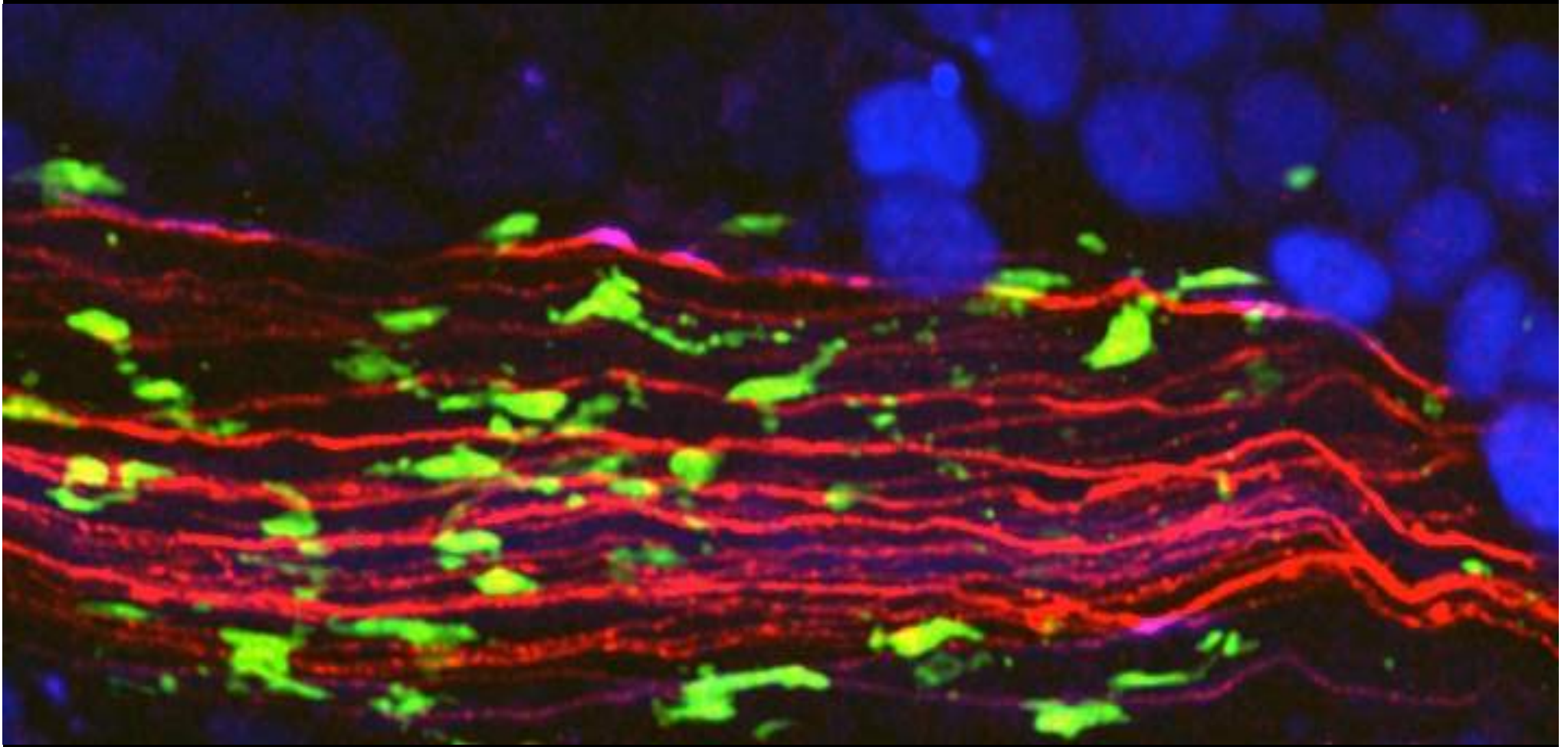


NeuroImmunoMetabolism

FAPESP – *Annus LX*
Aug 7th

Ana Domingos, PhD
Obesity Lab

Assoc. Professor
Neuroscience



An old phenomenon



Laughing Budah, circa 900 AD, China



Venus Willendorf 24.000-22.000 BCE, Austria

An old phenomenon



**Dona Carolina
1840(?) - 1919**

Daniel Lambert 1770-1809



**Pantagruel, 1532
Francois Rabelais**



(460-377BCE)

To treat obesity, Hippocrates, the “father of medicine,” suggested the following:

[o]bese people and those desiring to lose weight should perform hard work before food. Meals should be taken after exertion and while still panting from fatigue and with no other refreshment before meals except only wine, diluted and slightly cold. Their meals should be prepared with sesame or seasoning and other similar substances and be of a fatty nature as people get thus, satiated with little food. They should, moreover, eat only once a day and take no baths and sleep on a hard bed and walk naked as long as possible. [13]



VIVA O got dad



Jo Soares
Jan 16th 1938 -
Aug 5th 2022





The New York Times

THE SCIENCE OF FAT

After 'The Biggest Loser,' Their Bodies Fought to Regain Weight

Contestants lost hundreds of pounds during Season 8, but gained them back. A study of their struggles helps explain why so many people fail to keep off the weight they lose.

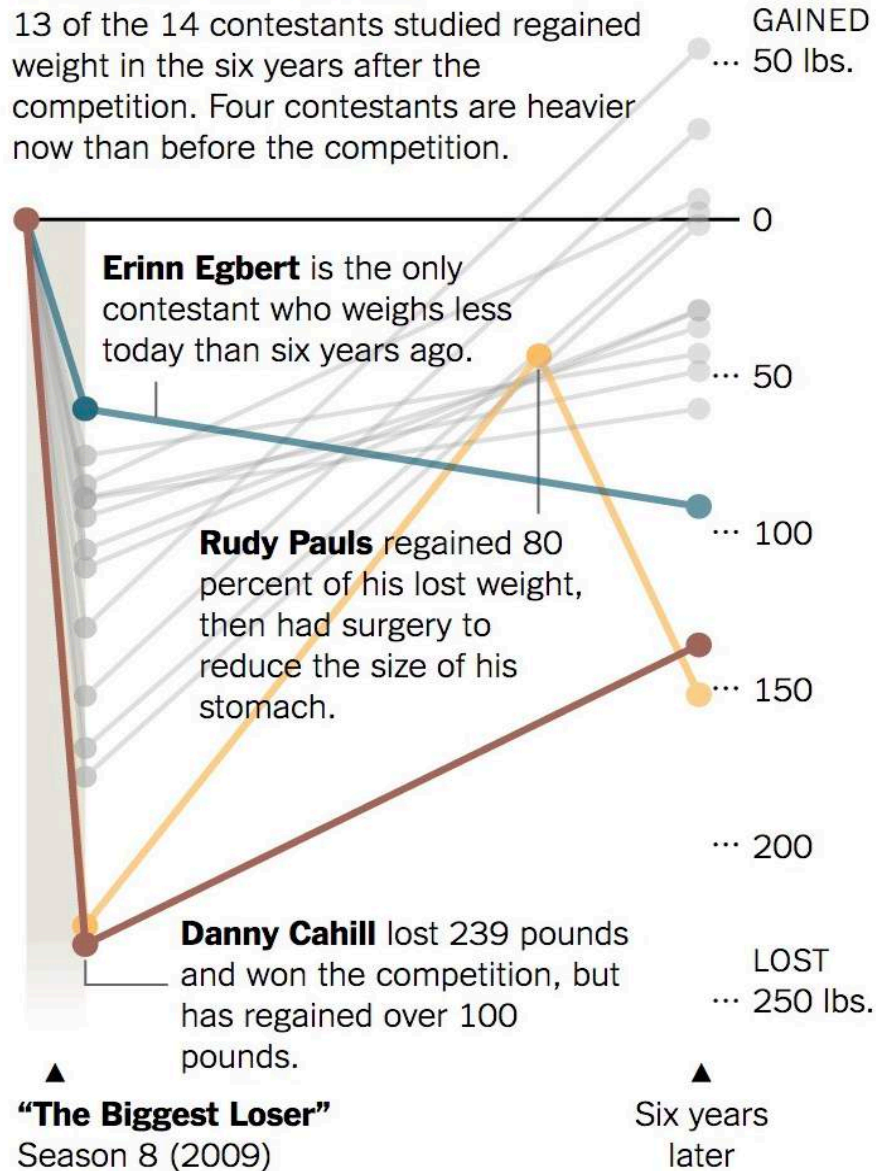


Biggest Losers Fight a Slower Metabolism

A study of contestants from “The Biggest Loser” found their metabolisms slowed during and after the competition, making it difficult to maintain weight loss.

REGAINING LOST WEIGHT

13 of the 14 contestants studied regained weight in the six years after the competition. Four contestants are heavier now than before the competition. Three contestants are lighter now than before the competition.



saúde + ciência

→ MITO

→ **AMAMENTAÇÃO PREVIENE A OBESIDADE**
Revisões de estudos não mostraram evidências do efeito do aleitamento materno na obesidade



→ **AULAS DE EDUCAÇÃO FÍSICA EVITAM A OBESIDADE INFANTIL**
Pesquisas mostram que as aulas não têm frequência, intensidade e duração suficientes para ter impacto no peso das crianças



→ **É MELHOR PERDER PESO GRADUALMENTE**
Não há diferenças no resultado a longo prazo entre um tipo de dieta que leva à perda inicial mais rápida ou mais lenta



← VERDADE

← **A GENÉTICA INFLUENCIA O PESO, MAS NÃO É TUDO**
Mudanças em outros fatores que causam a obesidade podem levar a uma redução significativa do peso



← **A CIRURGIA PODE SER UMA OPÇÃO EFICAZ**
Para pacientes obesos, o procedimento, quando indicado corretamente, leva à perda de peso e reduz o diabetes e o risco de morte.



← **FAMÍLIA UNIDA COMBATE A OBESIDADE**
O tratamento da obesidade infantil tem mais resultados quando há envolvimento dos pais e mudanças no ambiente familiar



DO "NEW YORK TIMES"

Um artigo publicado no "New England Journal of Medicine" que elenca mitos e fatos sobre obesidade e emagrecimento está causando controvérsia nos EUA.

David Allison, diretor do centro de pesquisas de nutrição e obesidade da Universidade do Alabama, e colegas apresentam uma lista com sete mitos, seis pressupostos não comprovados e nove fatos sobre a obesidade.

Entre os mitos e conceitos não provados estão as ideias de que aulas de educação física têm efeito no emagrecimento de crianças obesas, de que amamentação evita o problema e que os obesos devem evitar dietas radicais.

Entre os fatos está o poder de remédios emagrecedores, cirurgias bariátricas e de programas que oferecem refeições prontas ou substitutos na perda de peso.

Os especialistas em obesi-

de Nova York.

"O importante na perda de peso é como você muda o ambiente ligado à comida para fazer escolhas saudáveis."

MÉTODO

David Allison queria saber o que já está comprovado em relação à obesidade.

Uma ideia tida como verdadeira, por exemplo, é que as pessoas que tomam café da manhã são mais magras.

Mas essa noção é baseada em estudos feitos com pessoas que já tomavam café da manhã. Dois estudos que separaram as pessoas em grupos e avaliaram o impacto de comer ou não de manhã não mostraram o efeito emagrecedor da primeira refeição.

Portanto, indaga Allison, por que os pesquisadores continuam fazendo estudos que se limitam a relacionar magreza e café da manhã?

"Todo esse tempo e esforço são desperdiçados."

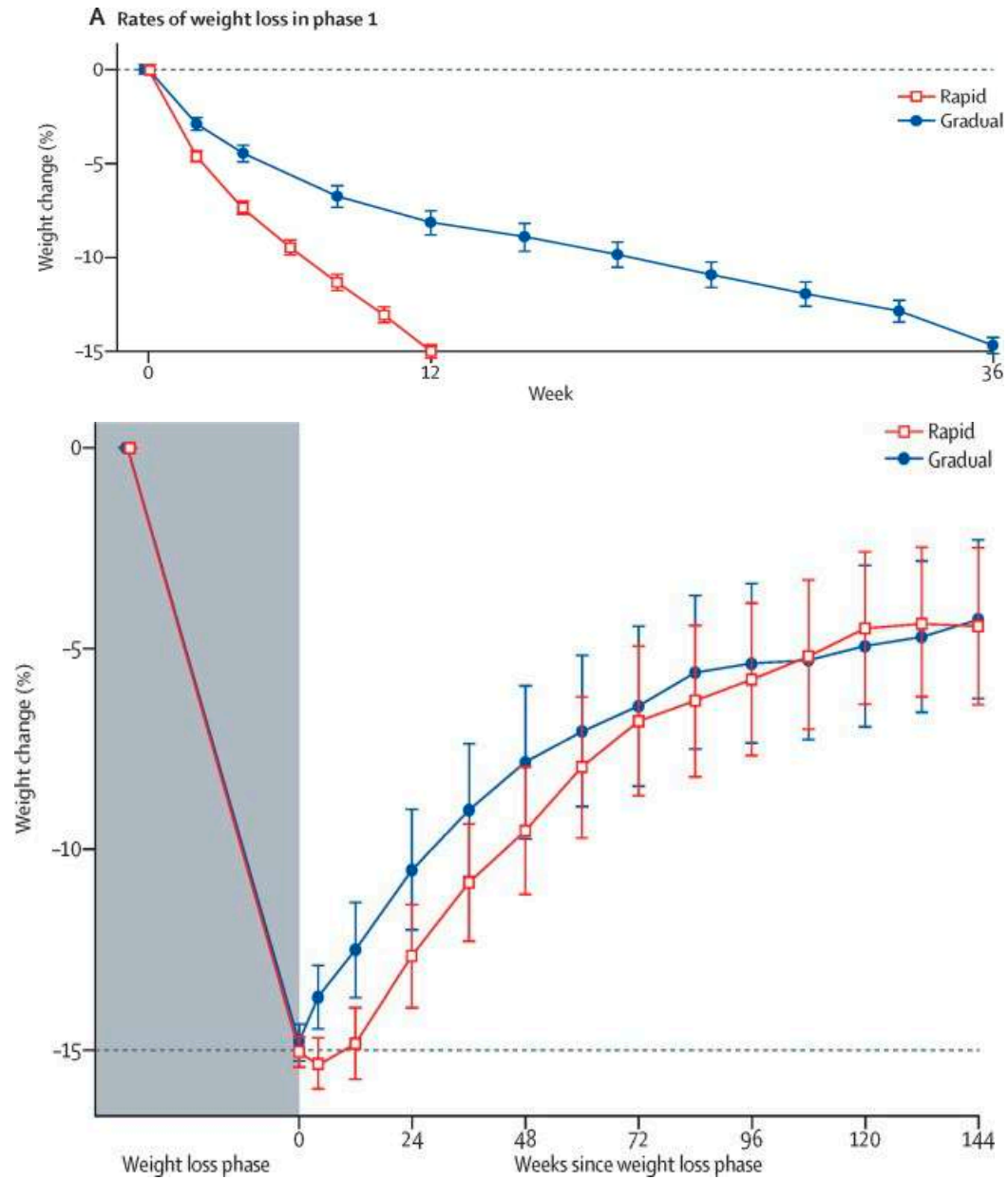
Outro problema com as

MITOS DA obesidade



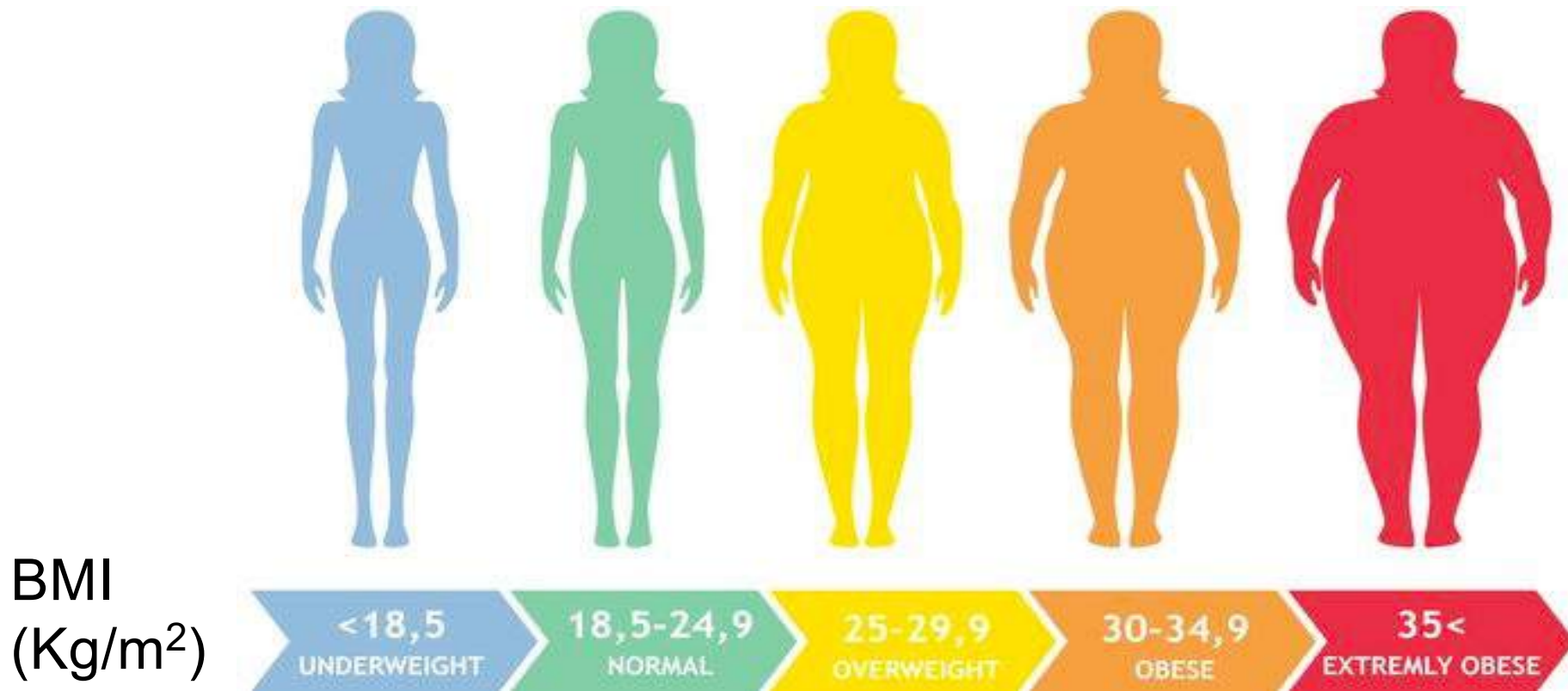
Are you more likely to maintain weight loss if you lose weight slowly?

That is the advice dieters often get, but randomized [studies](#) on 204 patient, say **NO**



Purcel et al,
Lancet, 2014

OBESITY

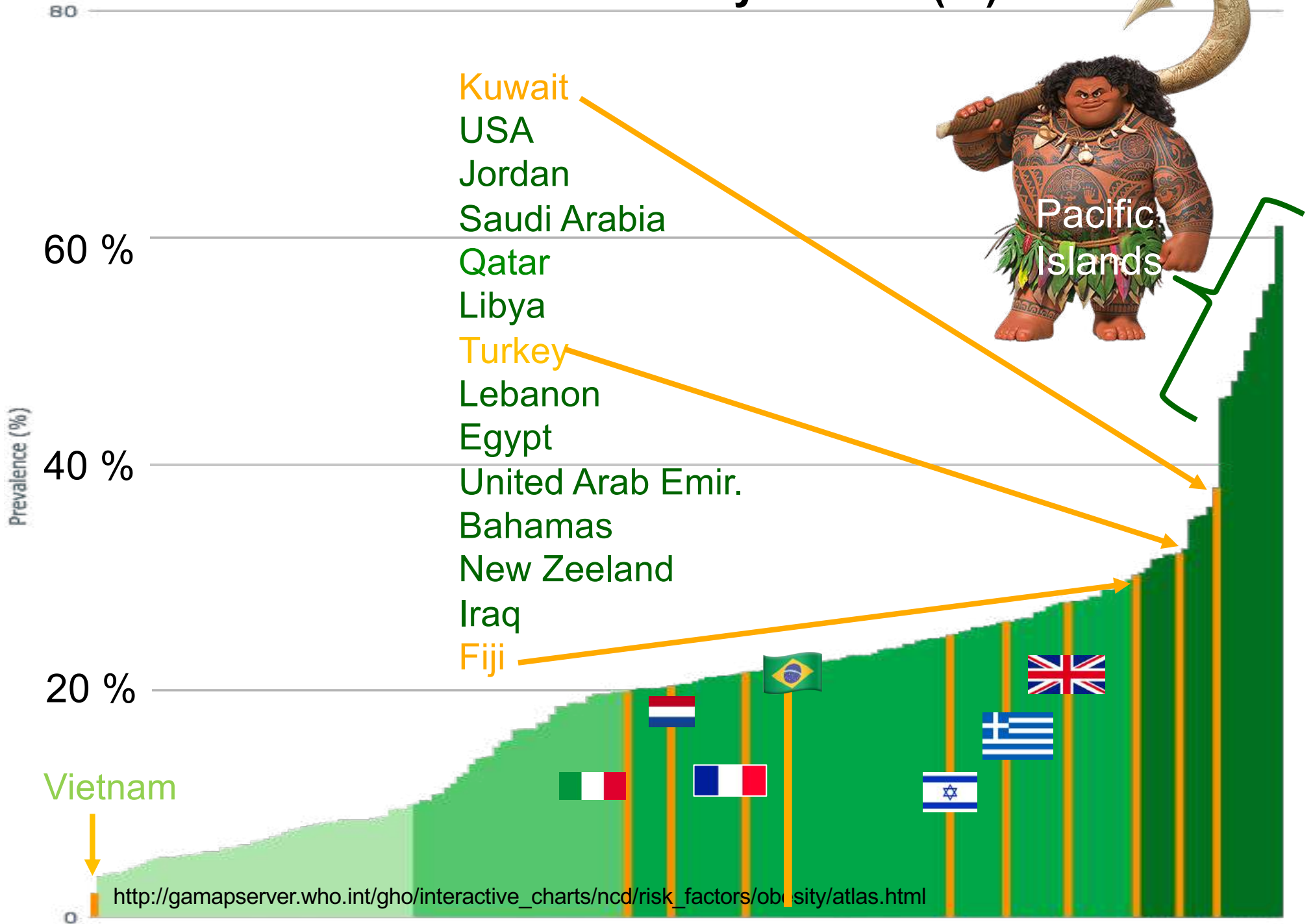


BMI
(Kg/m²)

Definitions based on ideal body weight – determined from actuarial tables as maximising life expectancy

Asia cutoffs : below 17,5 < 17,5 – 22,9 < 23 – 27,99 < 28&above

Worldwide Prevalence of Obesity in 2016 (%) : WHO



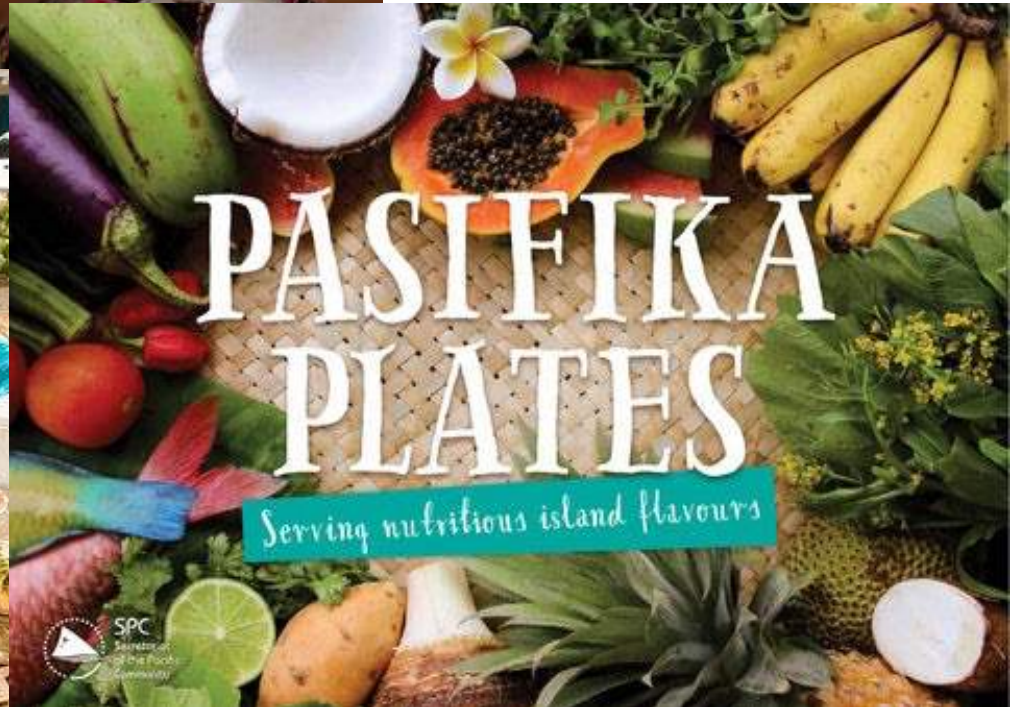
Traditional Italian Diet

80



0

Traditional Pacific Diet



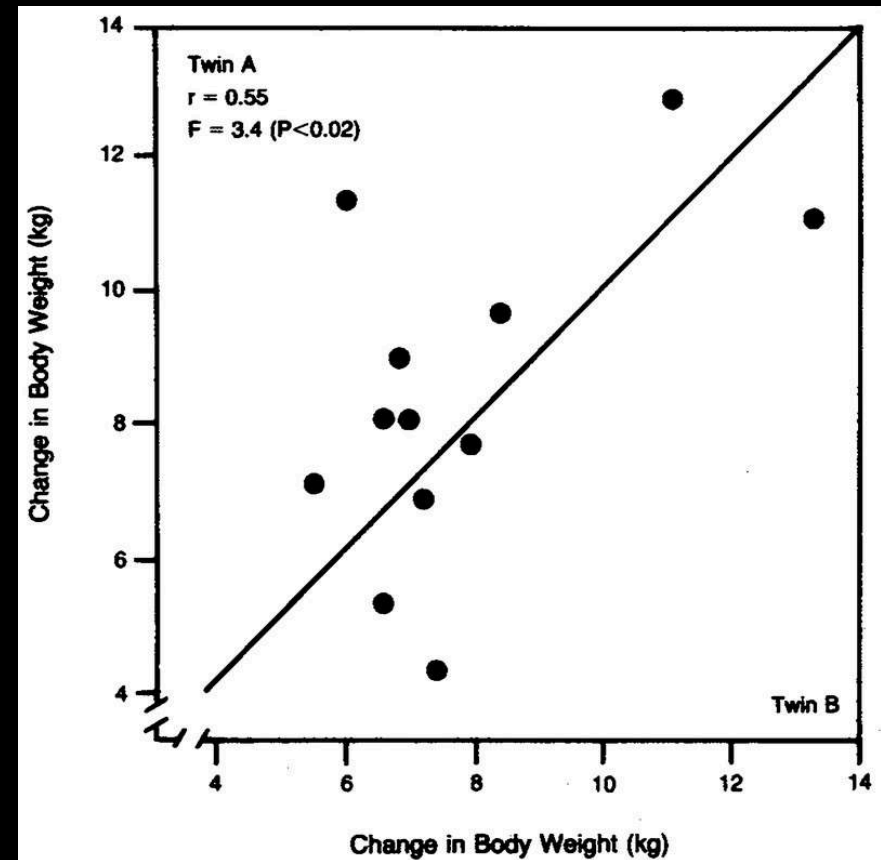
40% to 77% of BMI is determined by genetic factors

100 Days of Overfeeding drives
Similar weight gain
within identical Twin pairs

Identical Twins



Fraternal Twins



Which genetic factors?

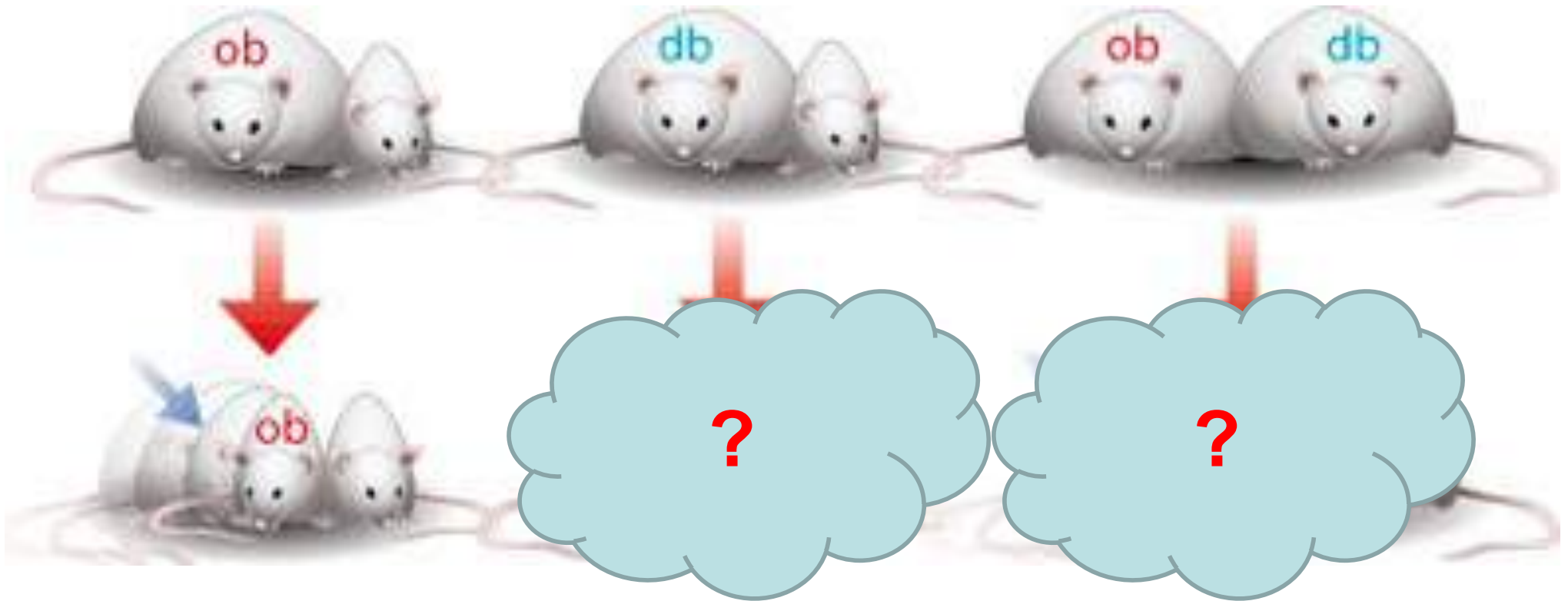


Douglas L. Coleman, 1931–2014
Lasker Award 2014



Genetically obese
With mendelian recessive
inheritance

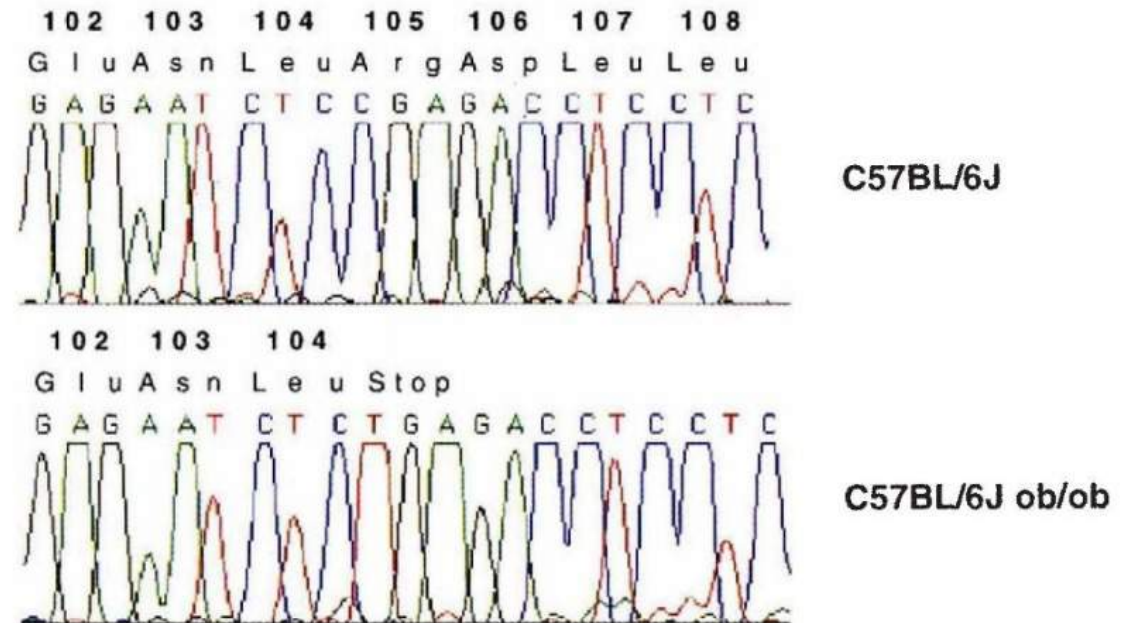
Parabiosis revealed a blood born signal



Molecular genetics revealed the identity of the signal: LEPTIN, conserved in mice and humans



Jeffrey M. Friedman
-Lasker Award 2014
-Breakthrough Award 2020



Zhang Y, et al, Friedman JM 1994 Positional cloning of the mouse obese gene and its human homologue. Nature

Recombinant leptin therapy reverses congenital leptin deficiency



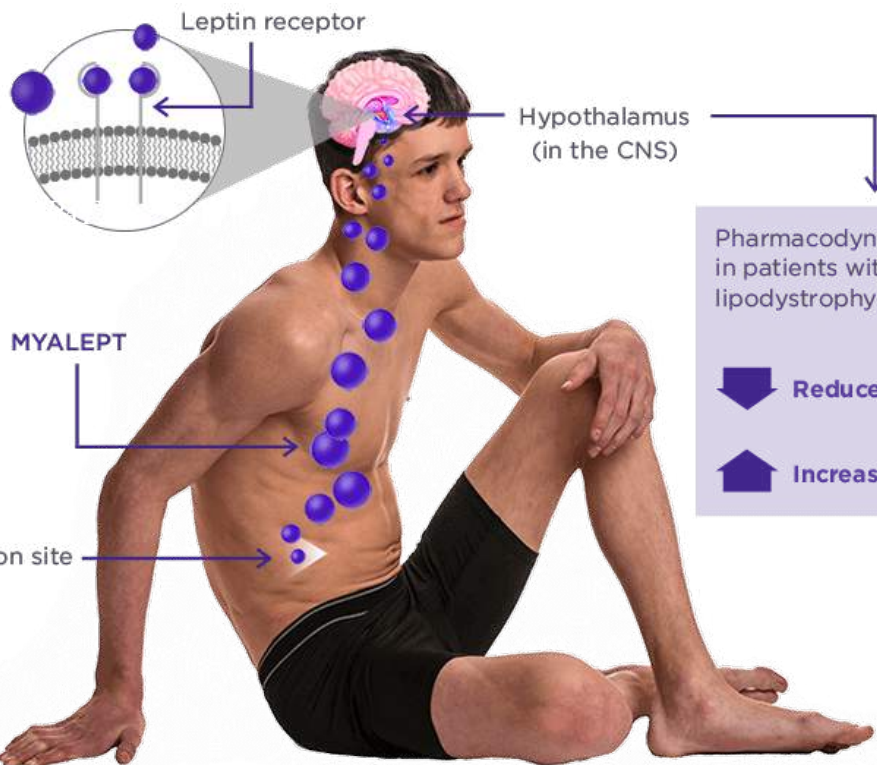
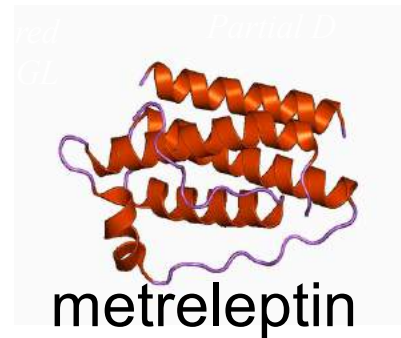
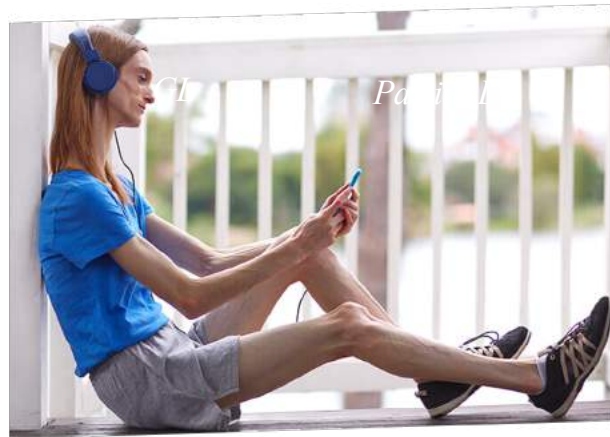
weight = 40kg, age 3yrs



weight = 29kg, age 8yrs

Farooqi et al 1999 NEJM

Leptin reverses metabolic syndrome in generalized lipodystrophy



Pharmacodynamic clinical studies in patients with generalized lipodystrophy suggest that MYALEPT

- Reduces food intake
- Increases insulin sensitivity

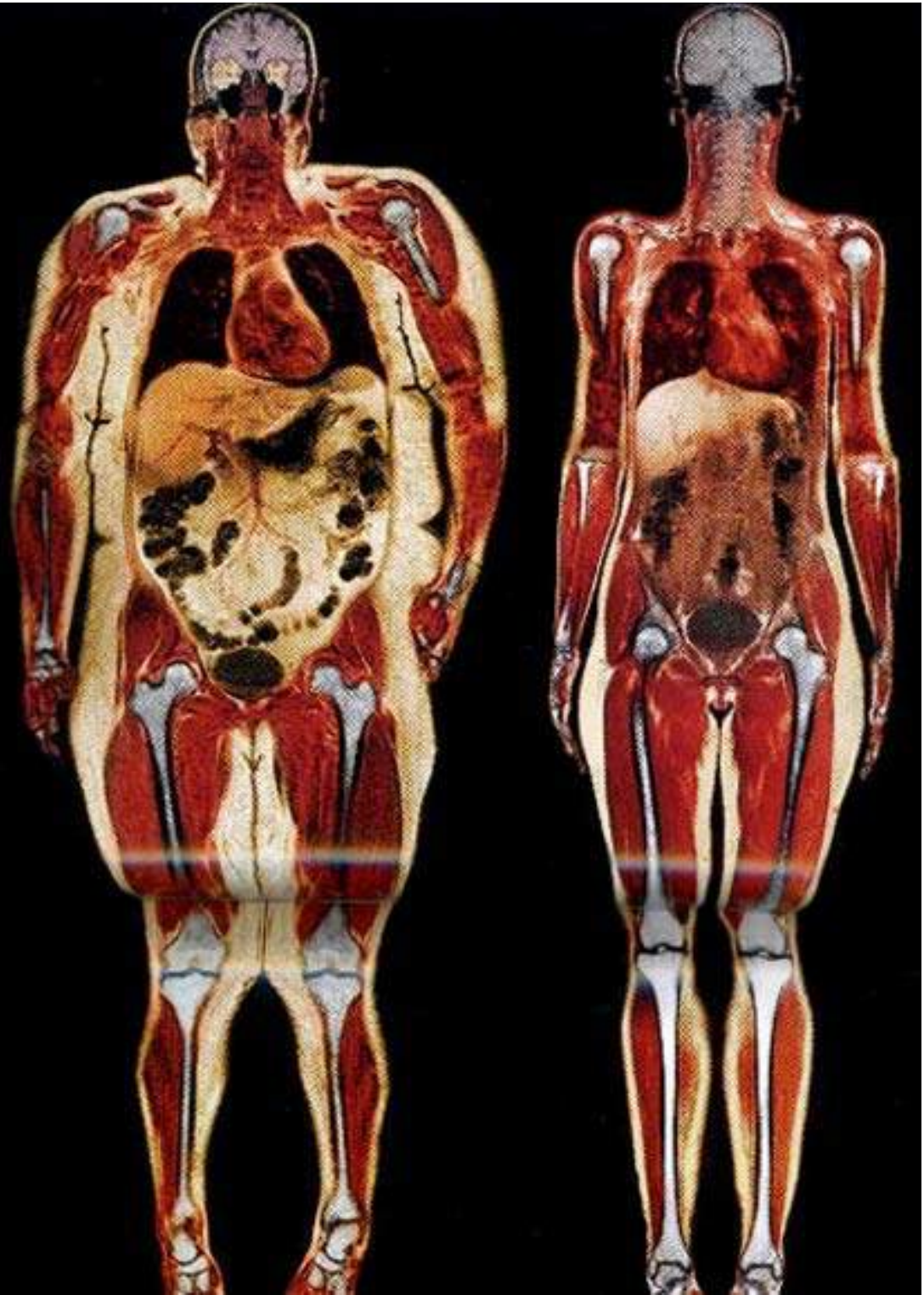


ADIPOSE TISSUE AS AN ENDOCRINE ORGAN

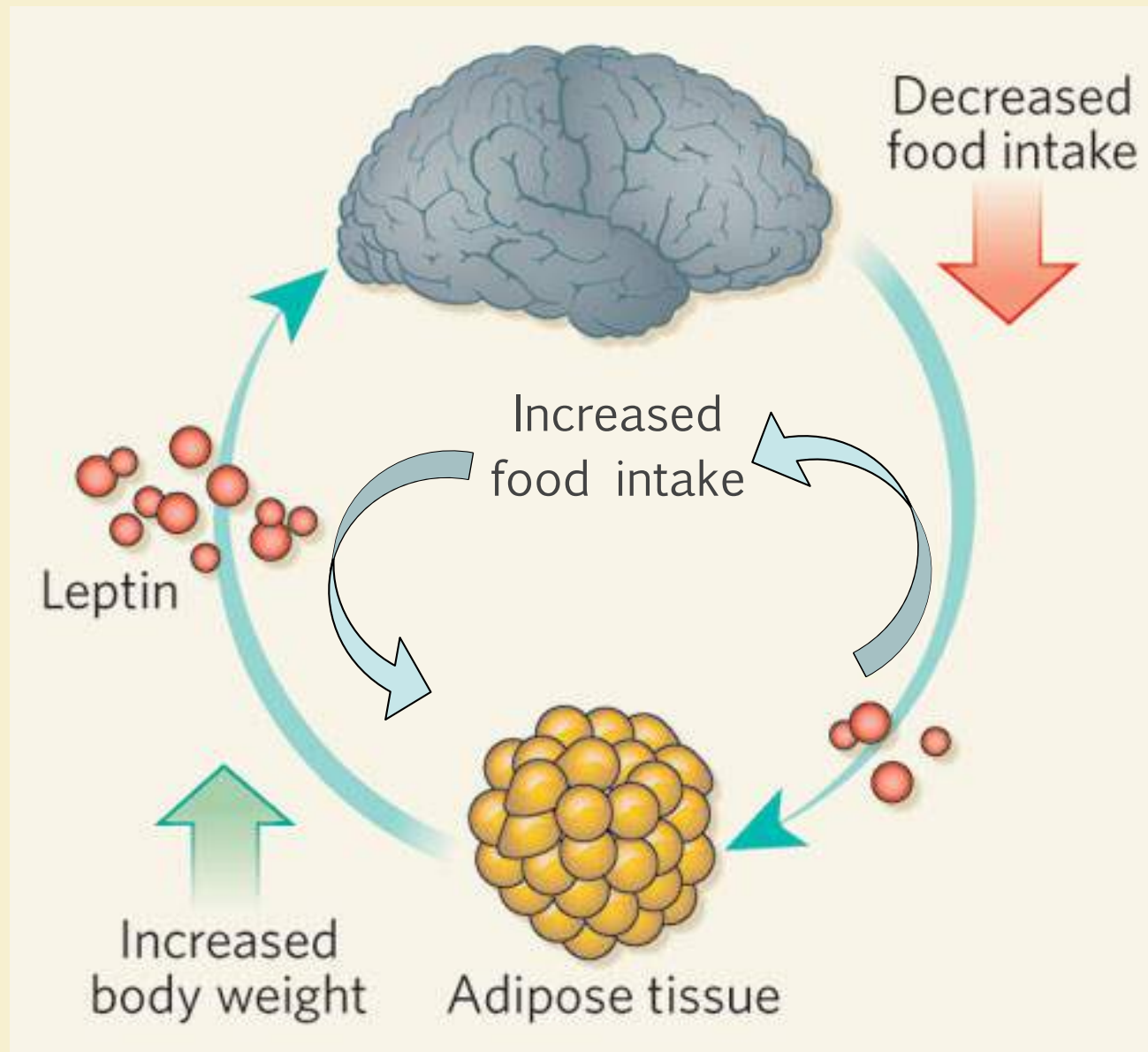
Hormone leptin



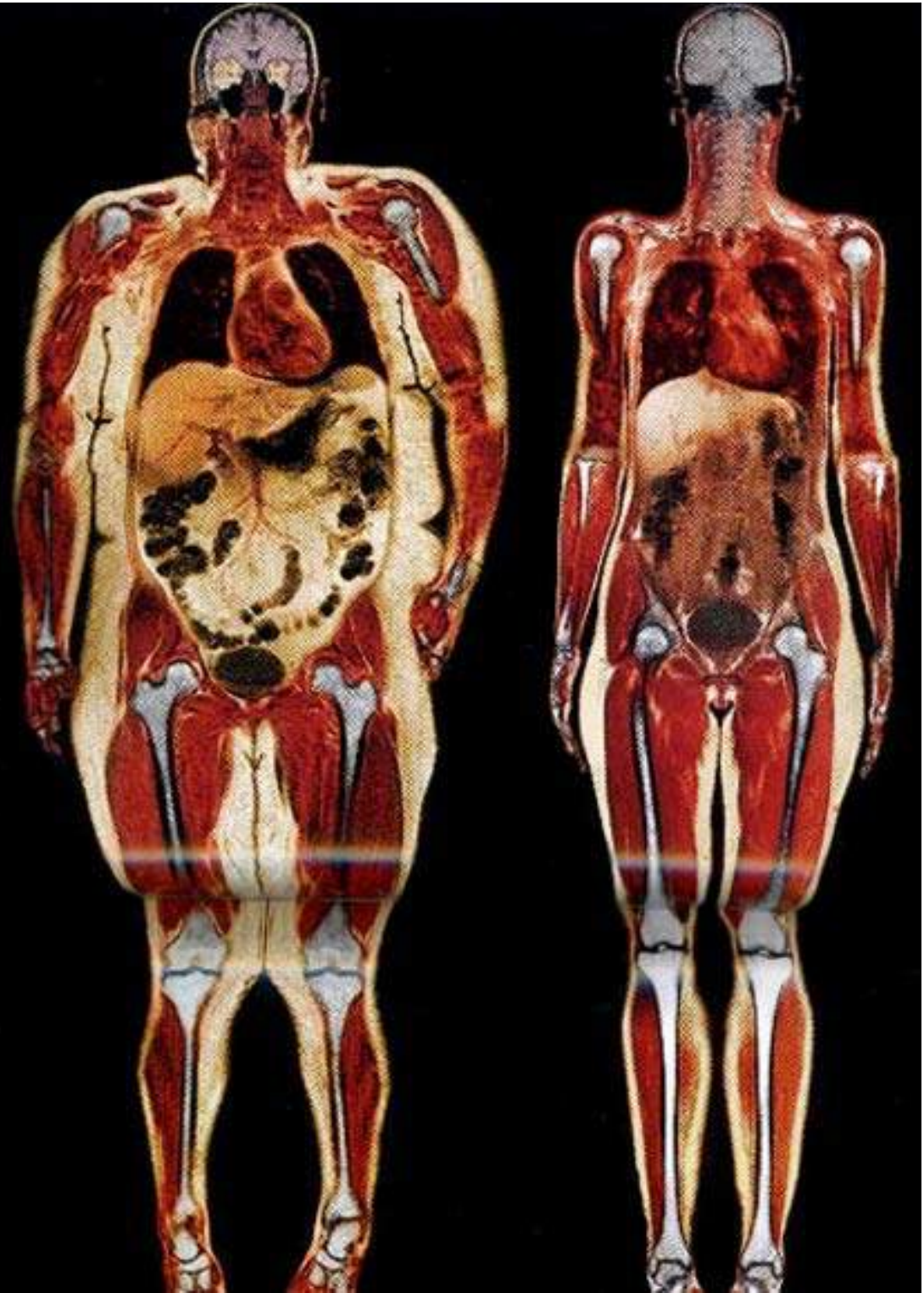
Multiple actions



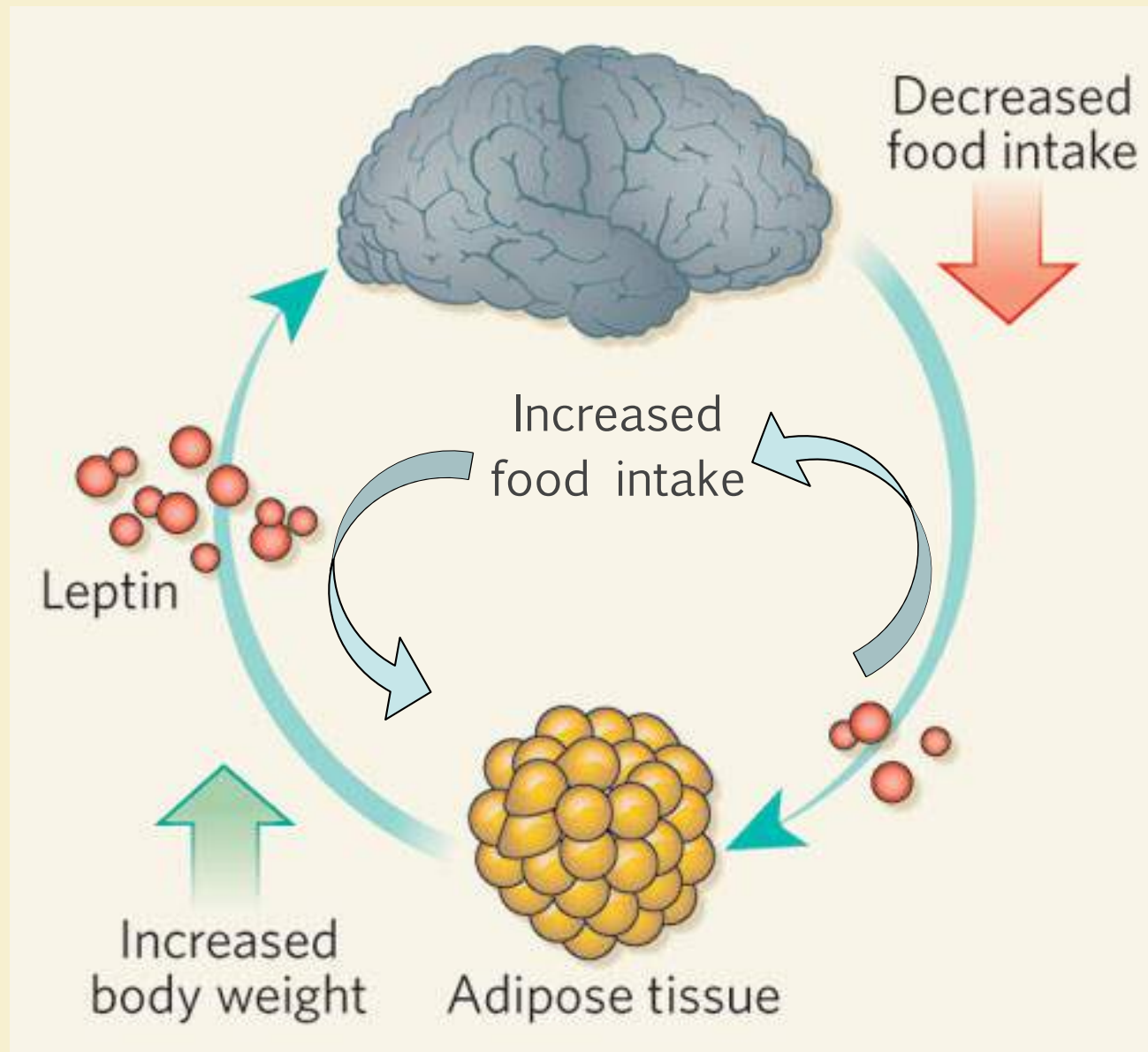
Leptin: an adipostat



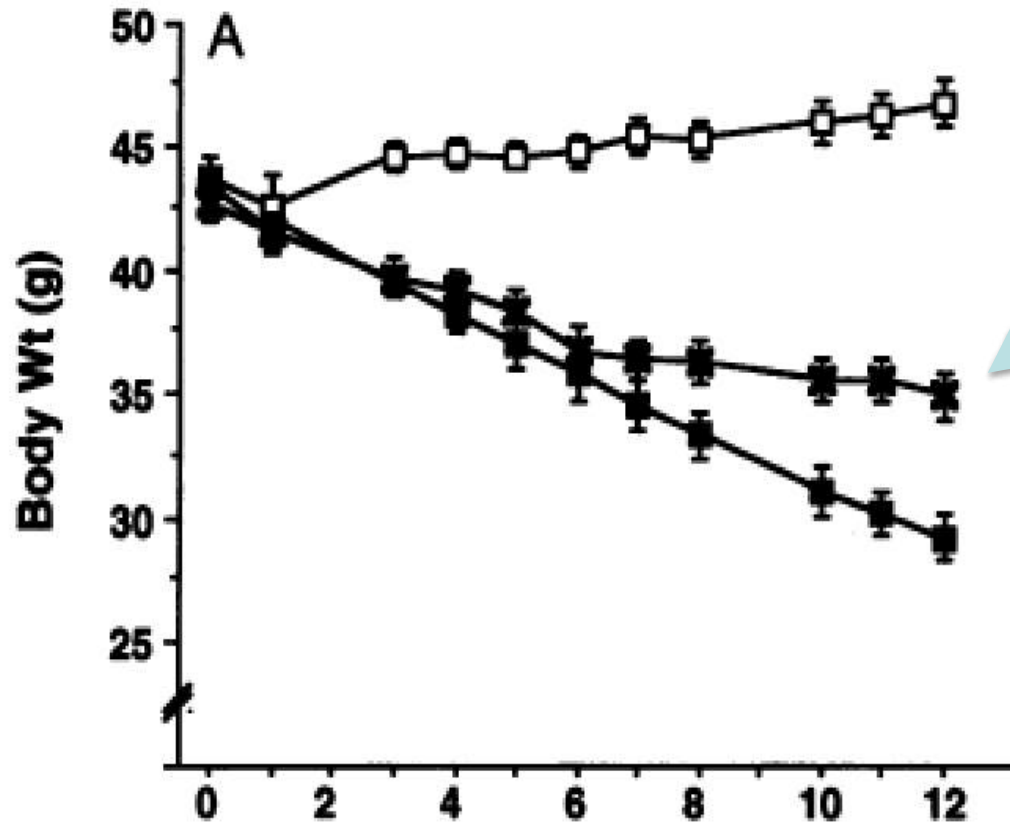
Leptin does not cure
Common obesity
Because
hyperleptinemia
causes
Leptin resistance



Leptin: an adipostat



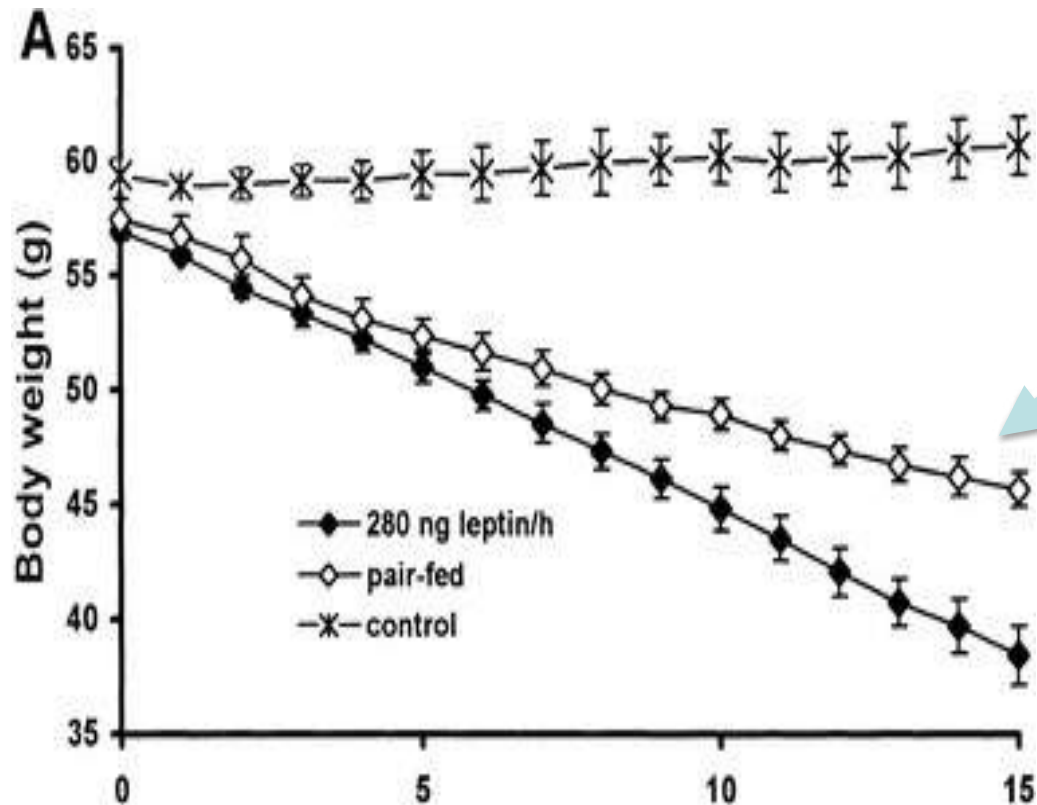
The weight loss effect of leptin action is not solely mediated by suppression of food intake



Ob/ob mice that are Pair-fed
To leptin-treated ob/ob mice
Do not lose weight to the same
extent



The weight loss effect of leptin action is not solely mediated by suppression of food intake



Ob/ob mice that are Pair-fed
To leptin-treated ob/ob mice
Do not lose weight to the same
extent

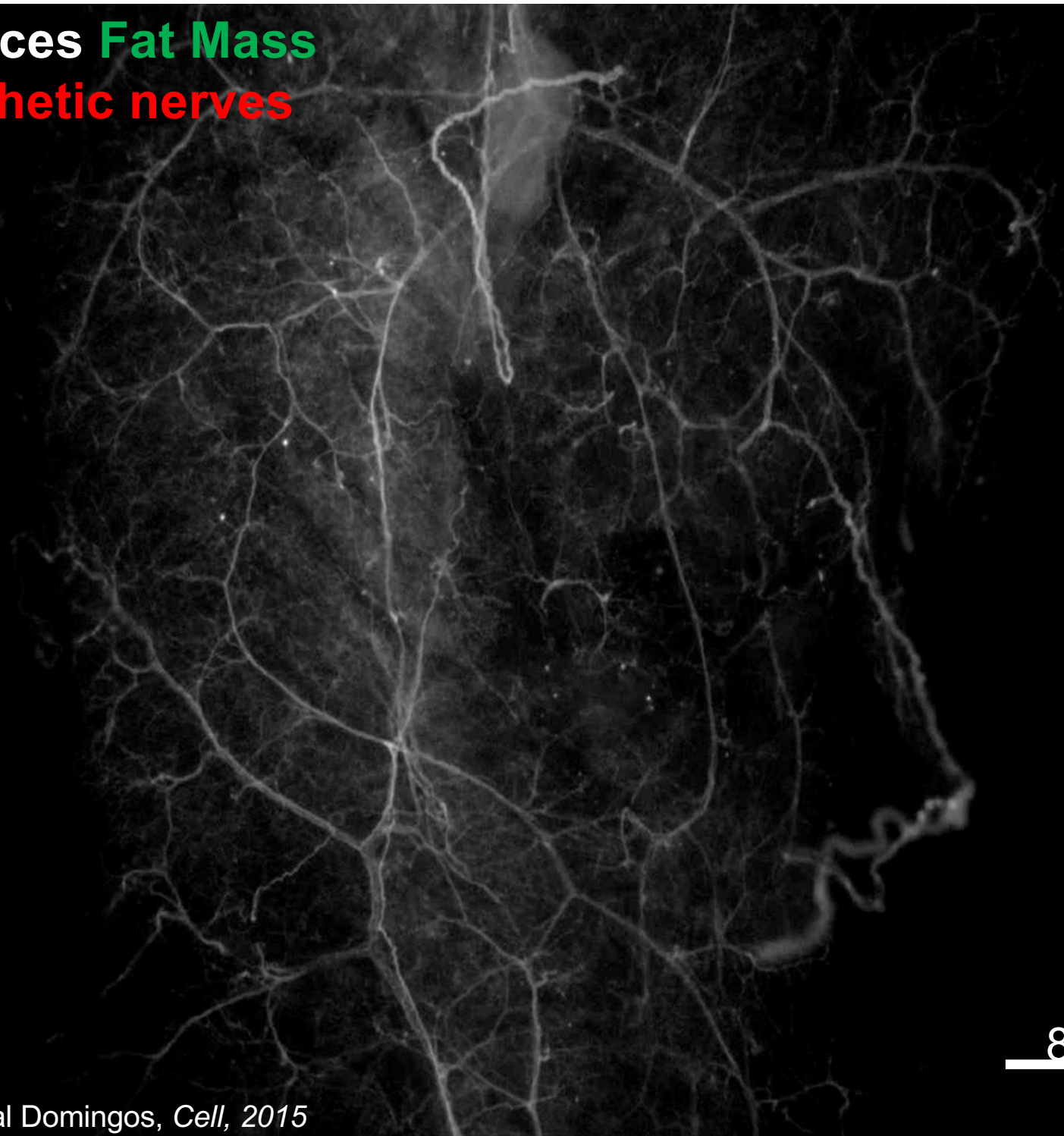


Leptin reduces **Fat Mass**
Via Sympathetic nerves

TH

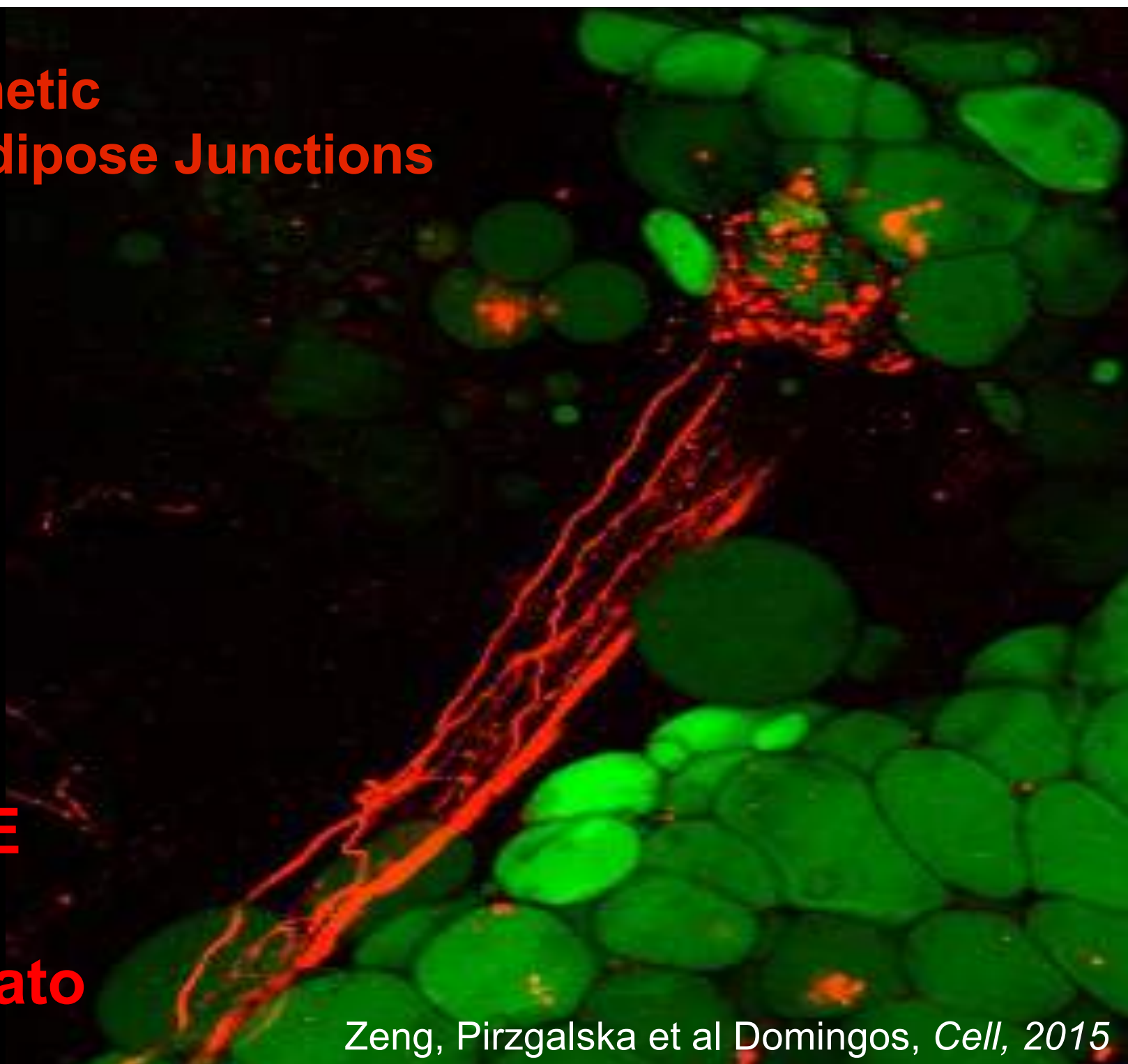
800um

Zeng, Pirzgalska et al Domingos, *Cell*, 2015



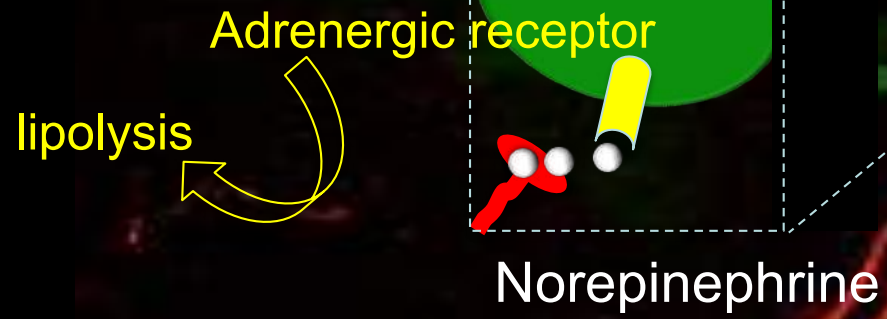
Sympathetic Neuro-adipose Junctions

TH-CRE
x
LSL-tomato



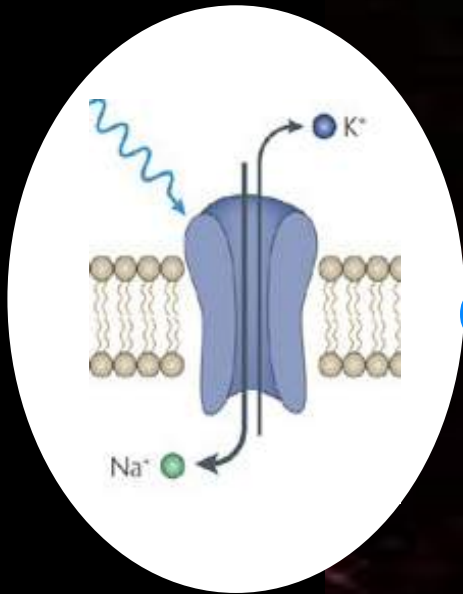
Zeng, Pirzgalska et al Domingos, *Cell*, 2015

Sympathetic Neuro-adipose Junctions



TH-CRE
X
LSL-tomato

Sympathetic Neuro-adipose Junctions

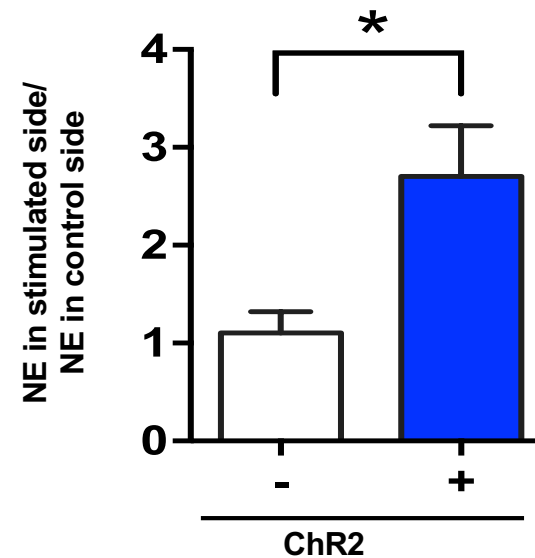
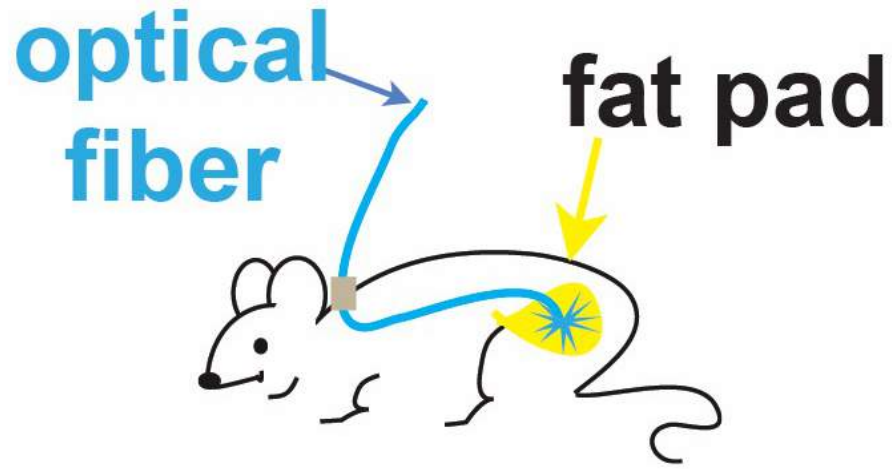


OPTOGENETICS

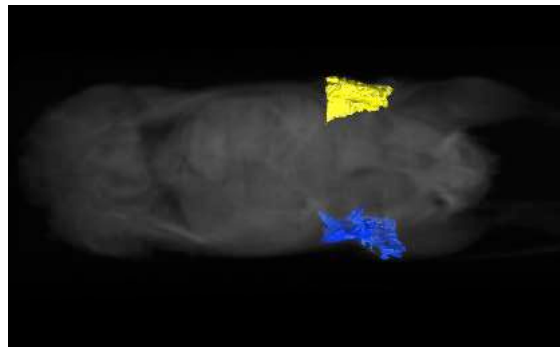
TH-CRE
X
LSL-ChR2

Zeng, Pirzgalska et al Domingos, *Cell*, 2015

Optogenetic stimulation of sympathetic neurons Drives NE release and lipolysis *in vivo*

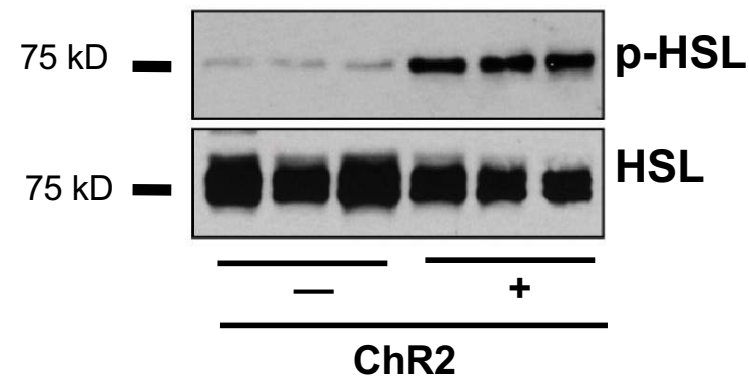
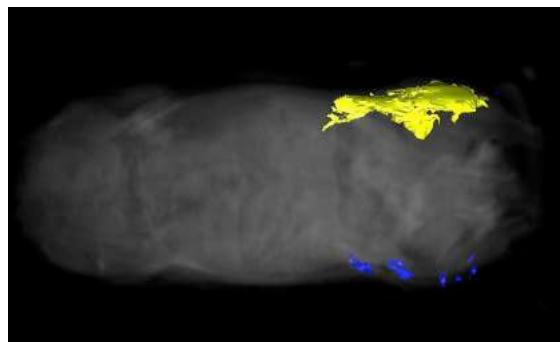


ChR2 -



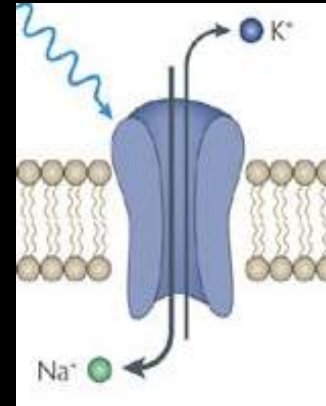
Light On
Right side

ChR2 +



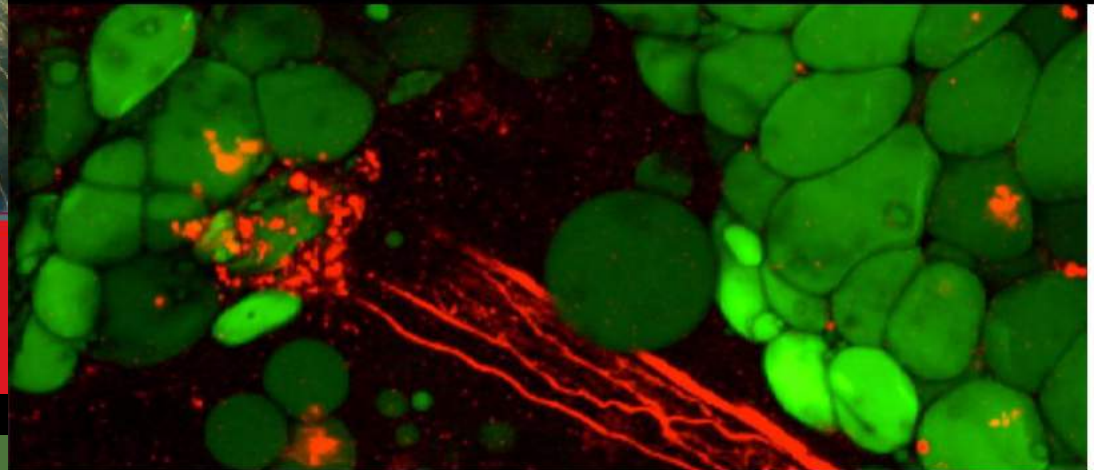


© Tony Lilley/Alamy Stock Photo



OPTOGENETICS

Science



Bundles of nerves (red) that surround some fat cells (green) are key to fat breakdown—and weight loss.

Ana Domingos, Instituto Gulbenkian de Ciência

AUTONOMIC NERVOUS SYSTEM

Zapping fat in WAT

A Sympathetic View on Fat by Leptin

Luis Varela¹ and Tamas L. Horvath^{1,*}

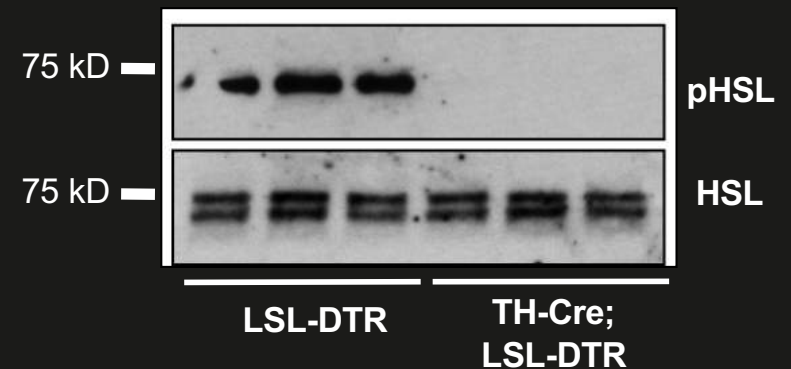
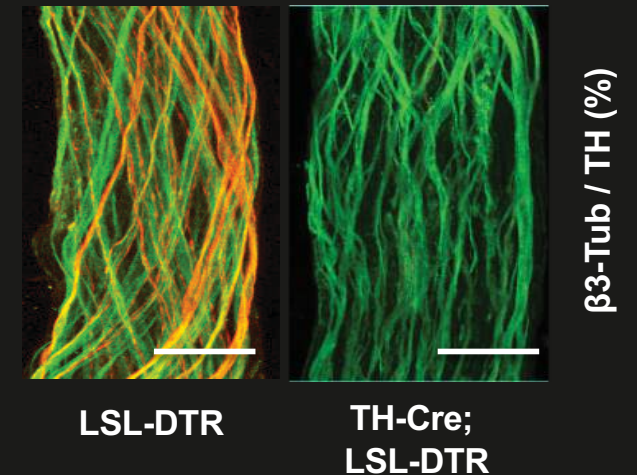
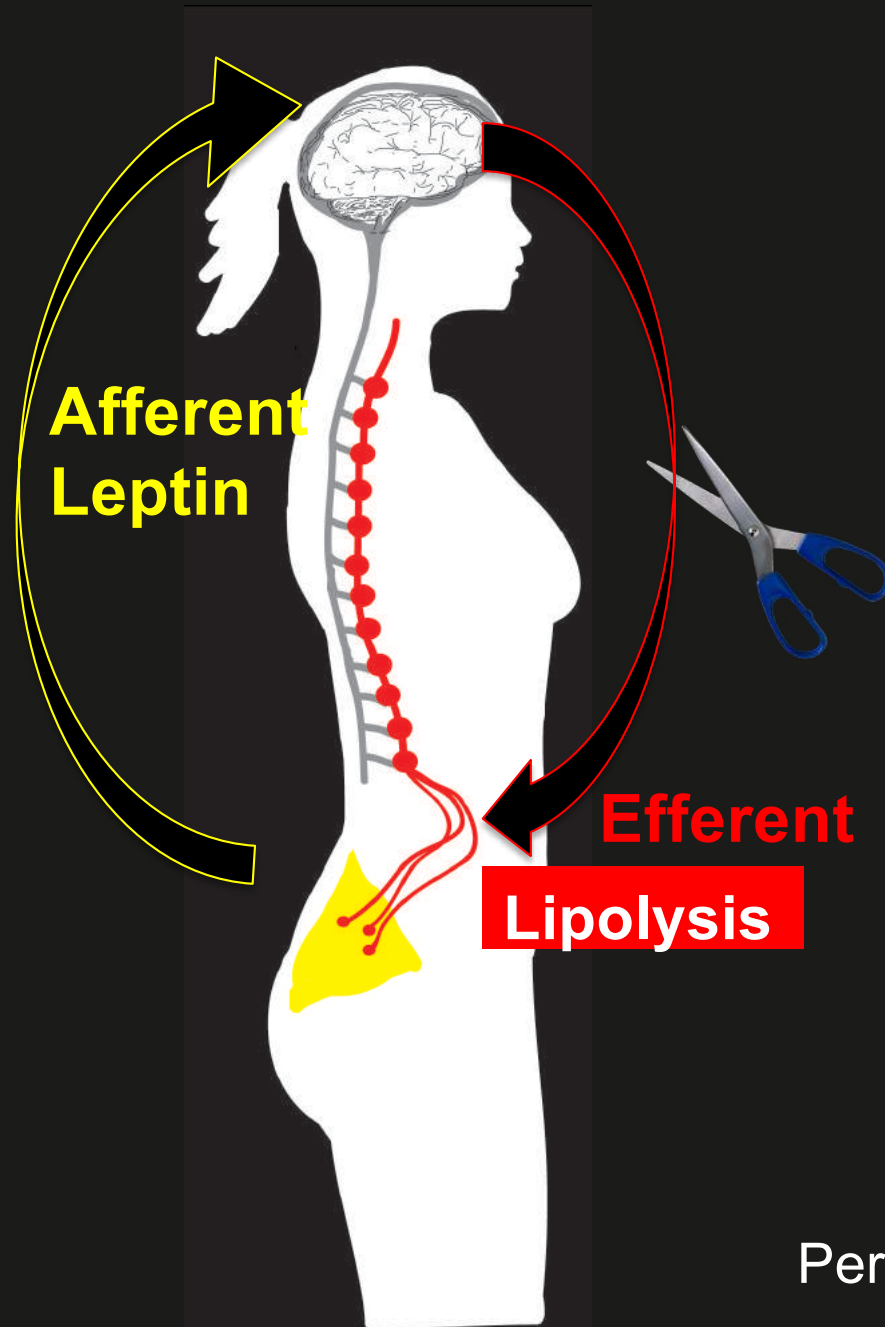
¹Program in Integrative Cell Signalling and Neurobiology of Metabolism, Section of Comparative Medicine, Yale University School of Medicine, New Haven, CT 06520, USA

*Correspondence: tamas.horvath@yale.edu
<http://dx.doi.org/10.1016/j.cell.2015.09.016>

Cell

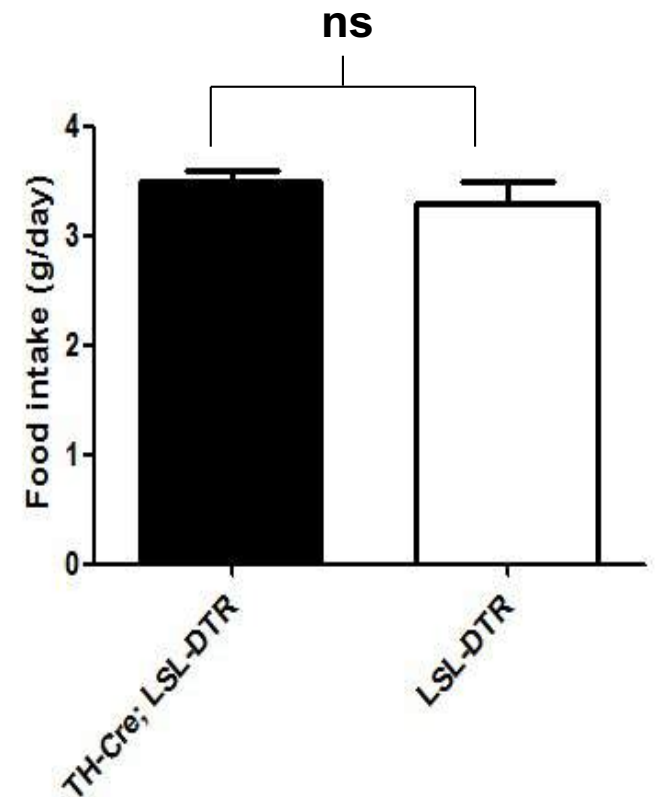
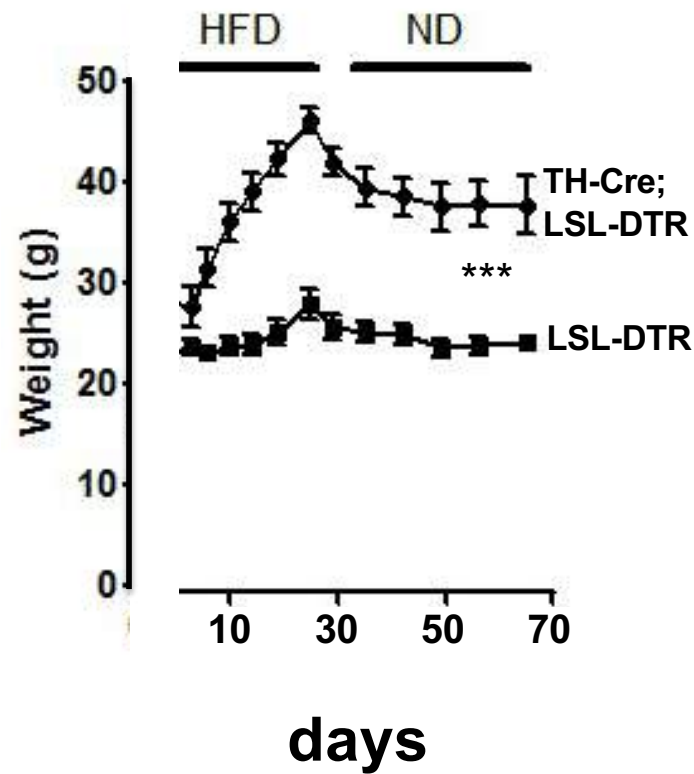
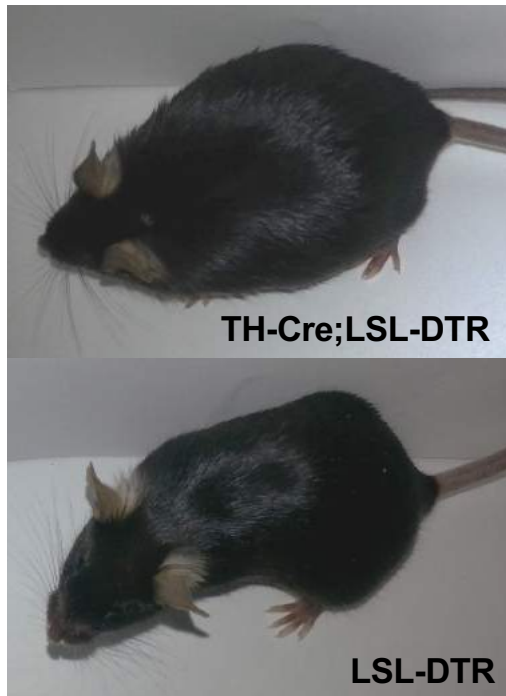
A closer look at the nerves that slim down your fat cells

Sympathetic Neuron-Adipose Connections Mediate Leptin-Driven Lipolysis



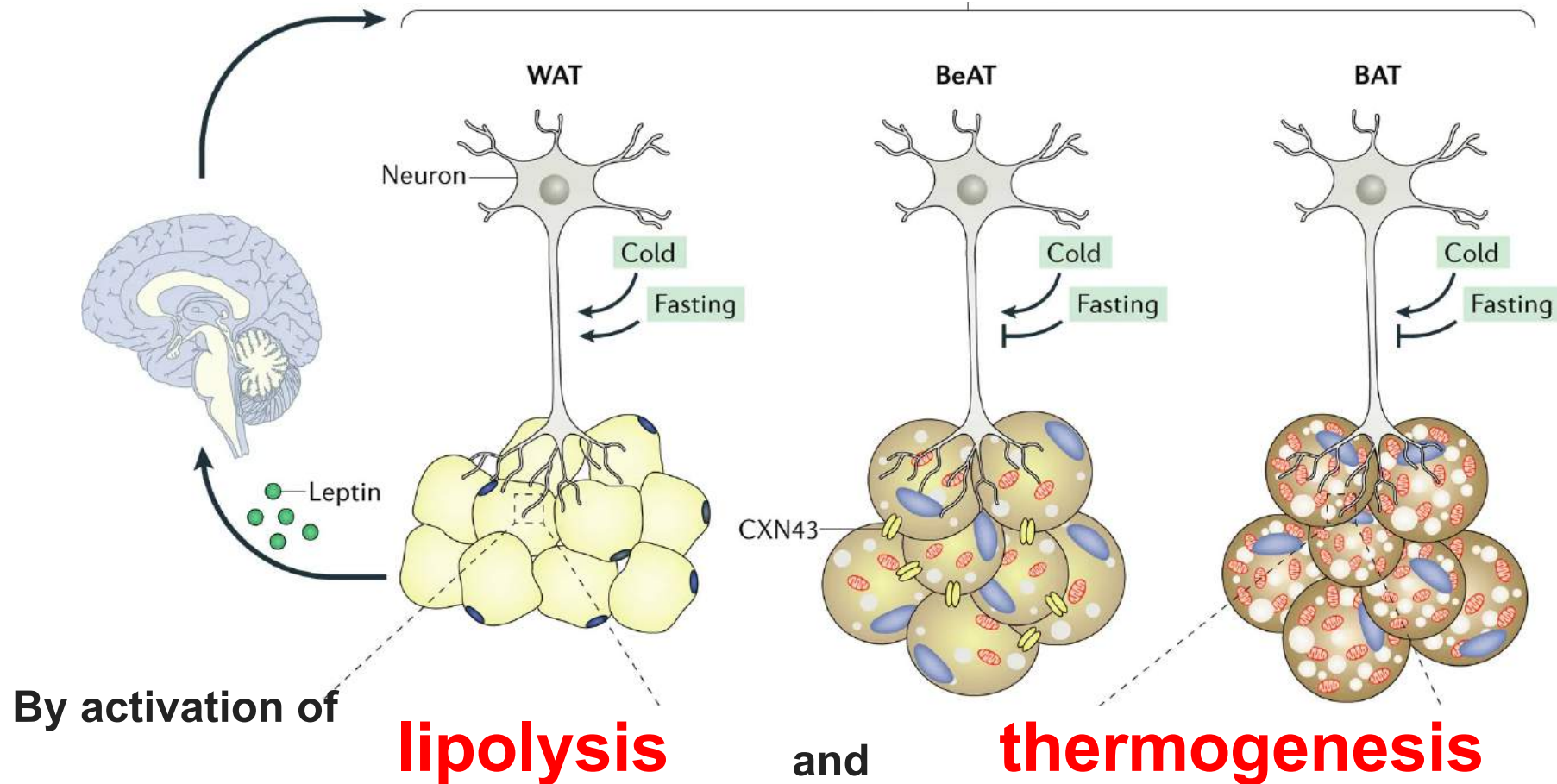
Zeng, Pirzgalska et al Domingos, *Cell*, 2015
Pereira, M et al Domingos, *Nature Comm*, 2017

Genetic sympathectomy mediates *fast & irreversible* obesity, independently of food intake



The Neuroendocrine Loop of Leptin action

Efferent Sympathetic axis

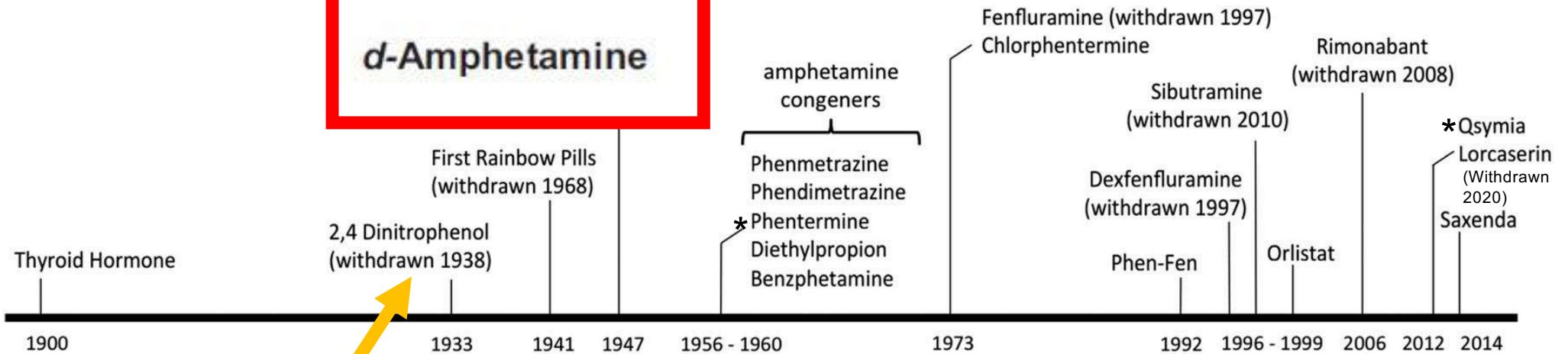
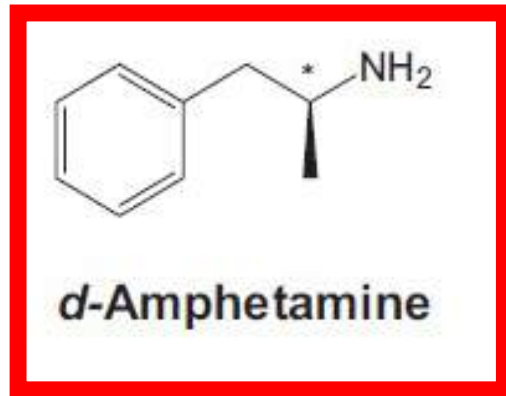


Zeng, Pirzalska et al Domingos, *Cell*, 2015
Pereira, et Al Domingos, *Nature Comm*, 2017

Caron, A. et al 2018 *Nature Reviews | Neuroscience*

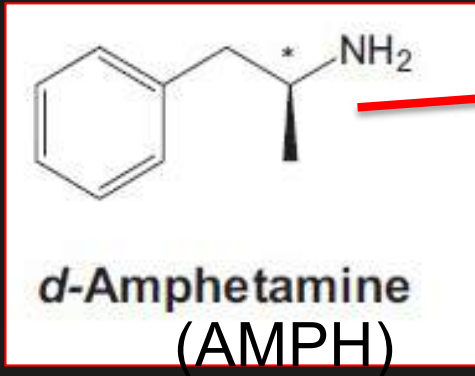
Legend:
WAT= white adipose tissue (AT). BAT=Brown AT. BeAT= Beige AT

Time line of pharmacotherapies used to treat obesity from 1900 until today.

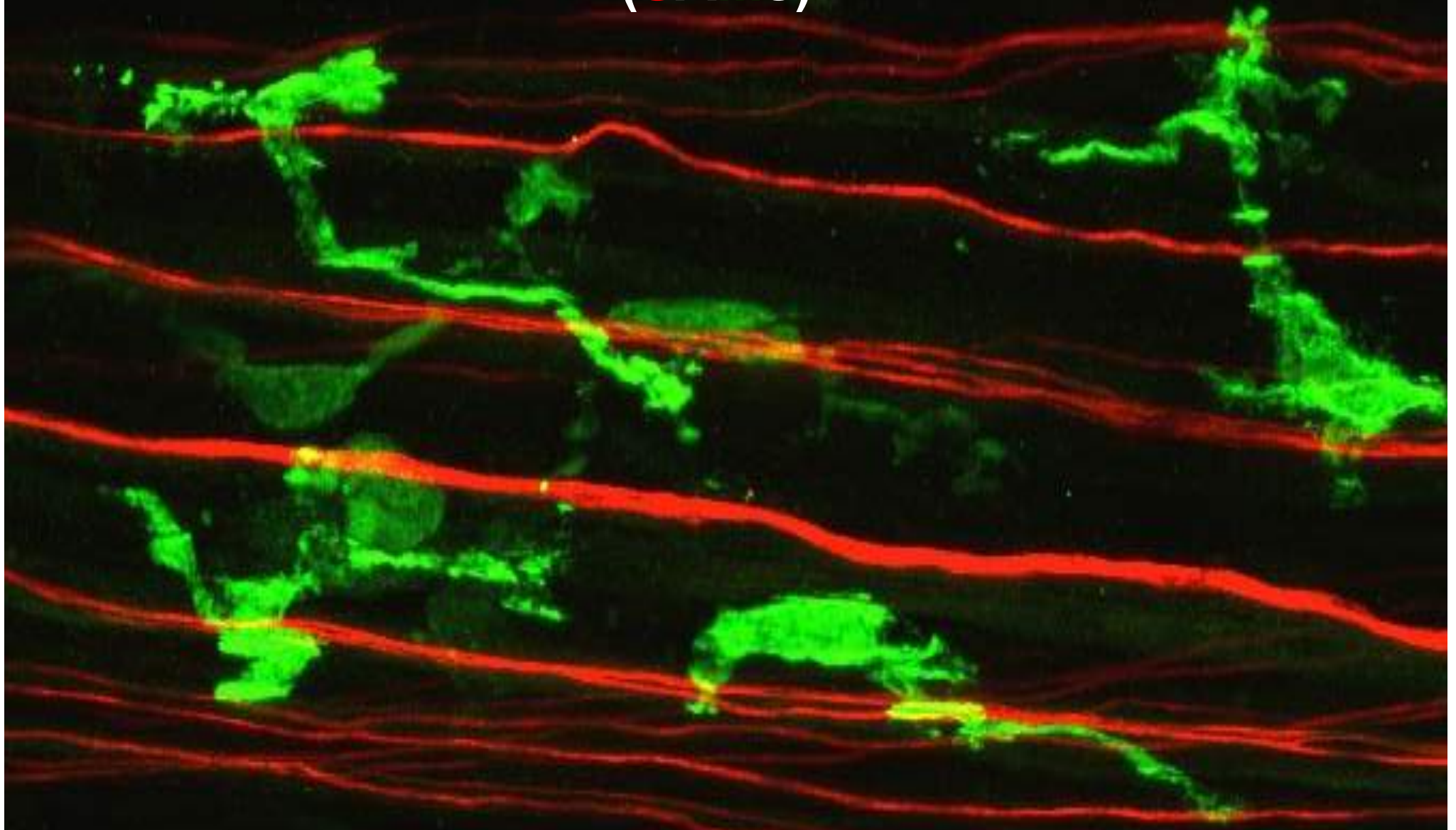


**Indirect
Sympathomimetics
Inhibit reuptake of
norepinephrine**





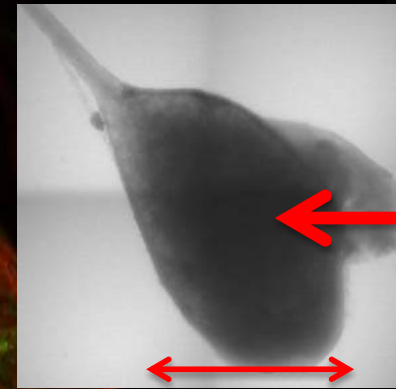
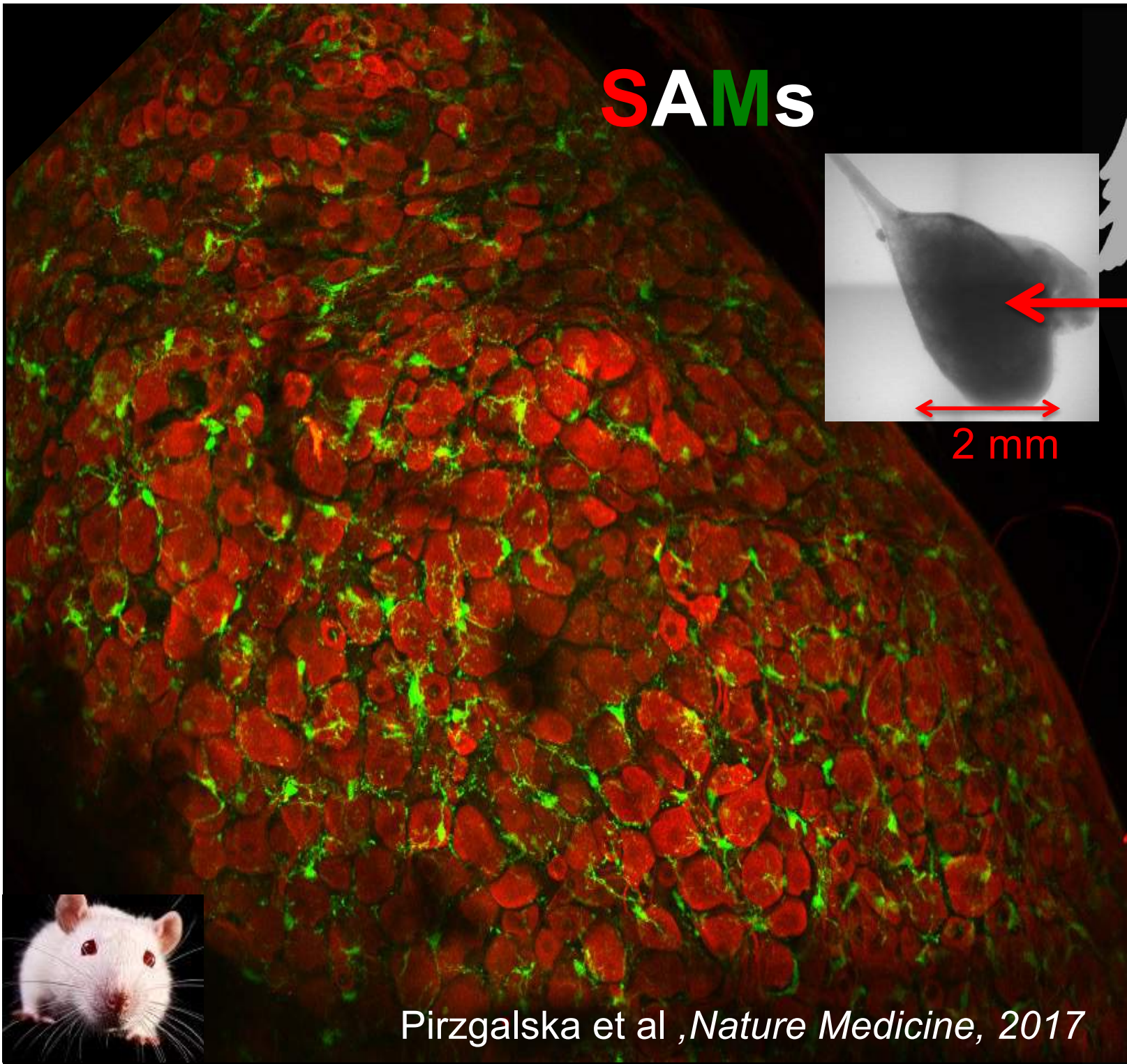
Sympathetic associated macrophages (SAMs)



Cx3cr1^{GFP/+} TH

Pirzgalska et al Domingos , *Nature Medicine*, 2017

SAMs

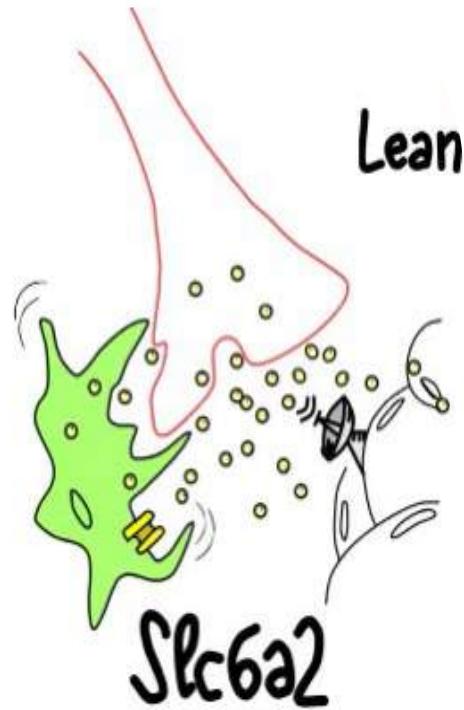


2 mm



Pirzgalska et al ,*Nature Medicine*, 2017

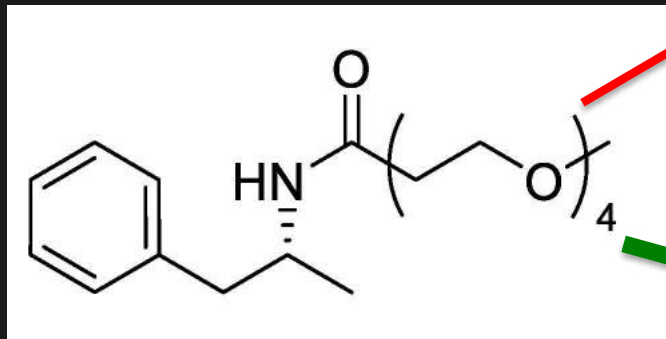
SAMs
contribute to
Obesity
By importing
And
metabolizing
norepinephrine



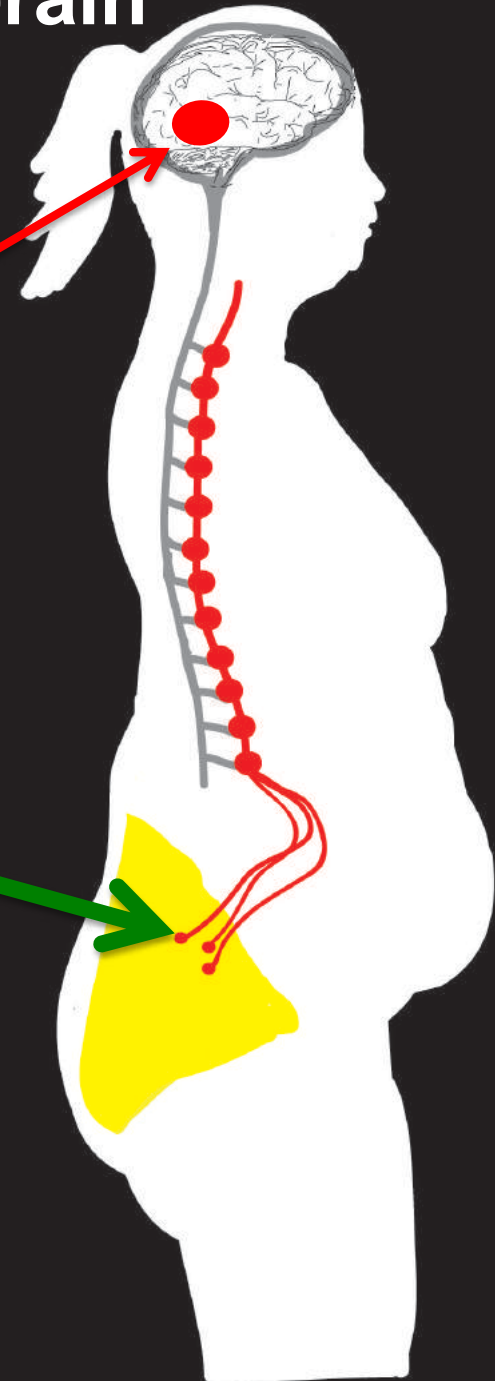
Slc6a2^{-/-}
Non-
neuronal



Chemically modify AMPH to avoid brain

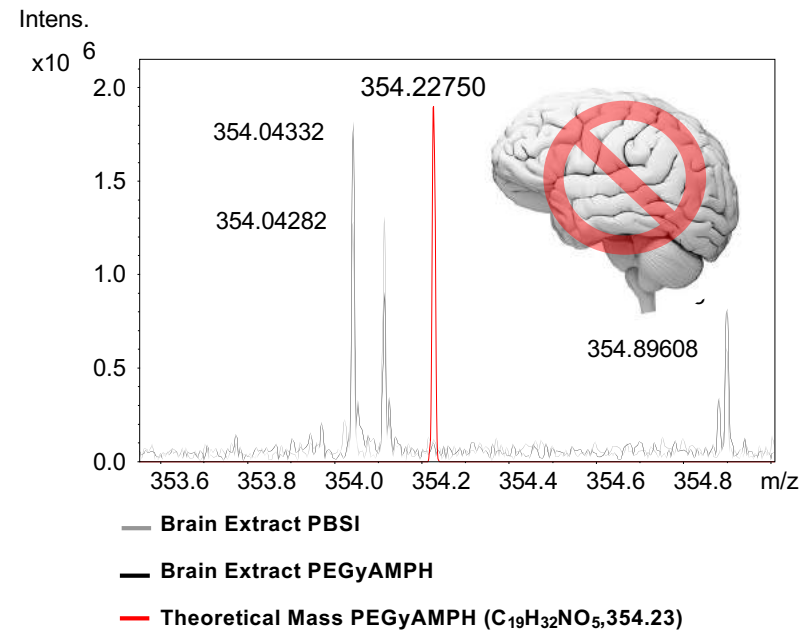
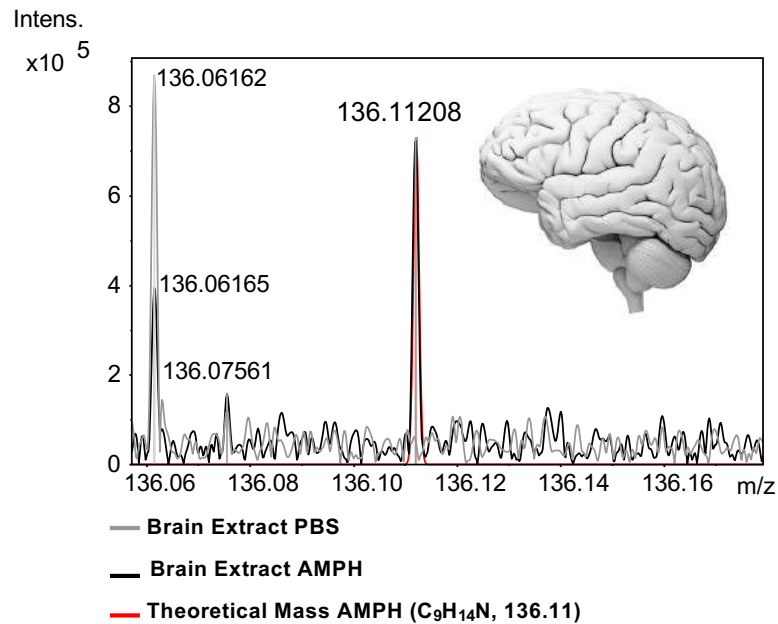
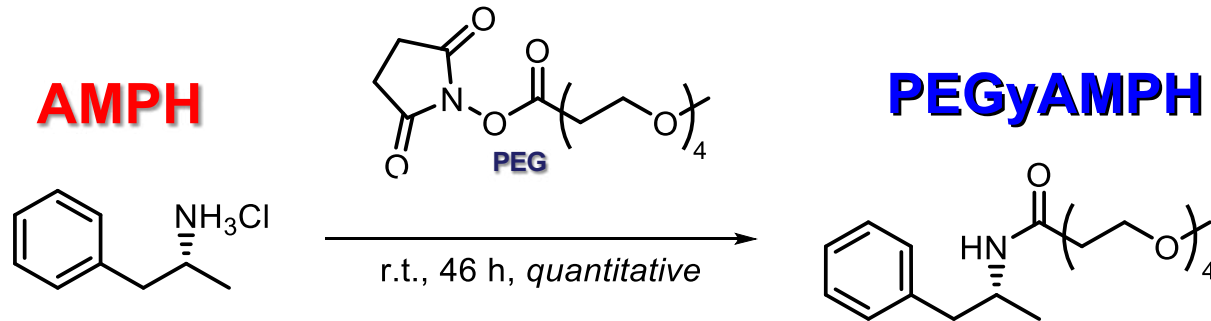


Gonçalo Bernardes,
Cambridge U.

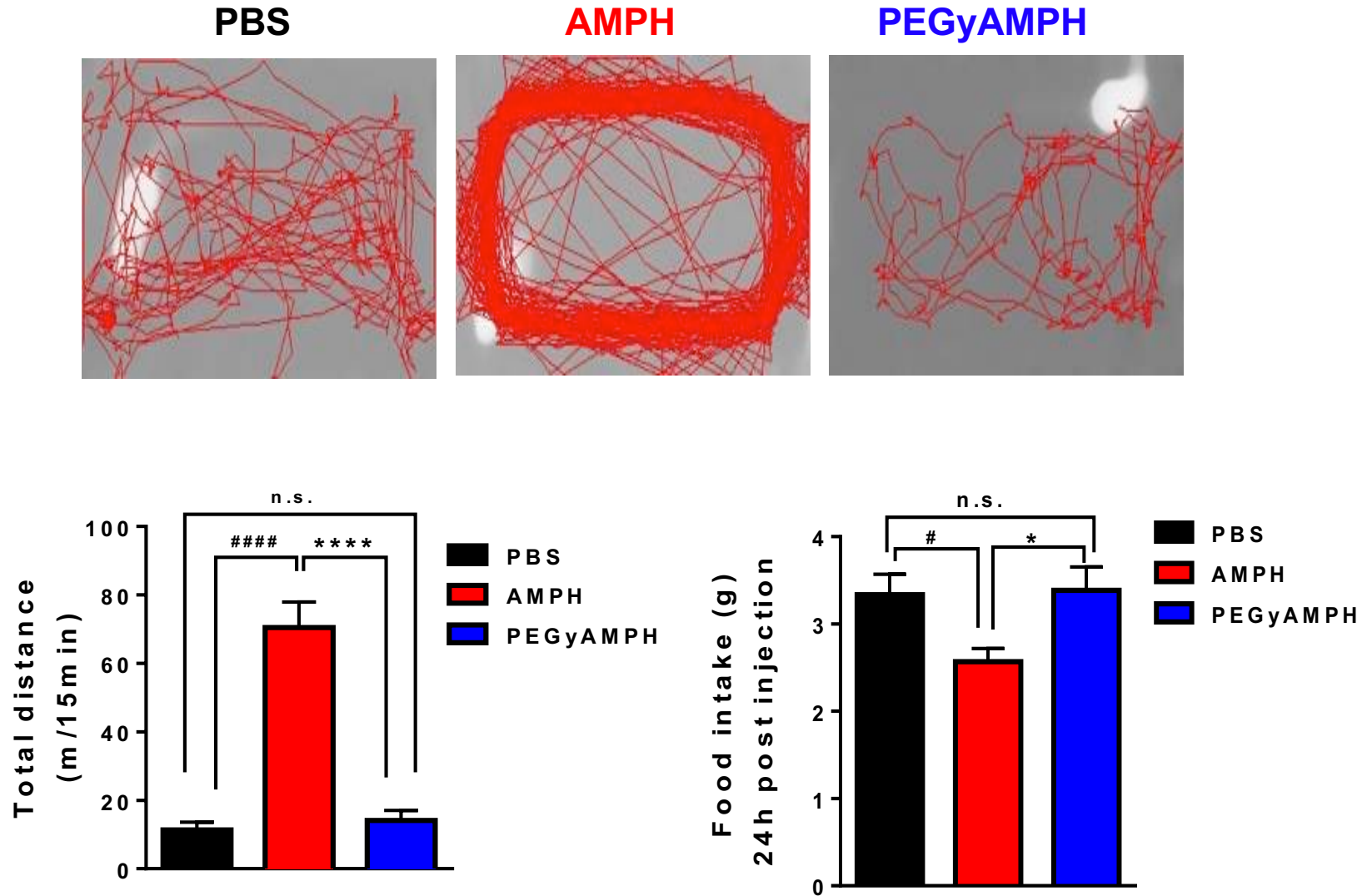


Mahu et al Domingos, Cell Metab 2020

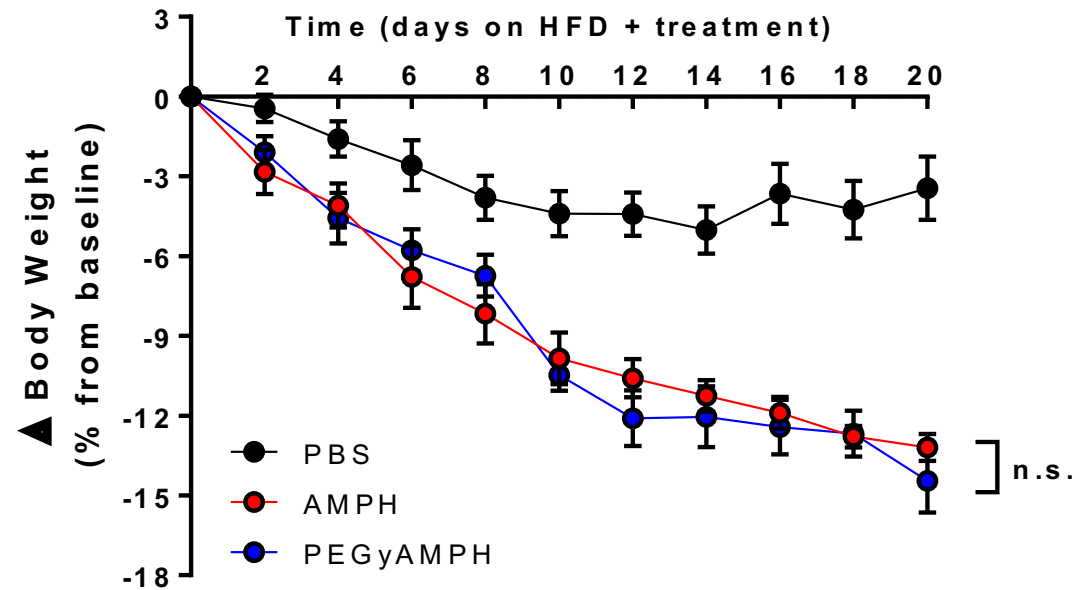
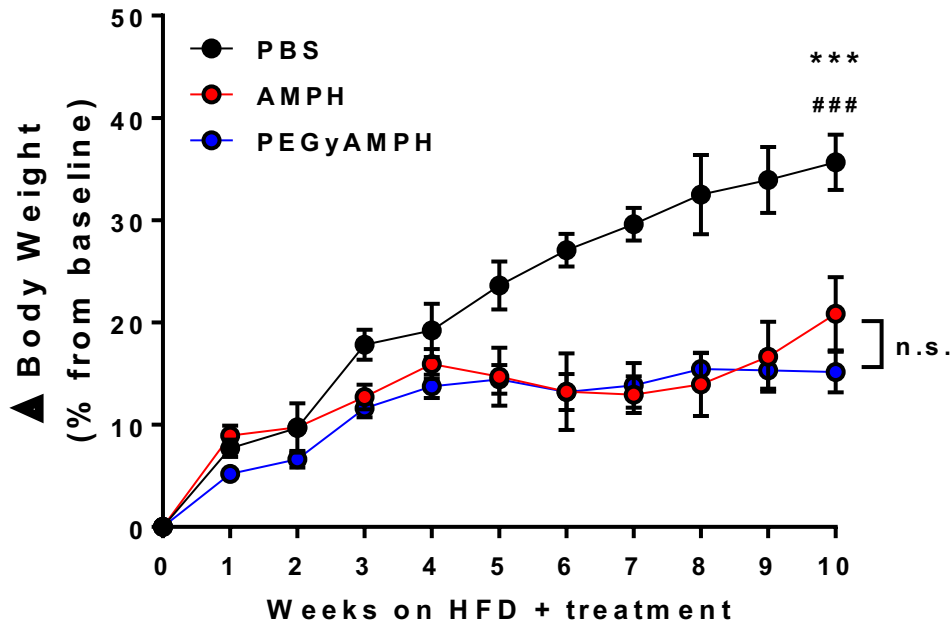
pegAMPH is brain-impermeable



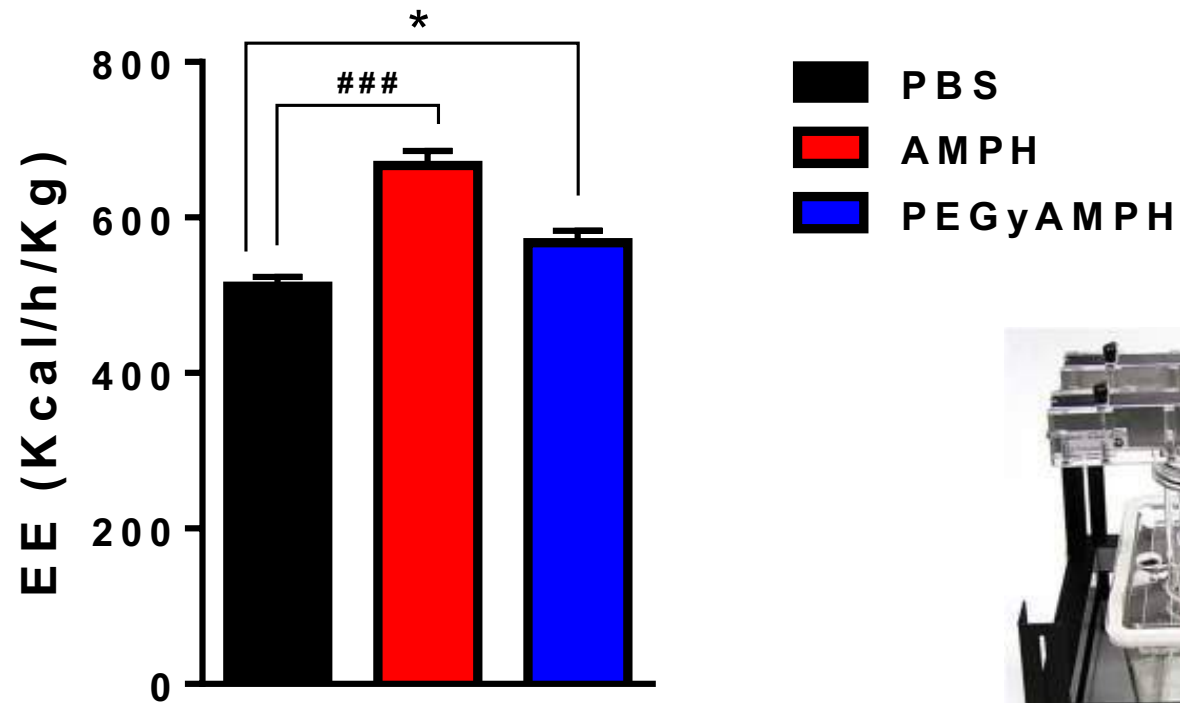
PegyAMPH does not induce hyperkinesia nor hypophagia



PEGy-AMPH defends against diet-induced obesity



PEGy-AMPH increases Energy Expenditure (EE)

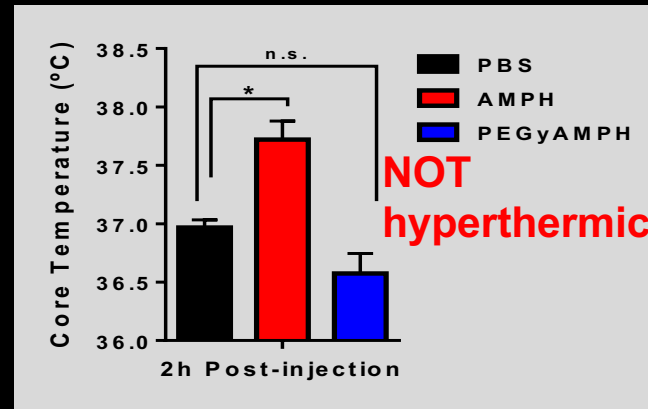
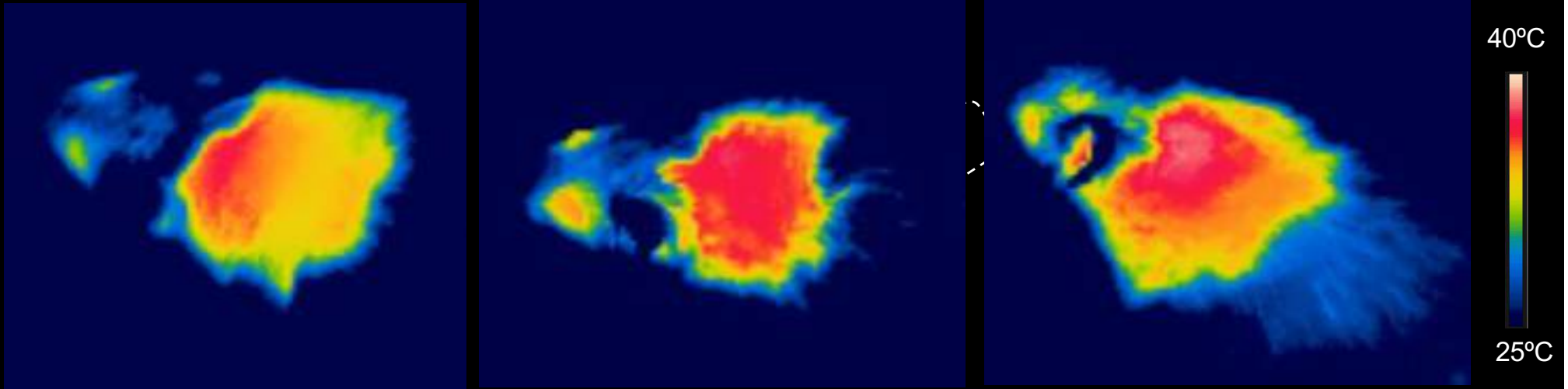


PEGy-AMPH increases thermogenesis

control

AMPH

PEGyAMPH



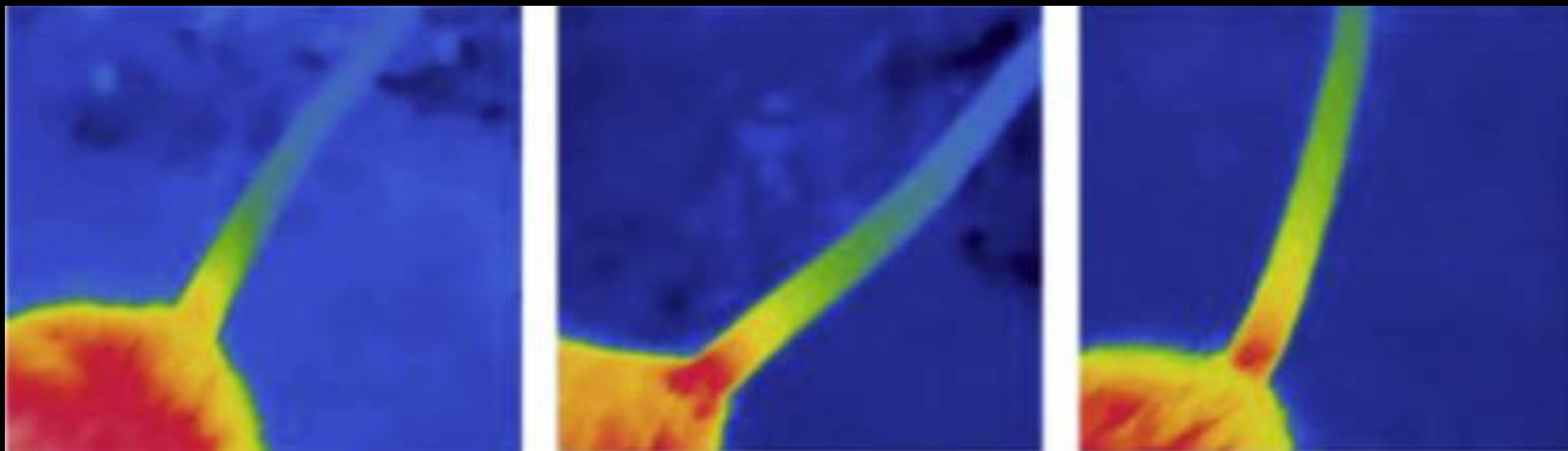
PEGy-AMPH increases thermal dissipation and prevents hyperthermia

control

AMPH

PEGyAMPH

35°C

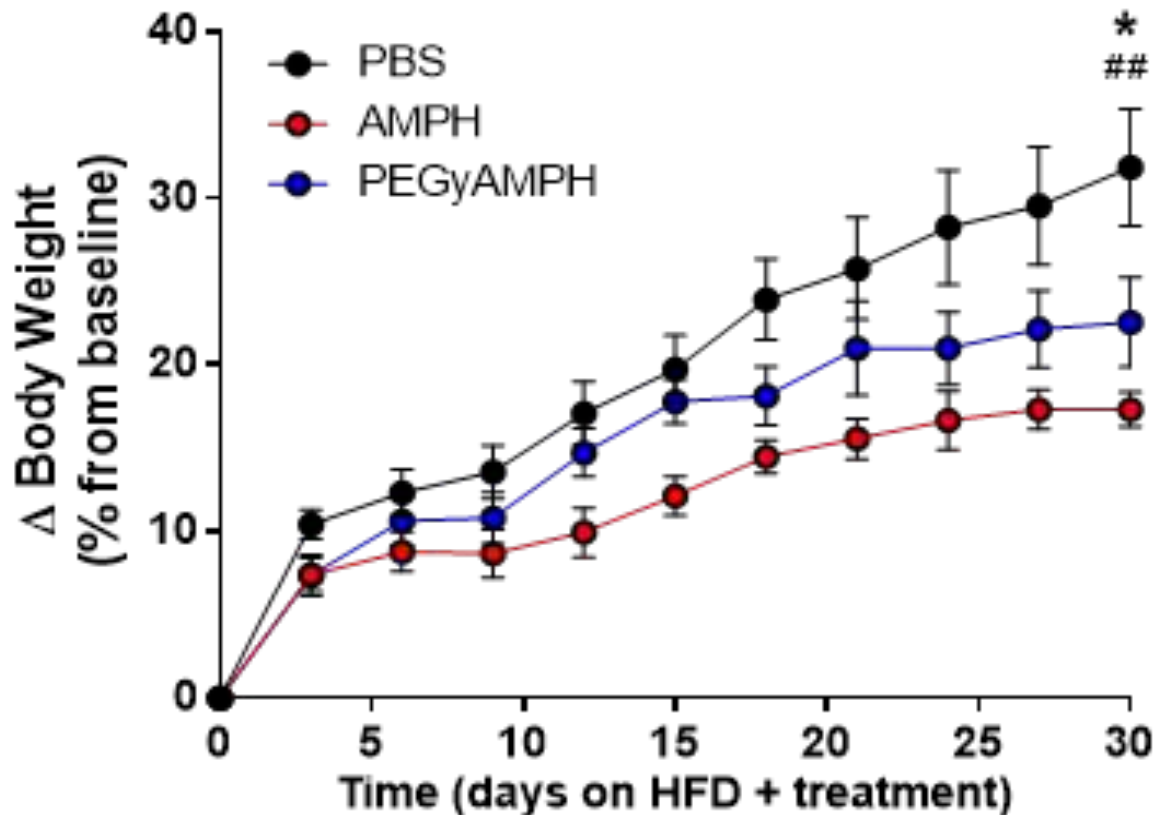


19°C

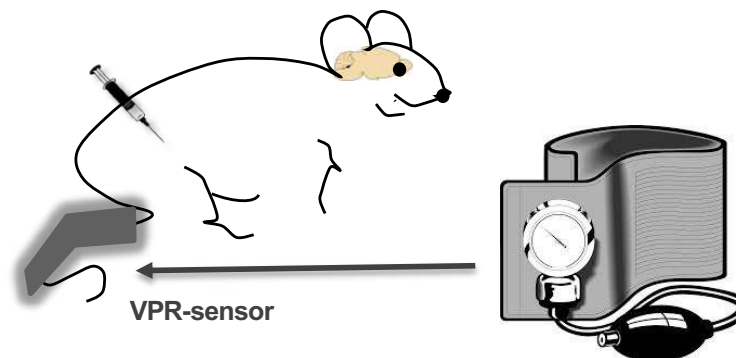
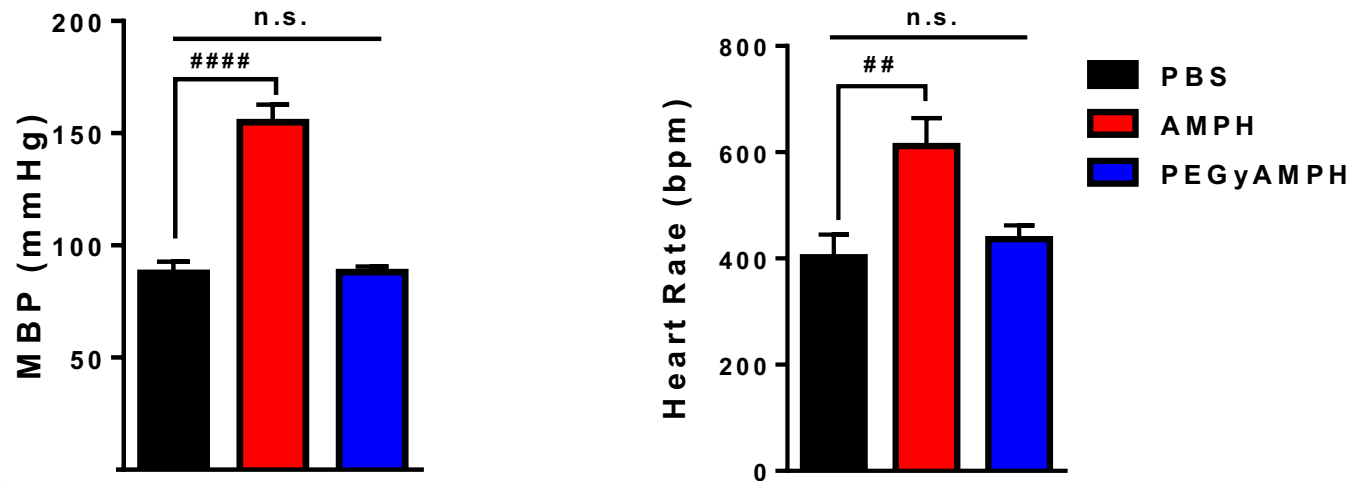


PEGy-AMPH mitigates obesity via thermogenesis coupled to heat dissipation

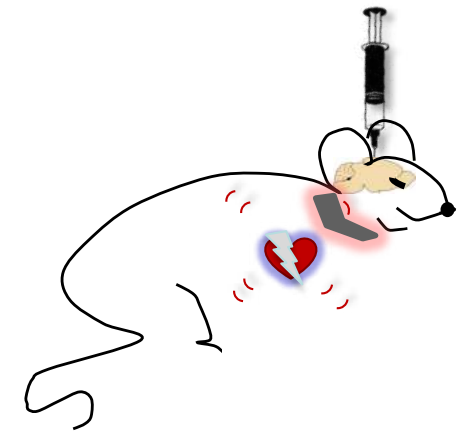
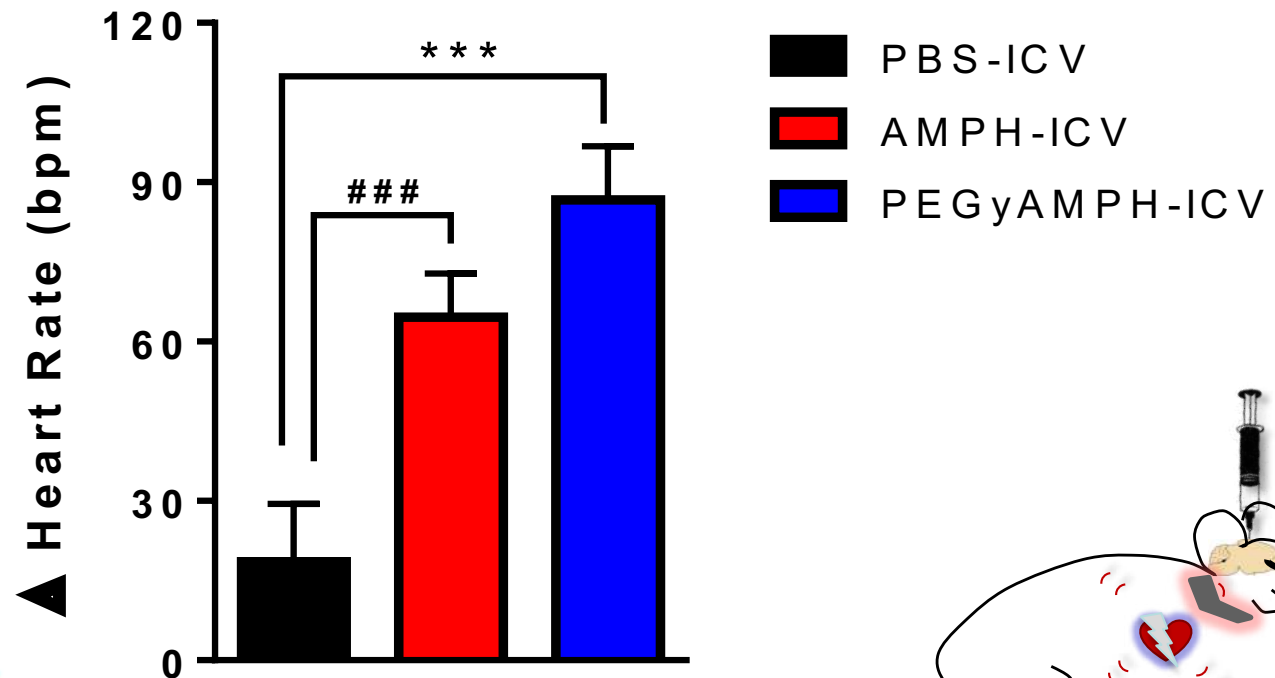
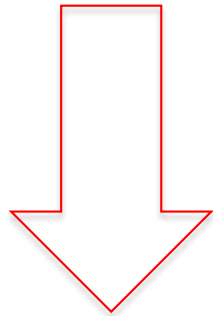
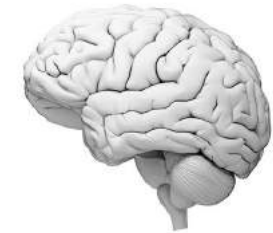
attenuation at thermoneutral temperature (32dgr)



PEGyAMPH does not trigger cardiac side effects (= Blood pressure & = Heart rate)



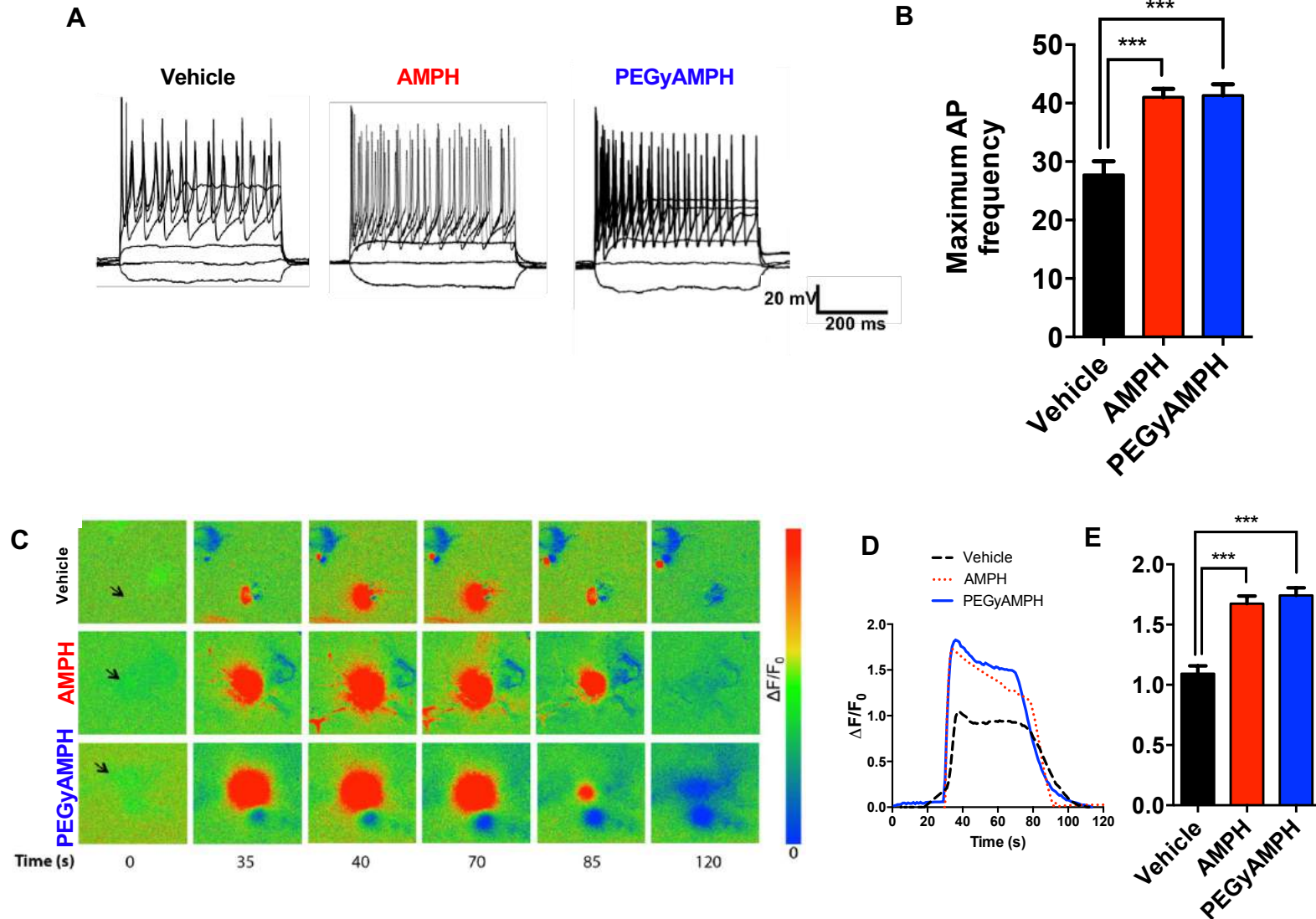
Direct delivery to the brain triggers cardiac side effects



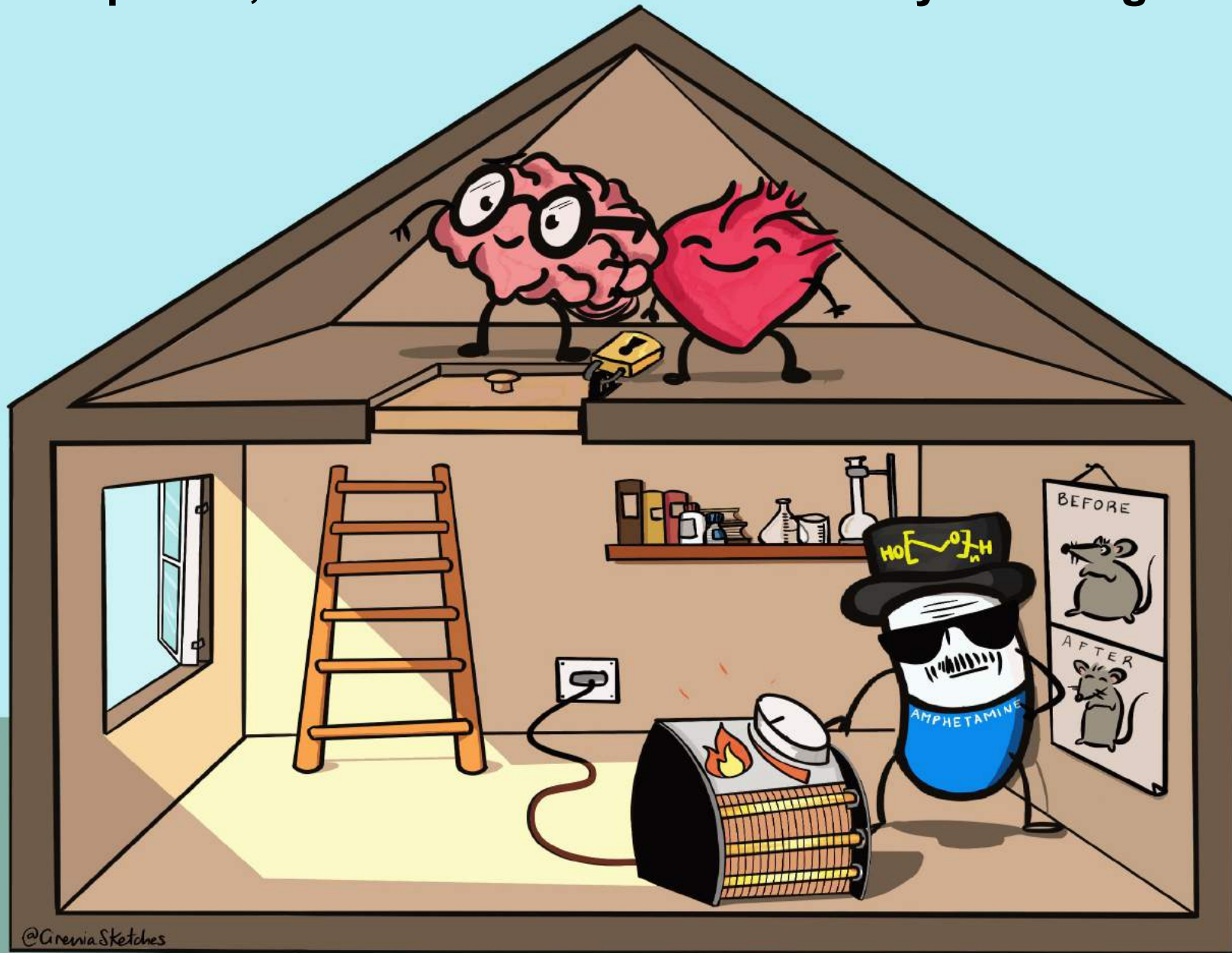
Mahu et al Domingos, *Cell Metab* 2020

Hassan J. *Neurosci* 2015 ; Liu, J. *Cardiovas Pharm* 1996

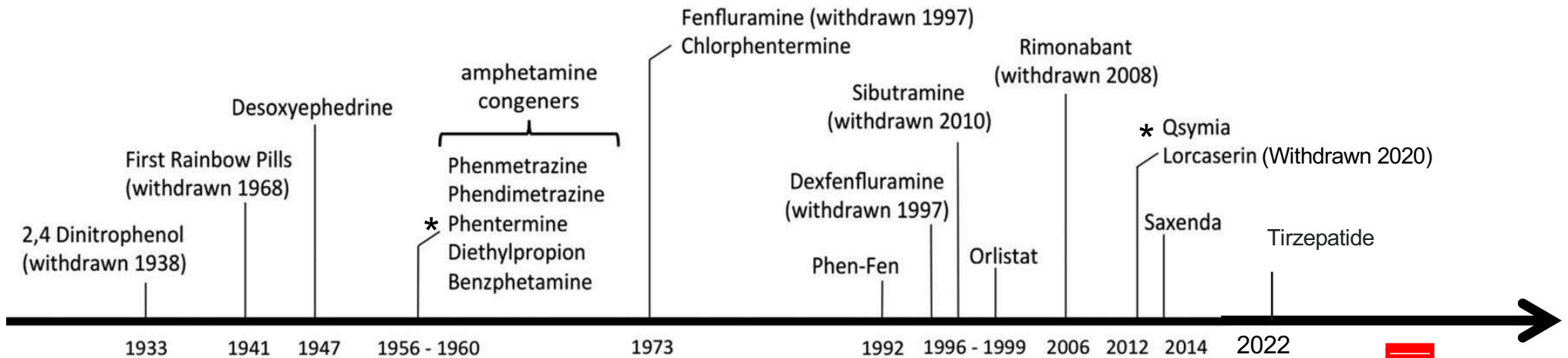
PEGy-AMPH facilitates SNS activity



A new class of **anti-obesity drugs** that couple thermogenesis to heat dissipation, and that are **cardio-neutral** by avoiding the **brain**

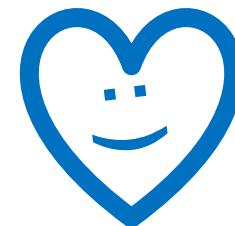


Time line of pharmacotherapies used to treat obesity: the future



**Indirect
Sympathomimetics**
Inhibit reuptake of
norepinephrine

Sympathofacilitators



Prohibiting *Sympathomimetics* does not block its use when the safe alternatives are too expensive



A descriptive study of adverse events from **clenbuterol** misuse and abuse for weight loss and bodybuilding.

Spiller HA, James KJ, Scholzen S, Borys DJ.

Subst Abus. 2013;34(3):306-12. doi: 10.1080/08897077.2013.772083.

PMID: 23844963

BACKGROUND: **Clenbuterol** is a beta2-agonist approved in the United States for veterinary use in nonfood animals. ...CASES: This was a retrospective chart review of **clenbuterol** exposures reported to 2 poison control centers. Misuse of **clenbuterol** for weight los ...



Clenbuterol (Clen): Cutting done right ...
clinicalschizophrenia.org



Clenbuterol for weight loss ...
cheapearplugstore.com



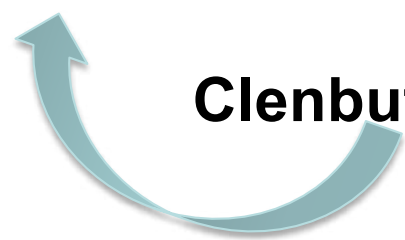
Clenbuterol for Bodybuilding and Weight ...
celebrateproductions.net



lacedc0rsets — Clenbuterol for weight ...
lacedc0rsets.tumblr.com



CLEN Fat Loss | Benefits and Side ...
youtube.com



Clenbuterol = ADRb2 agonist
=direct
Sympathomimetic

Screen-print of Google
Images
By Searching
"Clenbuterol"

KEYSTONE SYMPOSIA

NeuroImmunoMetabolism

Obesity at the crossroads between

NeuroImmunity and ImmunoMetabolism

Organizer: Ana Domingos

Co-organizer: Alan Saltiel

Beaver Run Resort, Breckenridge,
Colorado, USA

October 7th -11th , 2022



Ana Domingos, PhD

Editor in Chief, *AJP-Endocrinology and Metabolism*



average time to
first decision

average time to
PUBLICATION



2.0
months



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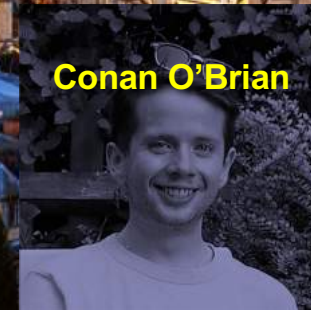
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