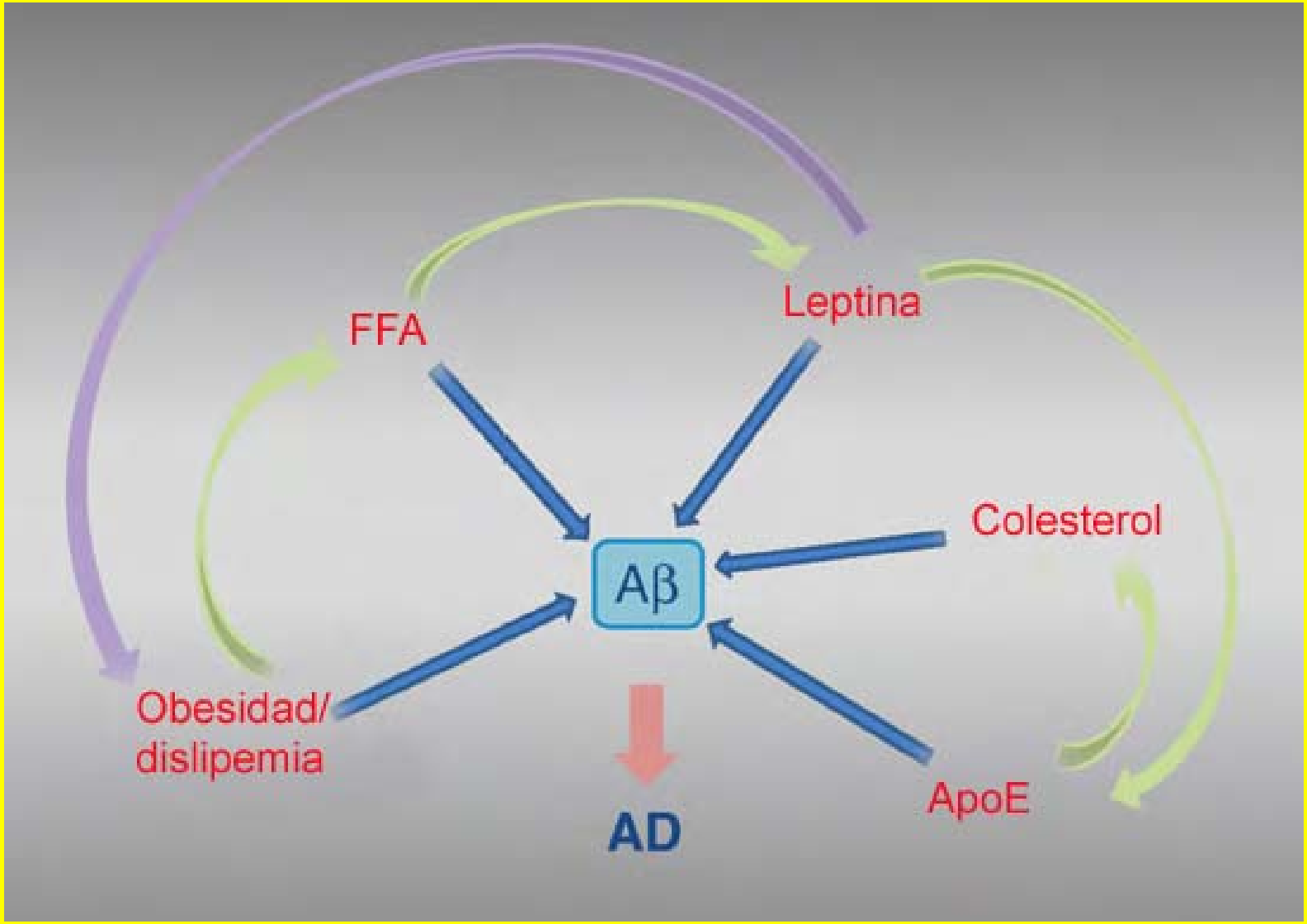


Figura 1. El tratamiento con leptina, y con el efecto combinado de leptina y amilina, aumenta significativamente los niveles de pGSK-β (Ser 9). (A) Extracto de tejido hipocampal de ratones C57BL/6J tratados con 1mg/Kg de leptina, 50ug/Kg de amilina y 25,6 mg/kg de Kainato, 24h. Se cargaron 30µg de proteina. (B) La densiometría muestra como la leptina y la amilina revierten los efectos de la exposición a kainato.

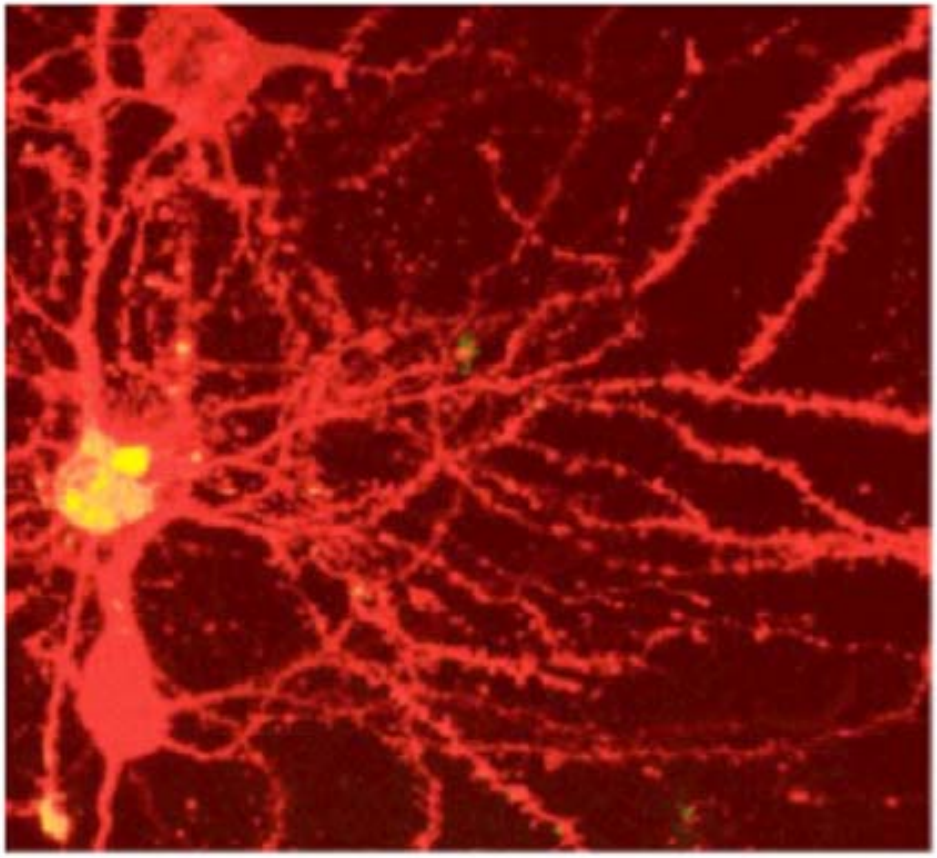


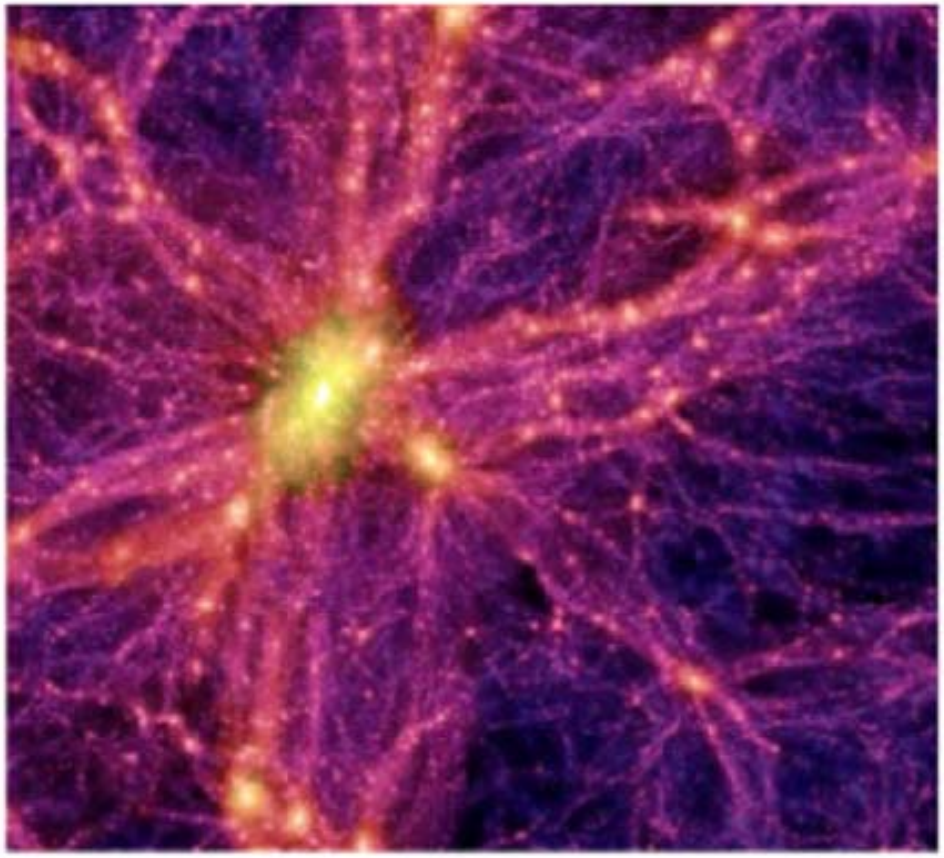
Sara Merlo et al.,
Alzheimer's disease: brain expression of a metabolic disorder?.
2010. Trends in Endocrinology and Metabolism Vol.21 No.9


INSULINA?¿
LEPTINA ?¿
AMILINA?¿

Espiral
Como el clavel sobre su vara,
como el clavel, es el cohete:
es un clavel que se dispara.
Como el cohete el torbellino:
sube hasta el cielo y desgrana
canto de pájaro en un pino.
Como el clavel y como el viento
el caracol es un cohete:
petrificado movimiento.
Y la espiral en cada cosa
su vibración difunde en giros:
el movimiento no reposa.
El caracol ayer fue ola,
mañana luz y viento, son,
eco del eco, caracola.

Octavio Paz





UNIVERSITAT ROVIRA I VIRGILI

La universitat pública de Tarragona

Departament de Bioquímica i Biotecnologia

FACULTAT DE MEDICINA I CIÈNCIES DE LA SALUT-FMCS REUS

Dr. Francesc Sureda

Sr. Ignacio Pedrós

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II Foro Social - Madrid
- 10 de junio 2010

La Lucha contra las Enfermedades Neurodegenerativas

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