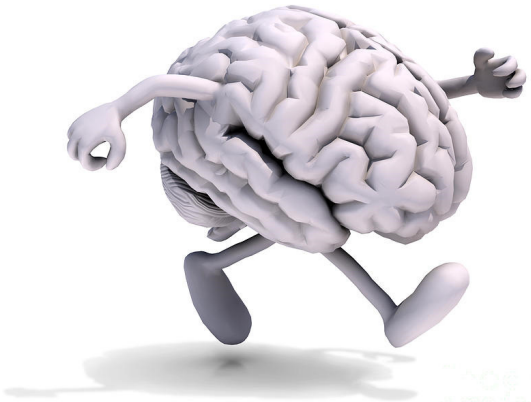
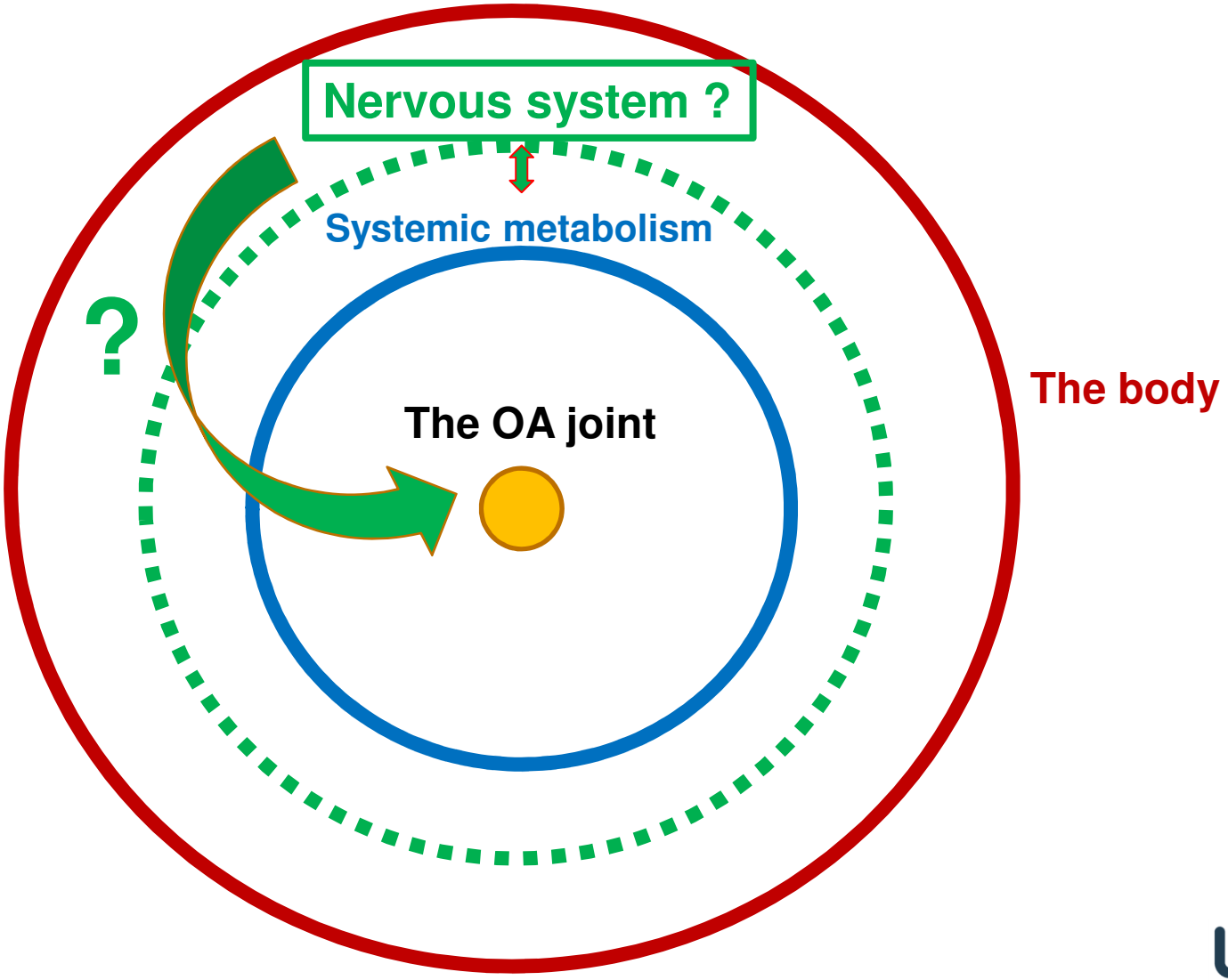
How can disturbances of the nervous system translate in OA phenotypes ?

Francis BERENBAUM

University Pierre & Marie Curie, INSERM UMRS_938 and AP-HP hôpital Saint-Antoine, Paris, France



AN INTEGRATIVE VIEW OF OA PATHOPHYSIOLOGY

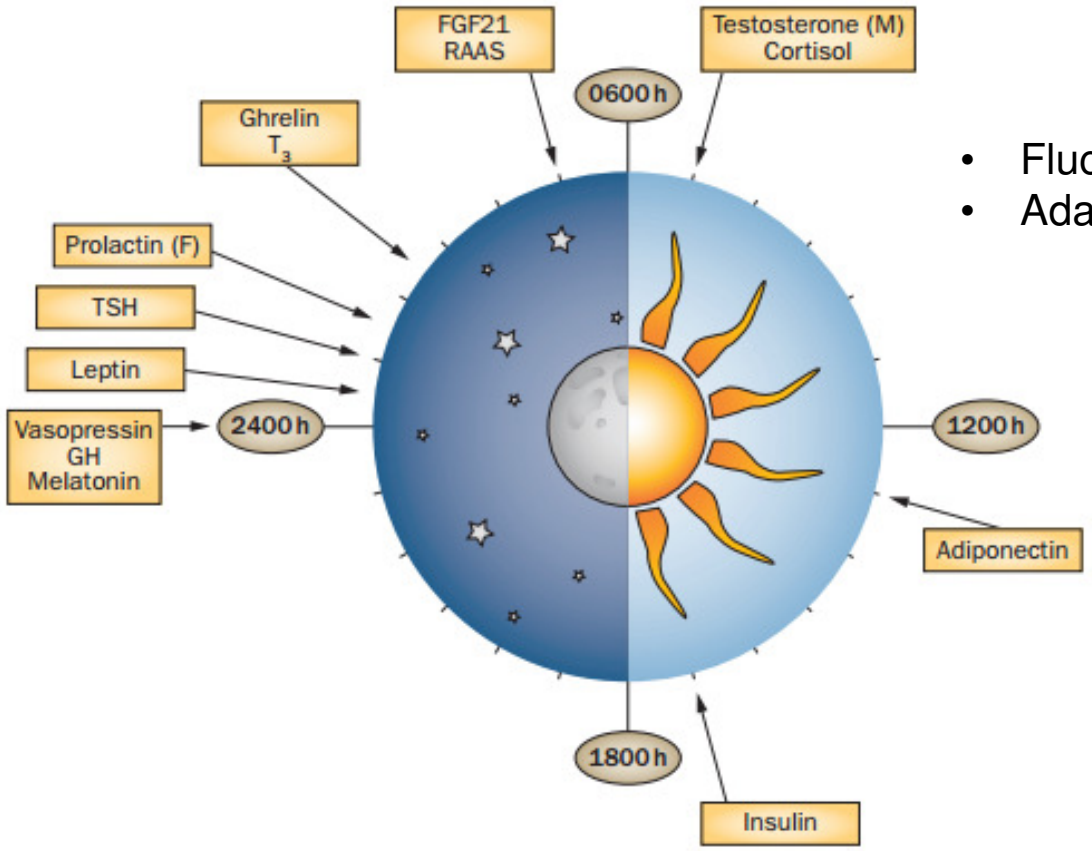


Inserm
Institut national
de la santé et de la recherche médicale

UPMC
SORBONNE UNIVERSITÉS

In the nervous system, which parts are devoted to communication between brain and periphery ?

The time of day at which circulating levels of key endocrine factors peak in humans



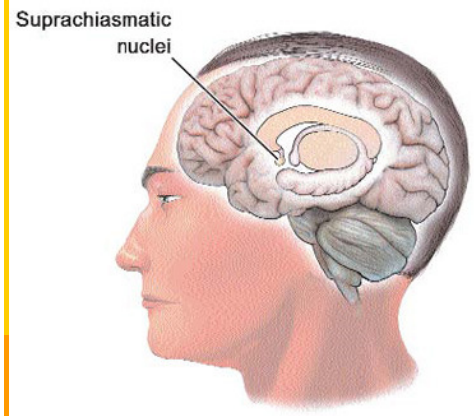
- Fluctuations over the course of the day
- Adaptation to stress

Gamble et al. Nature Rev Endoc 2014

Inserm
Institut national de la santé et de la recherche médicale

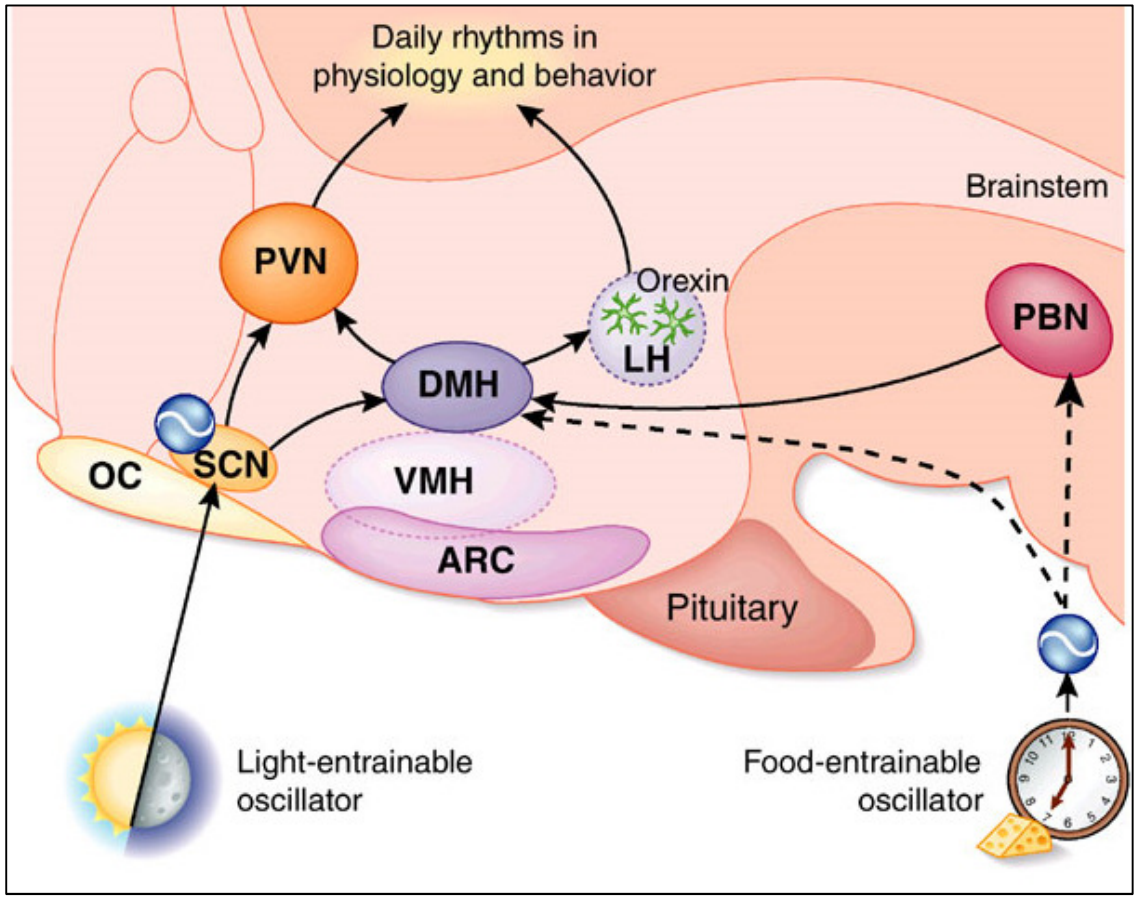
UPMC SORBONNE UNIVERSITÉS

CIRCADIAN PACEMAKER: THE SUPRACHIASMATIC NUCLEUS



Cermakian & Sassone-Corsi Nature Reviews Mol Cell Biol 2000

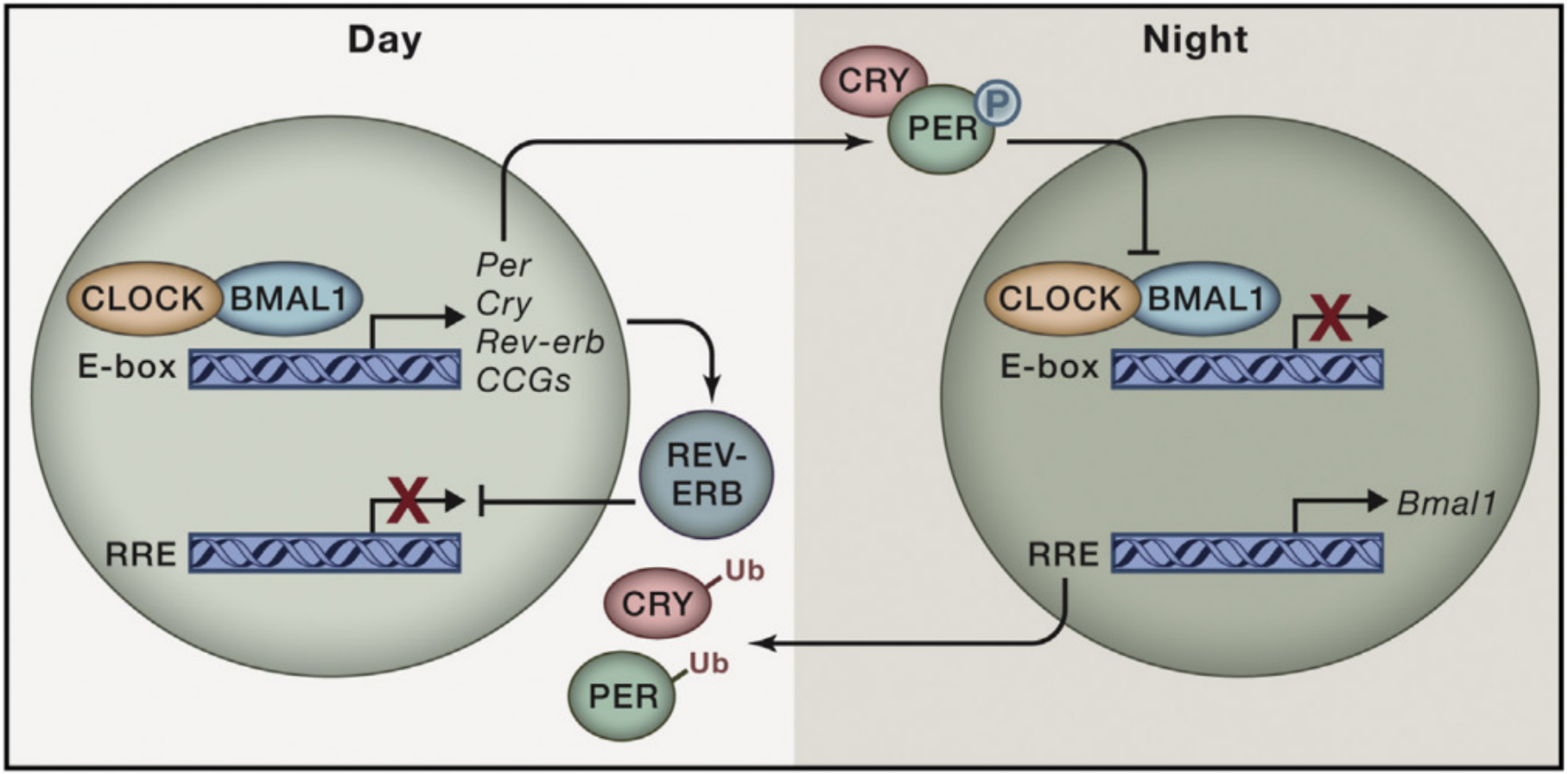
BRAIN OSCILLATORS



- Synchronization of circadian clock by daylight/dark signals and food
- Regulation of daily rhythms (hormones secretion, body temperature, locomotion)

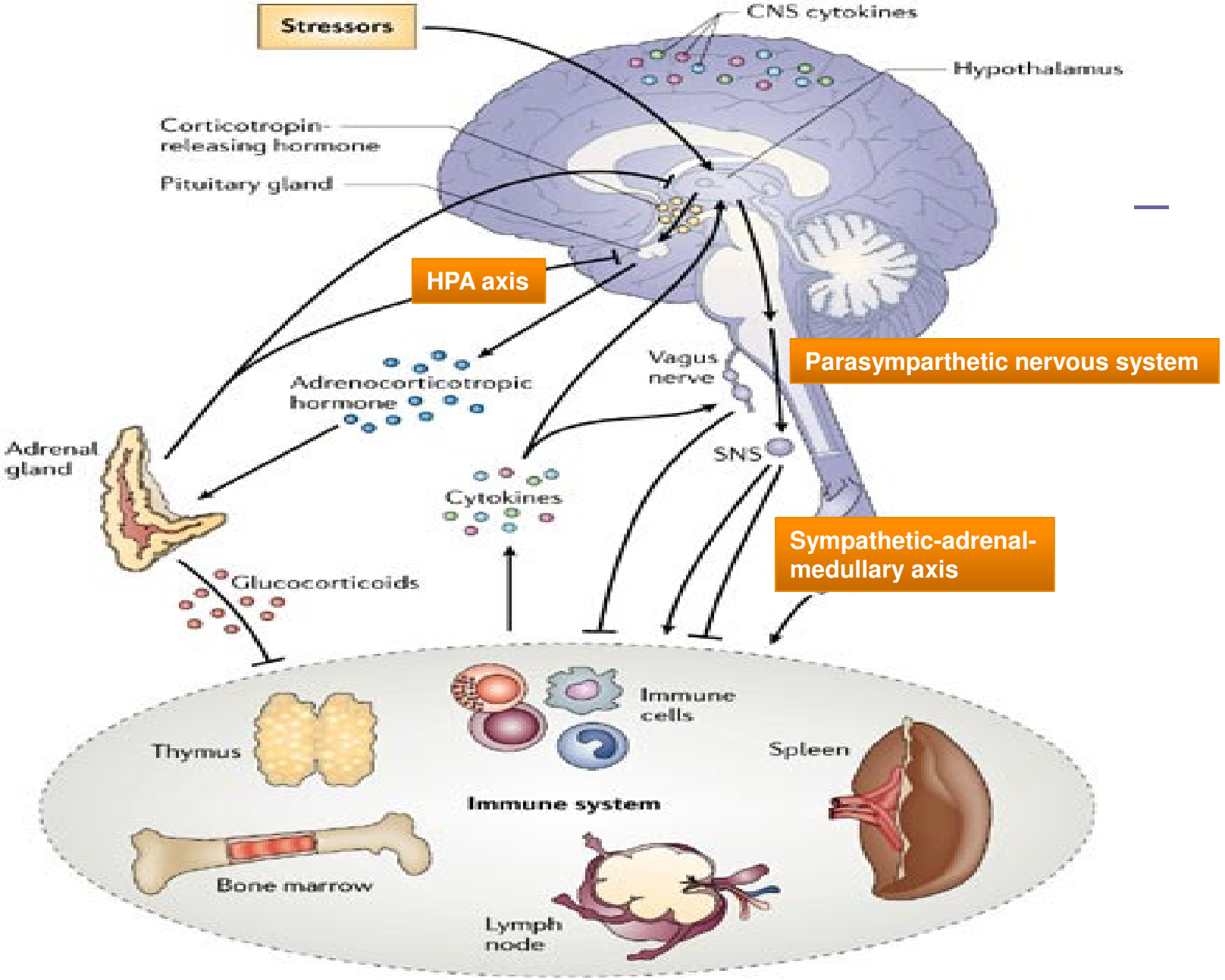
Herzog & Muglia 2006. Nature Rev Neurosc

The Molecular Organization of the Circadian Clock



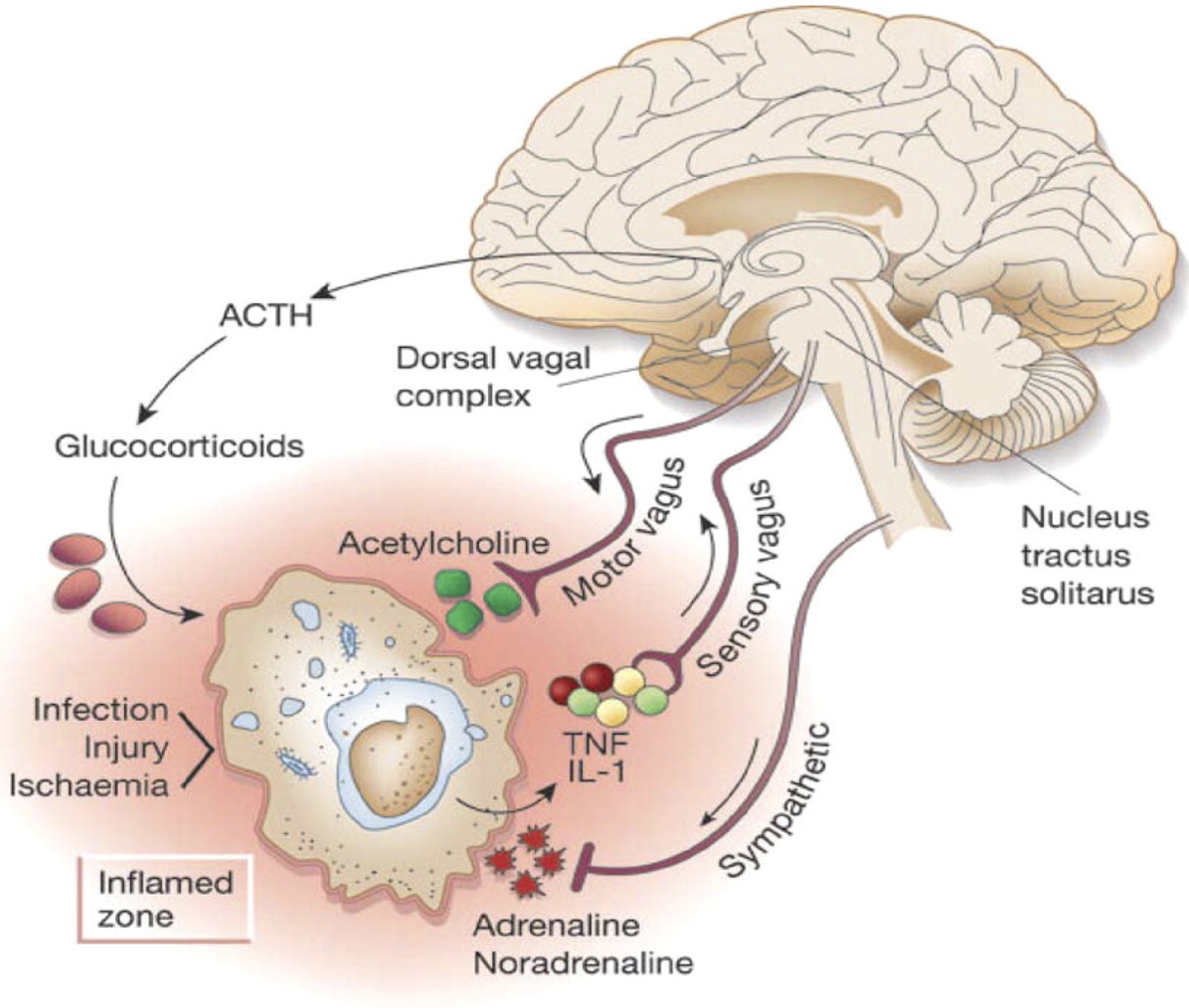
(Autoregulatory feedback loop)

Asher & Sassone-Corsi, Cell 2015



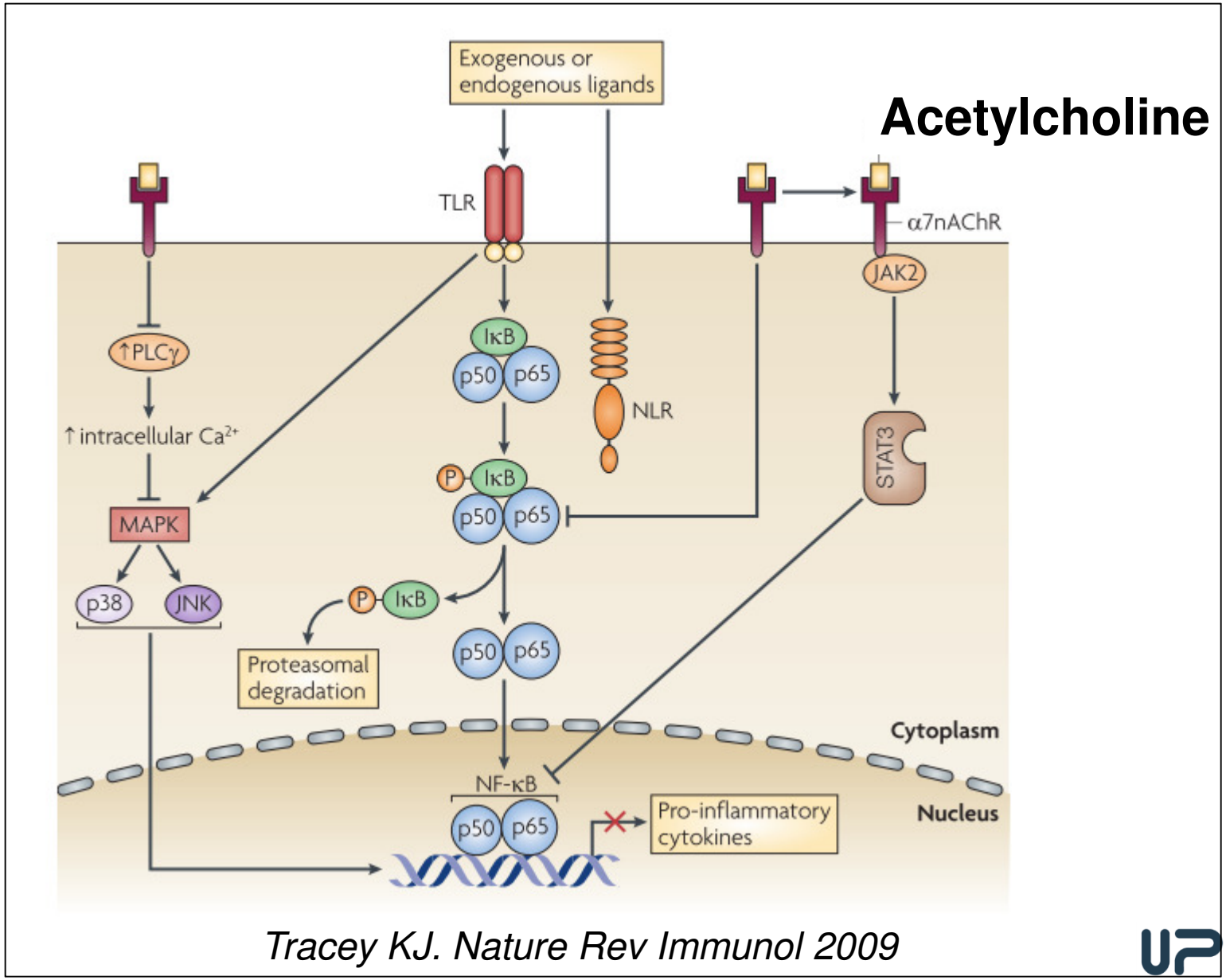
Sternberg. Nature Rev Immunol 2006

The Inflammatory reflex



Abboud FM. Am J Physiol Regul Integr Comp Physiol 2010

the cholinergic anti-inflammatory pathway



Tracey KJ. Nature Rev Immunol 2009

Inserm
Institut national de la santé et de la recherche médicale

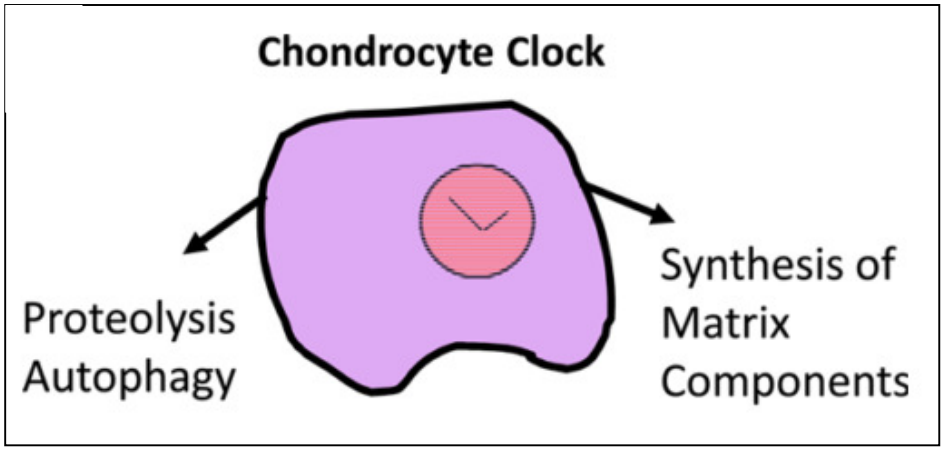
UPMC SORBONNE UNIVERSITÉS

How could the NS influence the OA process *directly* ?

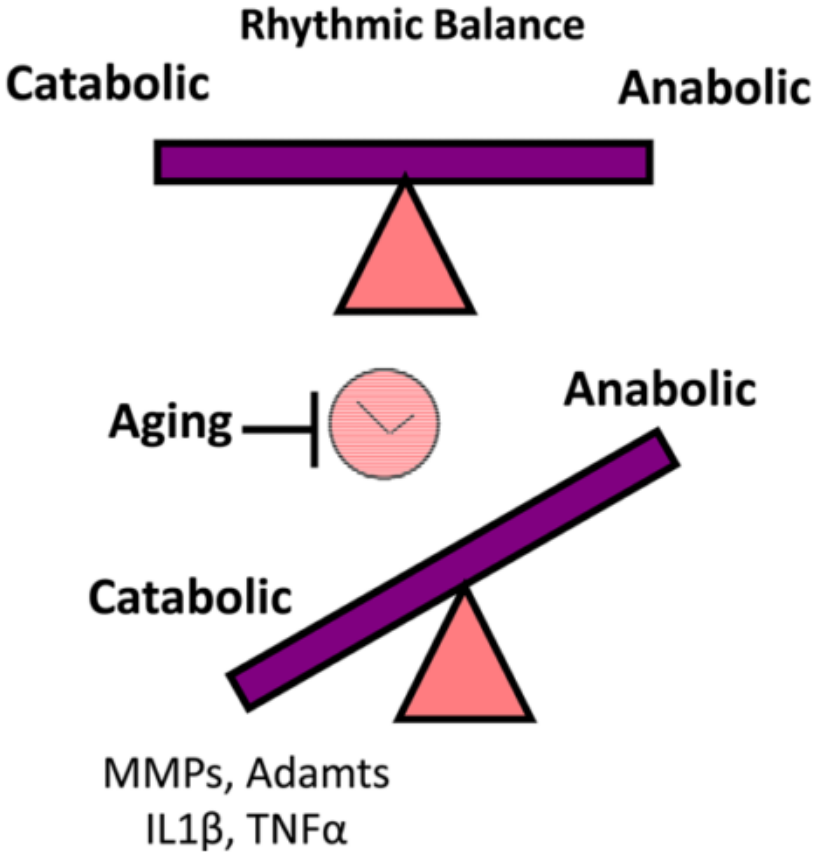
Inserm
Institut national
de la santé et de la recherche médicale

UPMC
SORBONNE UNIVERSITÉS

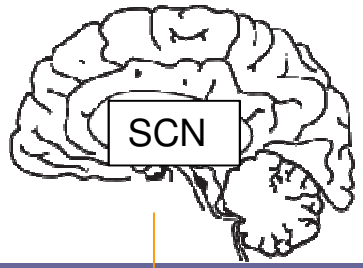
Desynchronization of chondrocyte clocks



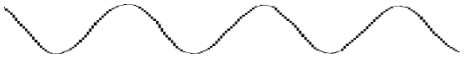
(Period close to 24h)

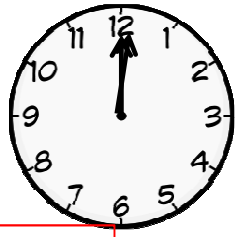


Gossan et al. Biogerontology 2014



Circadian release of hormones and neuromediators





Insulin
Adipokines

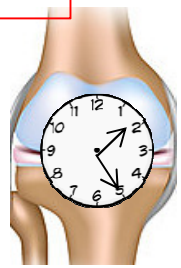
Locomotor activity

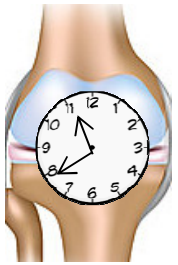
Masterclock deregulation with Met S

Masterclock deregulation with aging

Masterclock Deregulation with mechanical stress

Clock-controlled genes



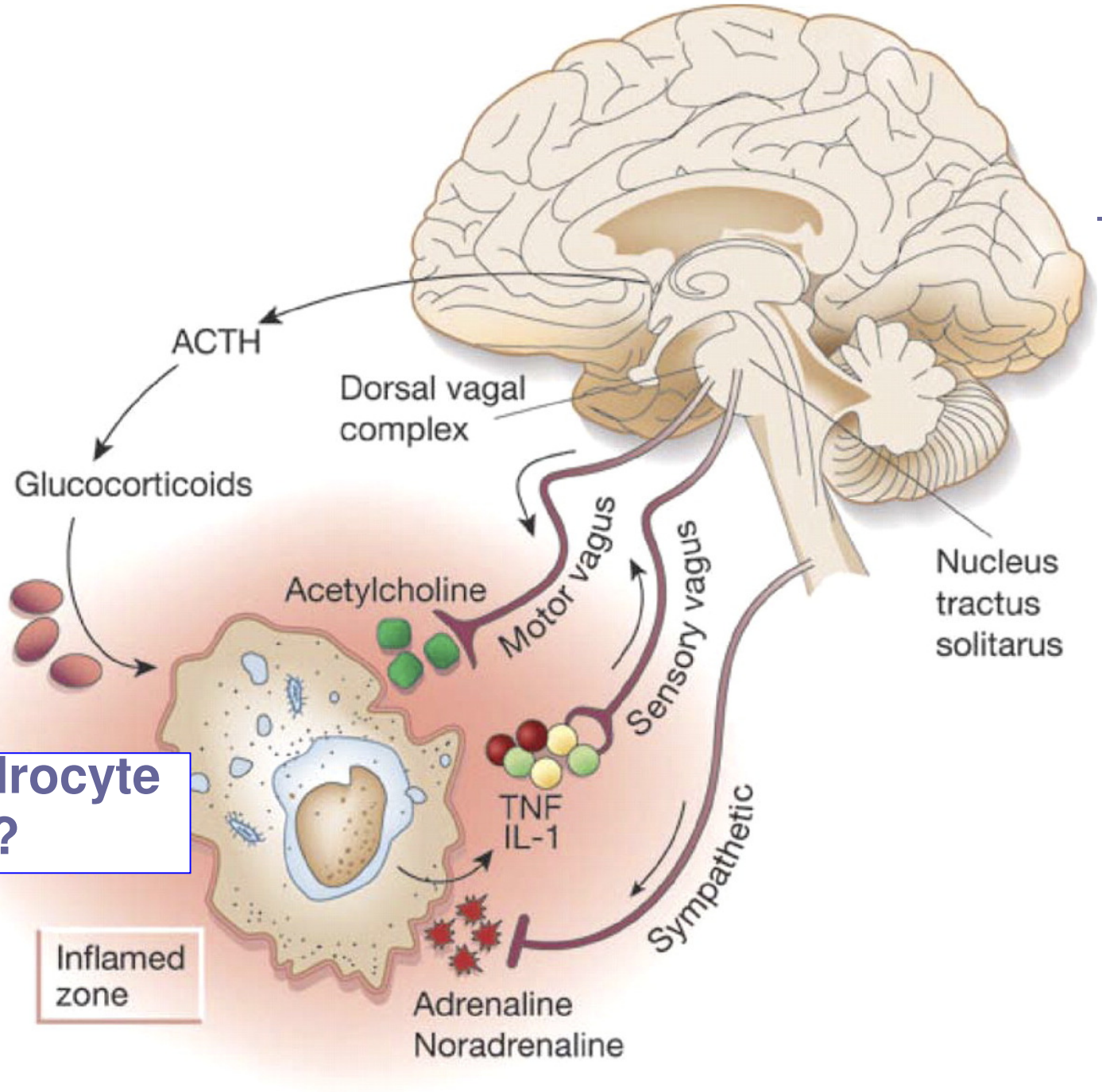


Metabolic OA **Aging OA** **Post-trauma OA**

Inserm
Institut national de la santé et de la recherche médicale

Berenbaum F. Arthritis Rheum 2013

UPMC SORBONNE UNIVERSITÉS



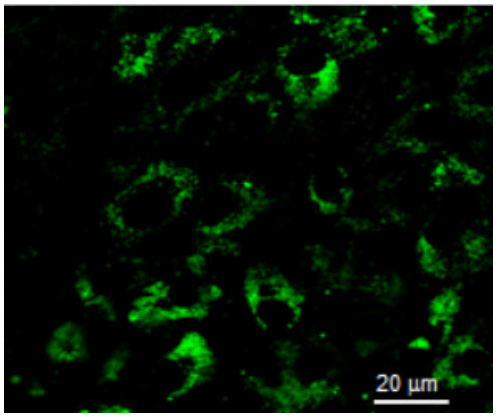
Chondrocyte ?

Inserm
Institut national de la santé et de la recherche médicale

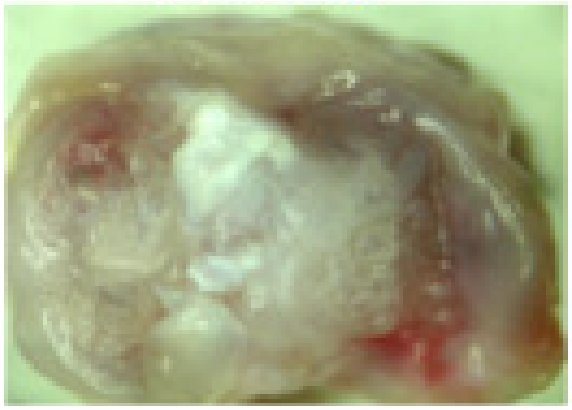
UPMC SORBONNE UNIVERSITÉS

PROTECTIVE EFFECT OF NICOTIN, A MUSCARINIC RECEPTOR LIGAND, IN THE MONOIODOACETATE RAT MODEL

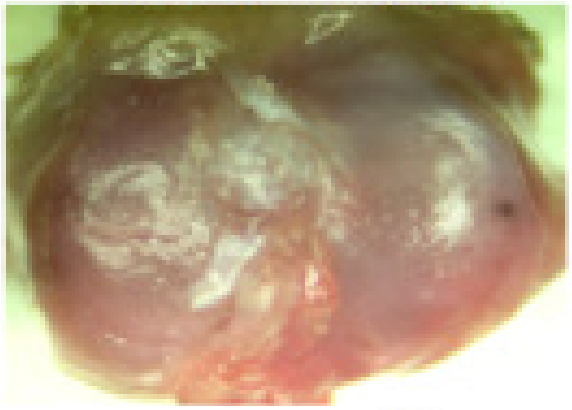
α7 nAChR expression

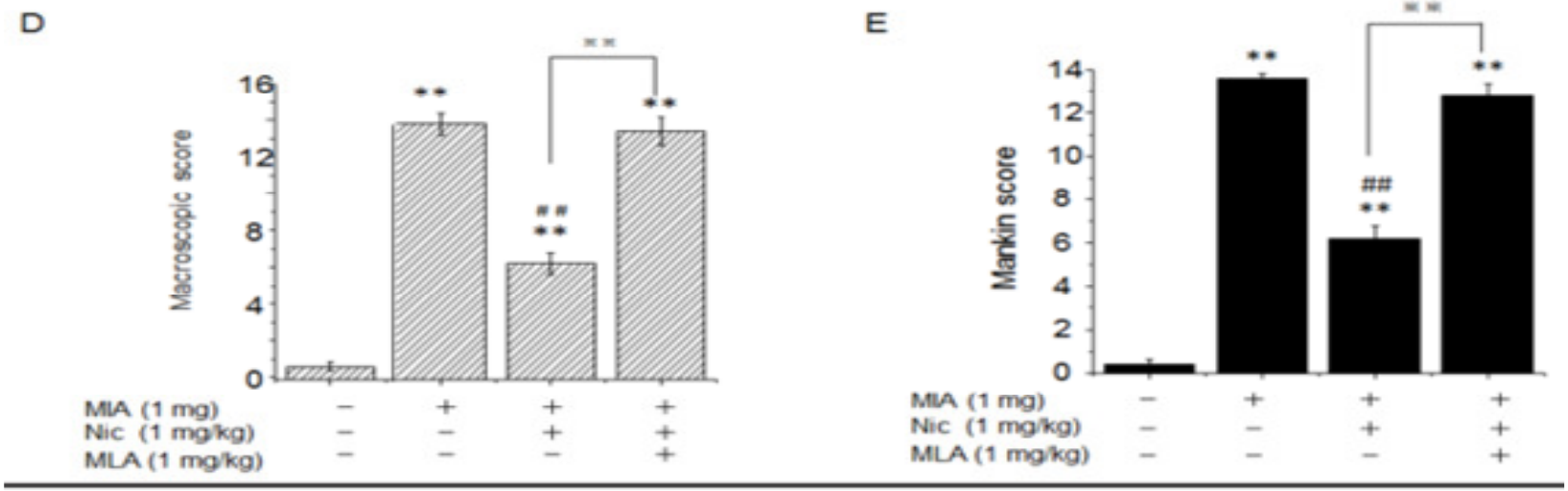


MIA 1mg



MIA + Nic 1mg/kg

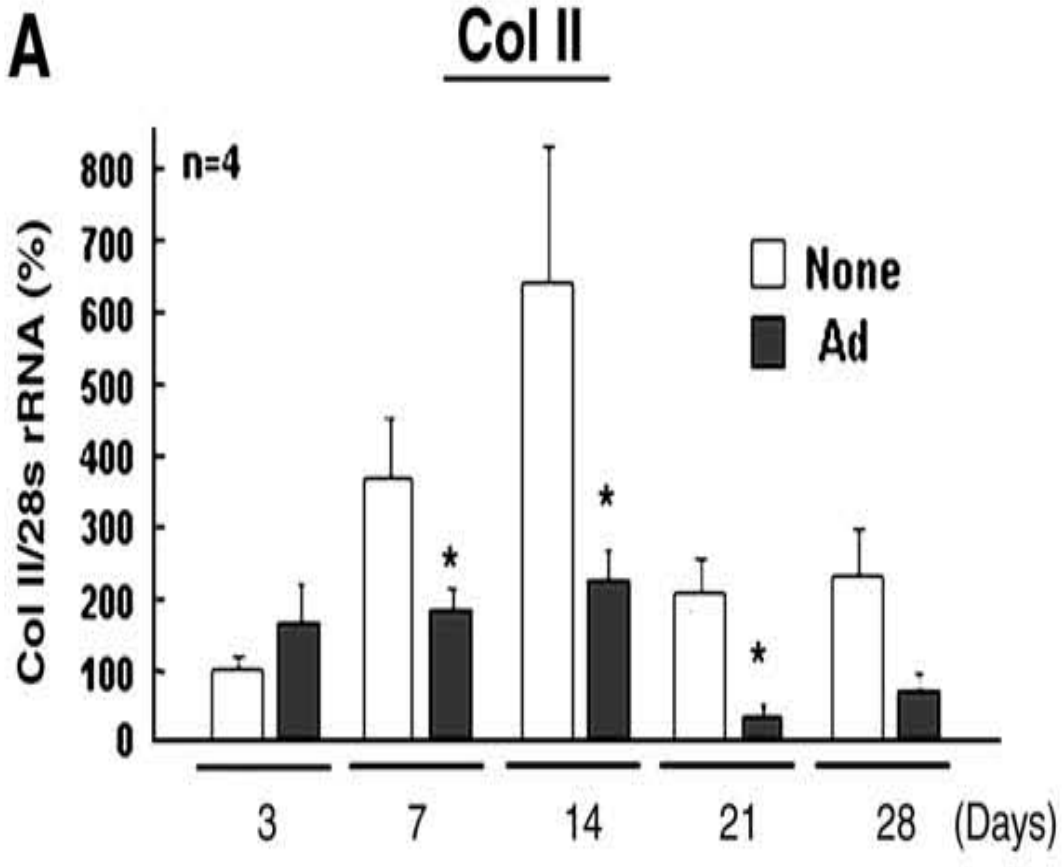




Liu et al. Cell Physiol Biochem 2015

EFFECT OF ADRENALINE ON CHONDROCYTE DIFFERENTIATION

ATDC5 cells



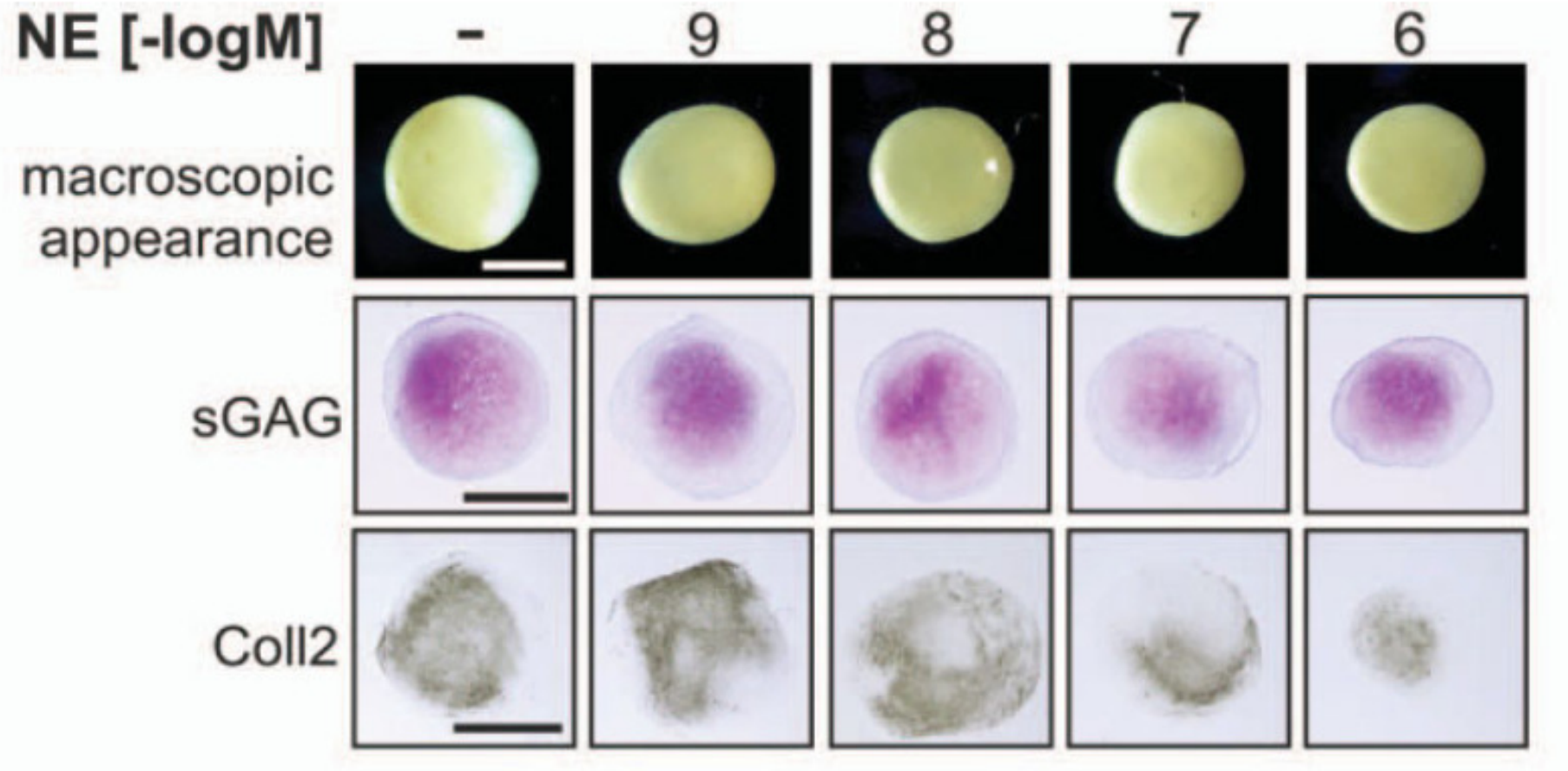
(Effect through β2-AR +++)

Takarada et al. Bone 2009

Inserm
Institut national de la santé et de la recherche médicale

UPMC SORBONNE UNIVERSITÉS

Effect of norepinephrine (NE), a AR agonist, on the chondrogenesis of mesenchymal stem cells



Jenei-Lanzl et al. A&R 2014

1966

ANNALS OF SURGERY
A Monthly Review of Surgical Science Since 1885

Effect of Sympathectomy on Development of Chronic Osteoarthritis:

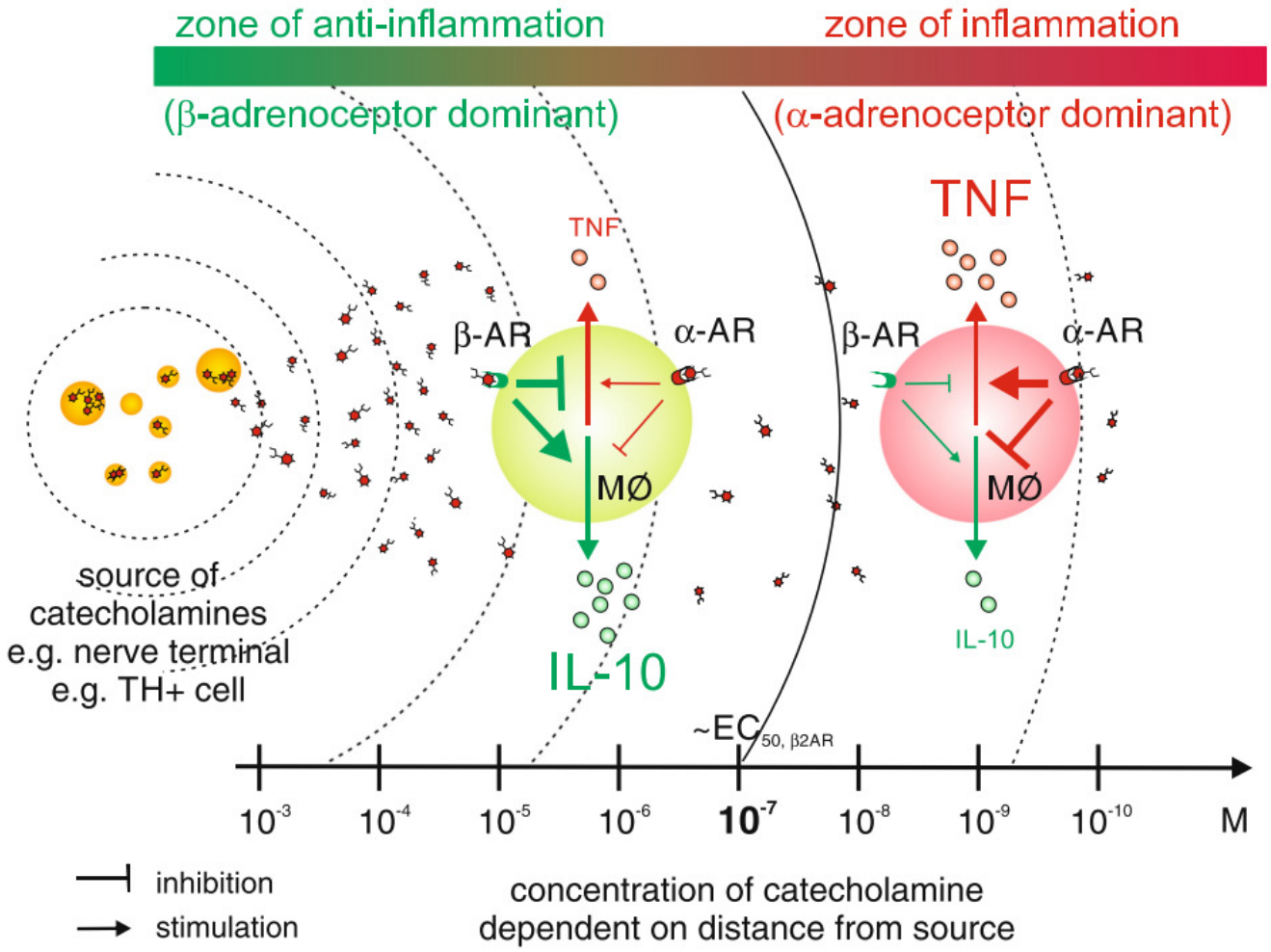
Case Report

GEORGE D. LILLY, M.D.

From the Department of Surgery, the Miami Heart Institute, Miami Beach, Florida

Vasospastic disease of the fingers of left hand
Left cervicodorsal sympathectomy

Catecholamine effects depend on the distance from catecholamine source



Pongratz & Straub. AR&T 2014

ROLE OF CATECHOLAMINES ON (SUBCHONDRAL ?) BONE

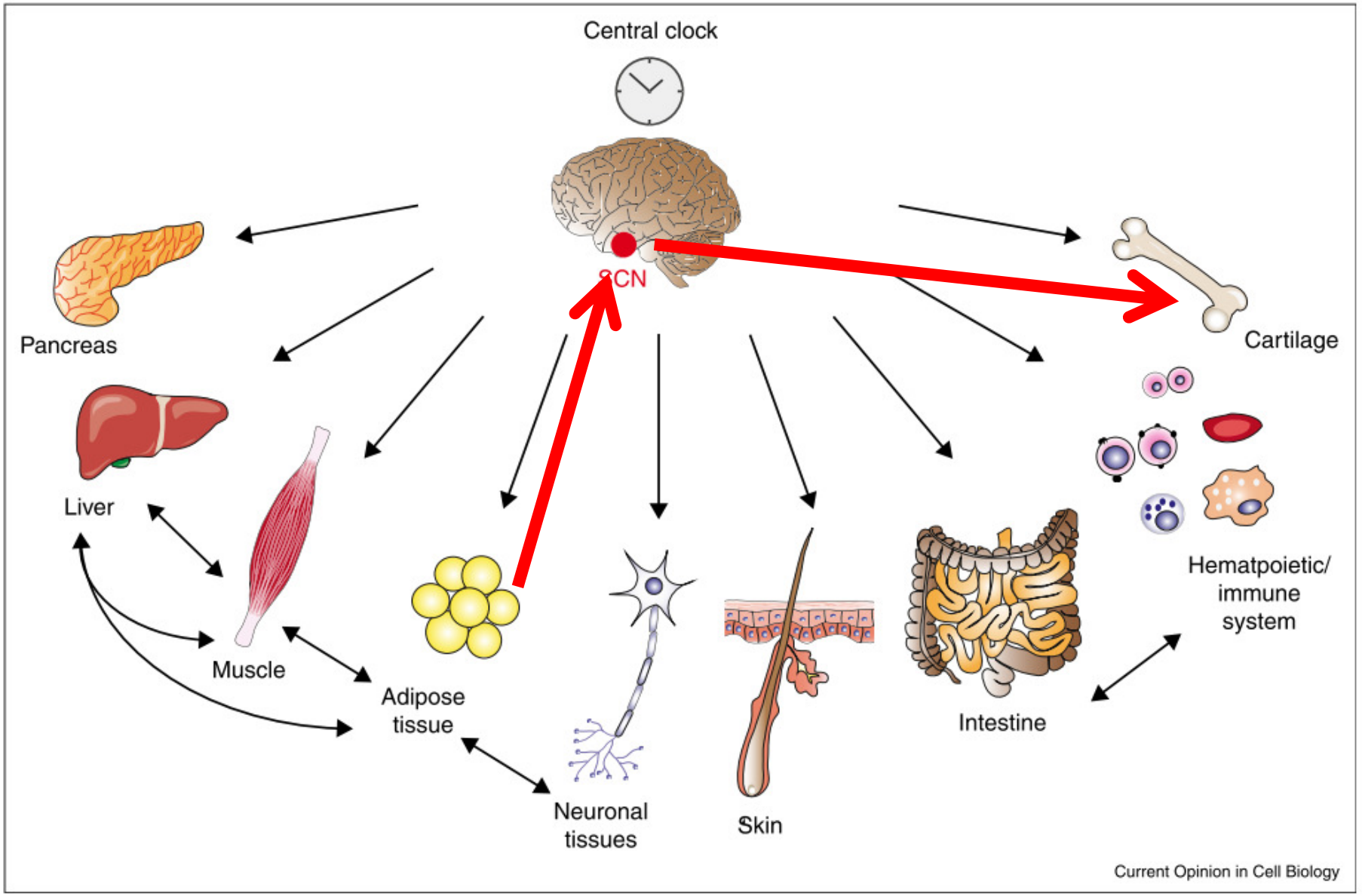
Catecholamines and bone

- Osteoblasts and osteocytes express βAR (mainly β2AR), (osteoclasts uncertain)
- βAR stimulation: bone resorption (RANKL and IL6 stimulation), inhibition of osteoblast proliferation
- Glucocorticoids stimulate β2AR expression
- βAR stimulation: Activation of circadian genes in osteoblasts

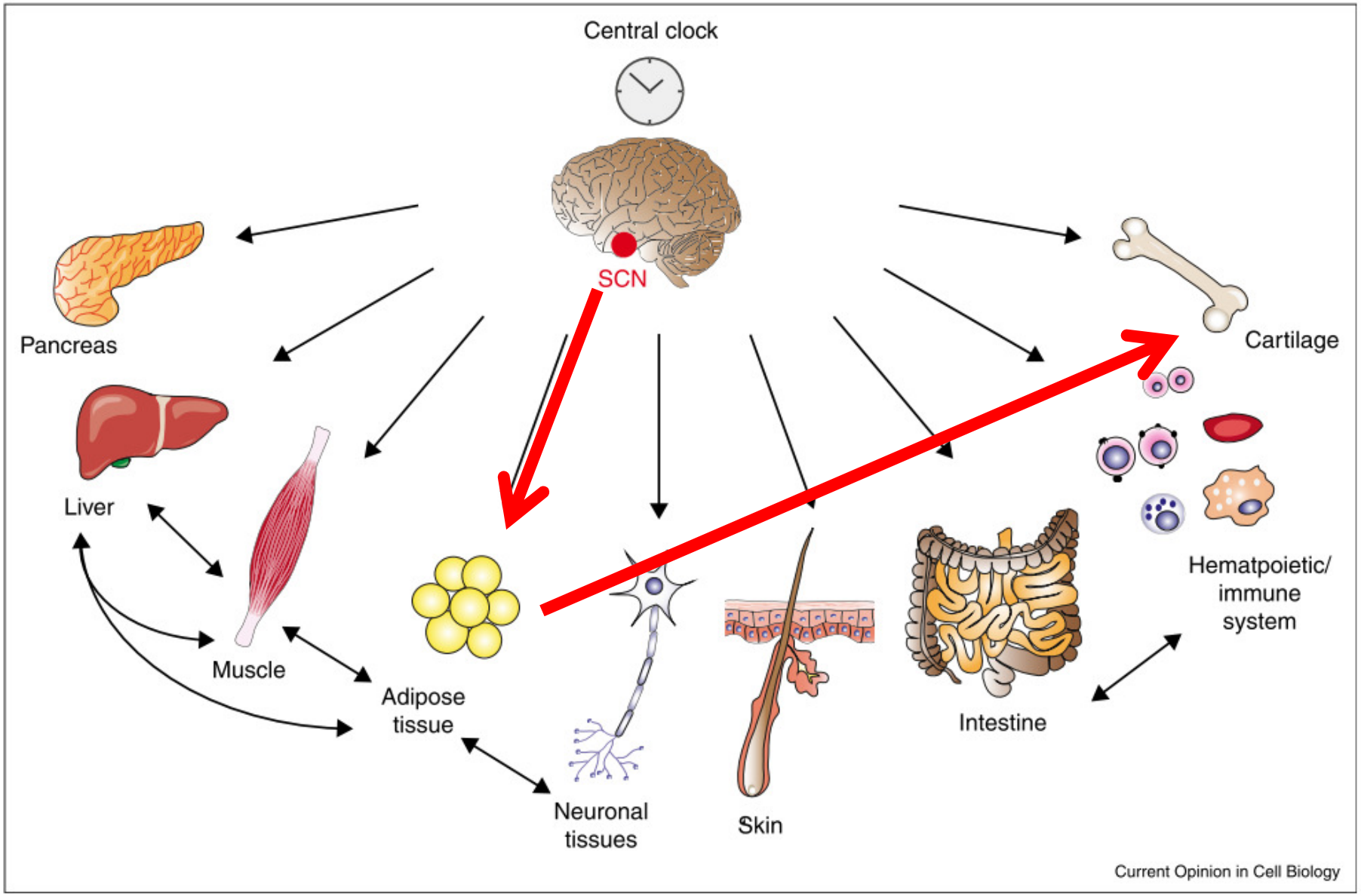
How could the NS influence the OA process *indirectly* ?

Inserm
Institut national
de la santé et de la recherche médicale

UPMC
SORBONNE UNIVERSITÉS



Janish et al. Curr Opin Cell Biol 2014



Janish et al. Curr Opin Cell Biol 2014

Cell

Time for Food: The Intimate Interplay between Nutrition, Metabolism, and the Circadian Clock

Gad Asher[1,*] and Paolo Sassone-Corsi[2,*]

Cell

Neural Control of Energy Balance: Translating Circuits to Therapies

Laurent Gautron,[1,*] Joel K. Elmquist,[1,2] and Kevin W. Williams[1,3,*]

Diurnal Variation in Vascular and Metabolic Function in Diet-Induced Obesity

Divergence of Insulin Resistance and Loss of Clock Rhythm

Madhu J. Prasai, Romana S. Mughal, Stephen B. Wheatcroft, Mark T. Kearney, Peter J. Grant, and Eleanor M. Scott

DIABETES, VOL. 62, JUNE 2013

MAY 2014 NATURE MEDICINE

A new role for the brain in metabolic control

Jose B C Carvalheira, Justin I Odegaard & Ajay Chawla

Institut national de la santé et de la recherche médicale

Science AAAS

2005

Obesity and Metabolic Syndrome in Circadian *Clock* Mutant Mice

Fred W. Turek,[1,3] Corinne Joshu,[3,4*] Akira Kohsaka,[3,4*] Emily Lin,[3,4*] Ganka Ivanova,[2,4] Erin McDearmon,[3,5] Aaron Laposky,[3] Sue Losee-Olson,[3] Amy Easton,[3] Dalan R. Jensen,[6] Robert H. Eckel,[6] Joseph S. Takahashi,[1,3,5] Joseph Bass[2,3,4†]

editorial

Diabetes, Obesity and Metabolism 16 (Suppl. 1): 1–3, 2014.

The mind and the belly: a glance at how the nervous system directs metabolism

Mammalian circadian clock and metabolism – the epigenetic link

Marina Maria Bellet and Paolo Sassone-Corsi*

Department of Pharmacology, Unite 904 Inserm 'Epigenetics and Neuronal Plasticity', School of Medicine, University of California, Irvine, Irvine, CA 92697, USA

*Author for correspondence (psc@uci.edu)

Journal of Cell Science 123, 3837-3848

ELSEVIER

Contents lists available at ScienceDirect

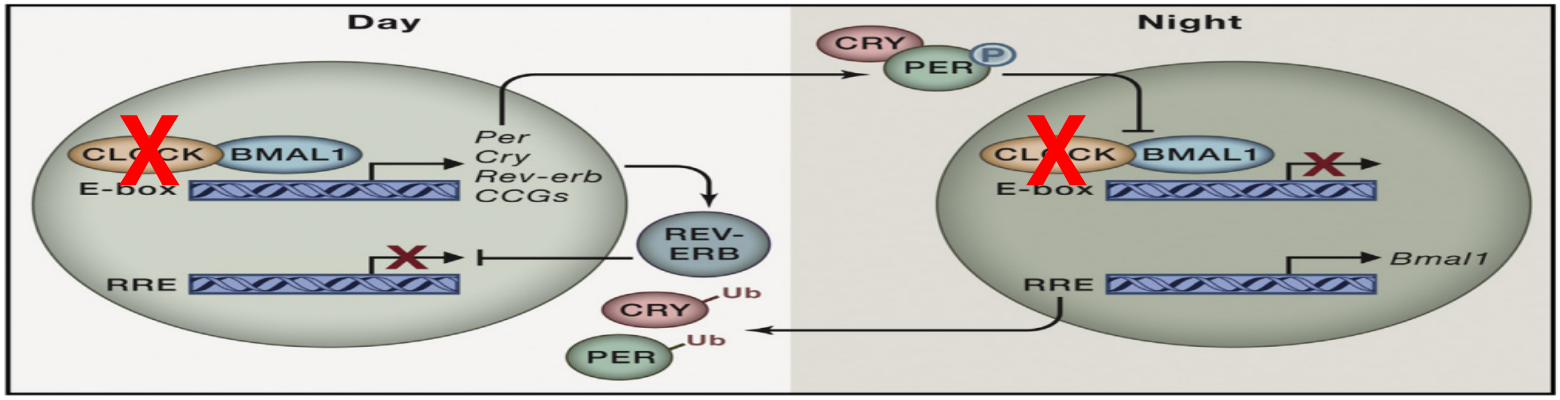
Best Practice & Research Clinical Gastroenterology

3

The gut–brain axis in obesity

CrossMark

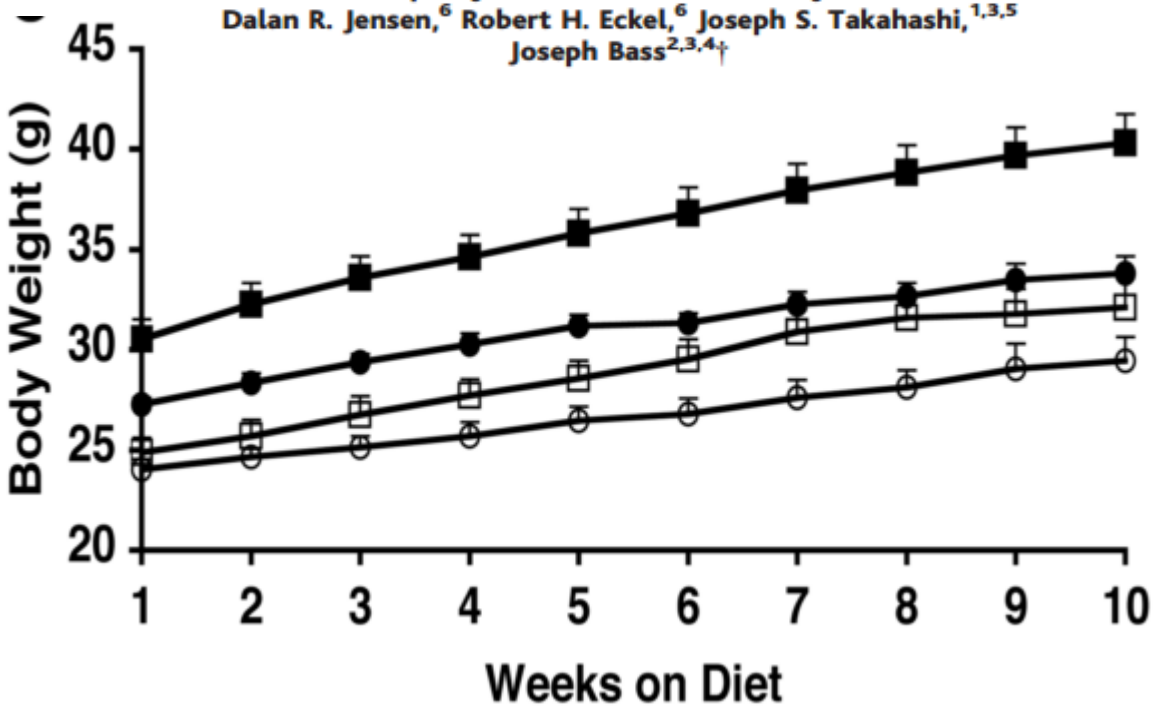
Helena Buhmann, Med. Pract. [a],
Carel W. le Roux, PhD, Prof. Dr. Med. [b, c],
Marco Bueter, PhD, PD Dr. Med. [d, e, *]



Obesity and Metabolic Syndrome in Circadian *Clock* Mutant Mice

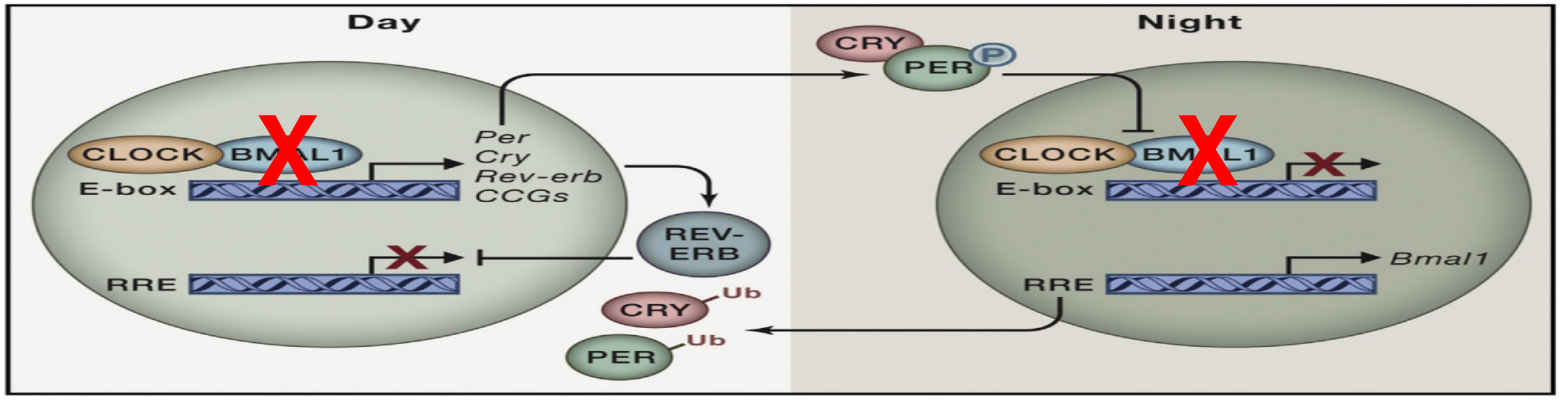
Science
AAAS

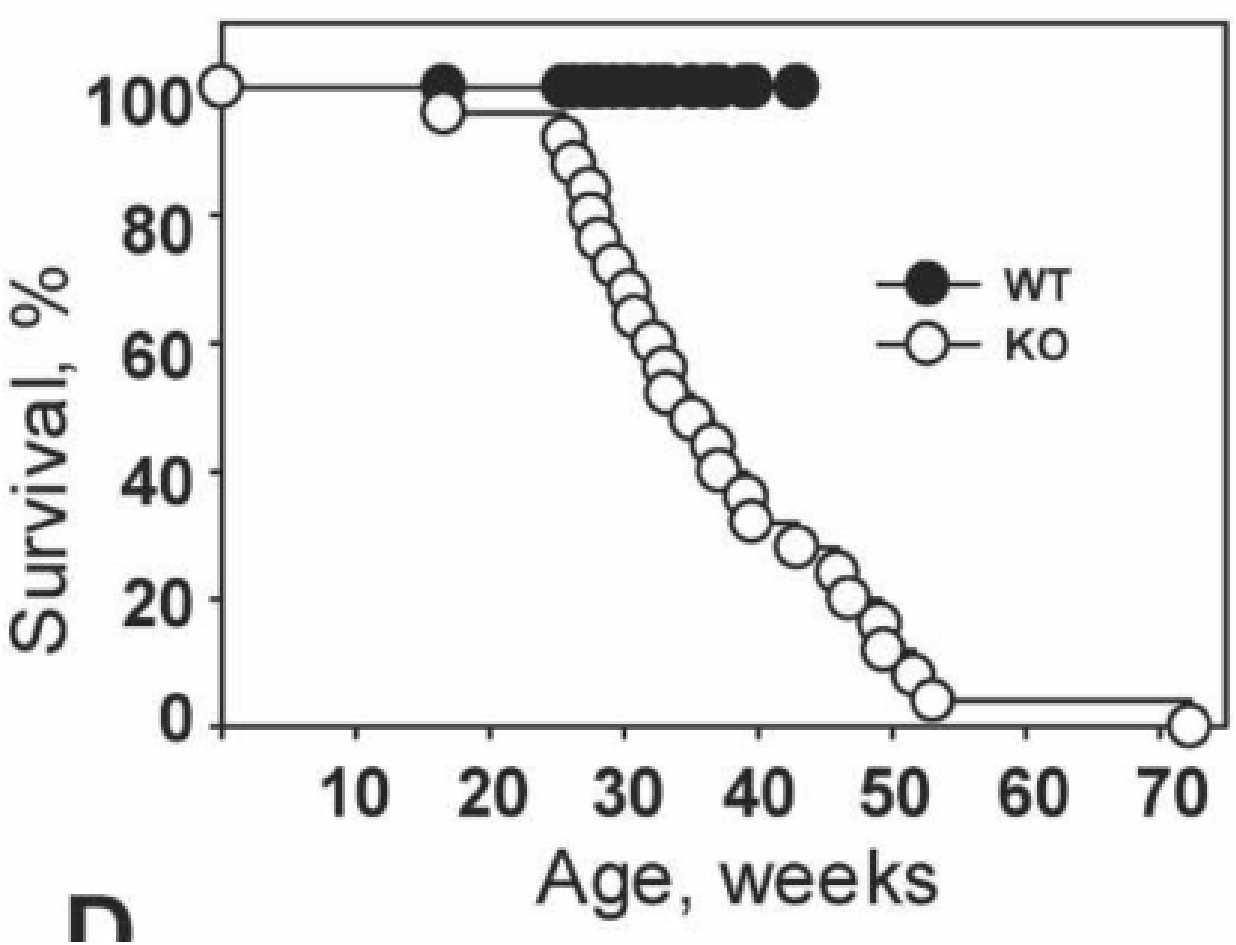
Fred W. Turek,[1,3] Corinne Joshu,[3,4*] Akira Kohsaka,[3,4*]
Emily Lin,[3,4*] Ganka Ivanova,[2,4] Erin McDearmon,[3,5]
Aaron Laposky,[3] Sue Losee-Olson,[3] Amy Easton,[3]
Dalan R. Jensen,[6] Robert H. Eckel,[6] Joseph S. Takahashi,[1,3,5]
Joseph Bass[2,3,4†]



Inserm
Institut national de la santé et de la recherche médicale

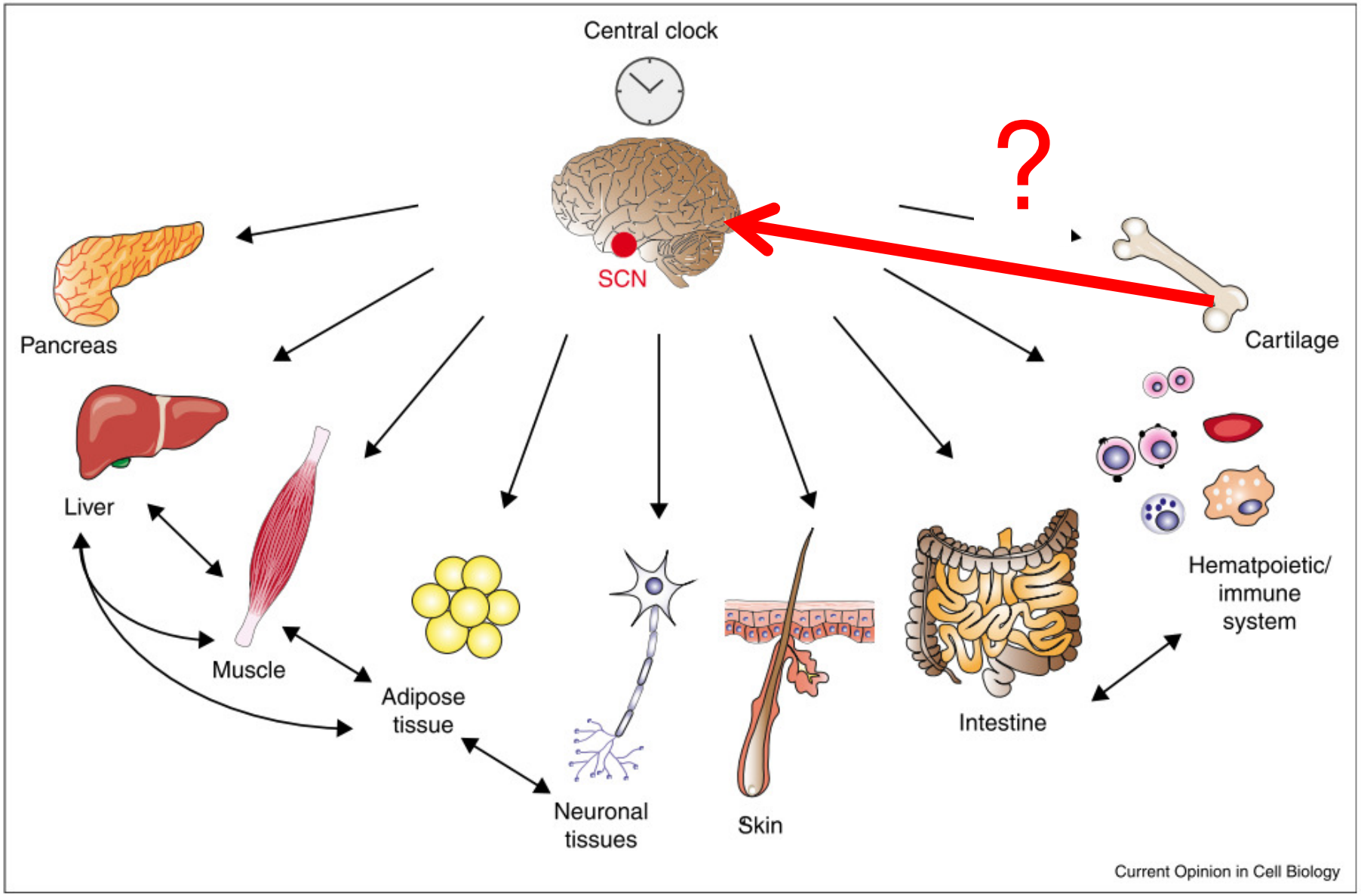
UPMC
SORBONNE UNIVERSITÉS





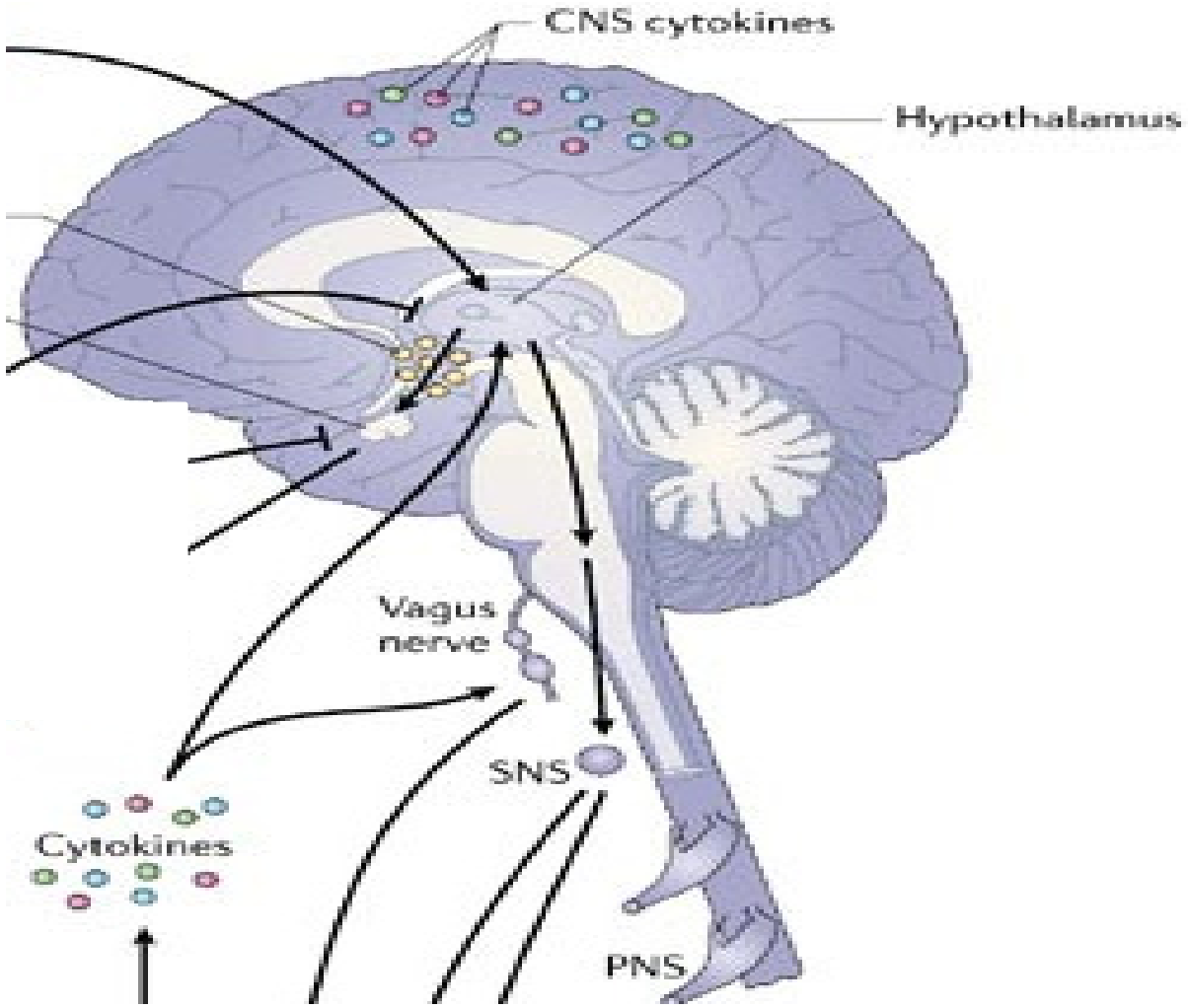
Kondratov et al. Genes Dev 2006

Can OA influence the brain ?



Janish et al. Curr Opin Cell Biol 2014

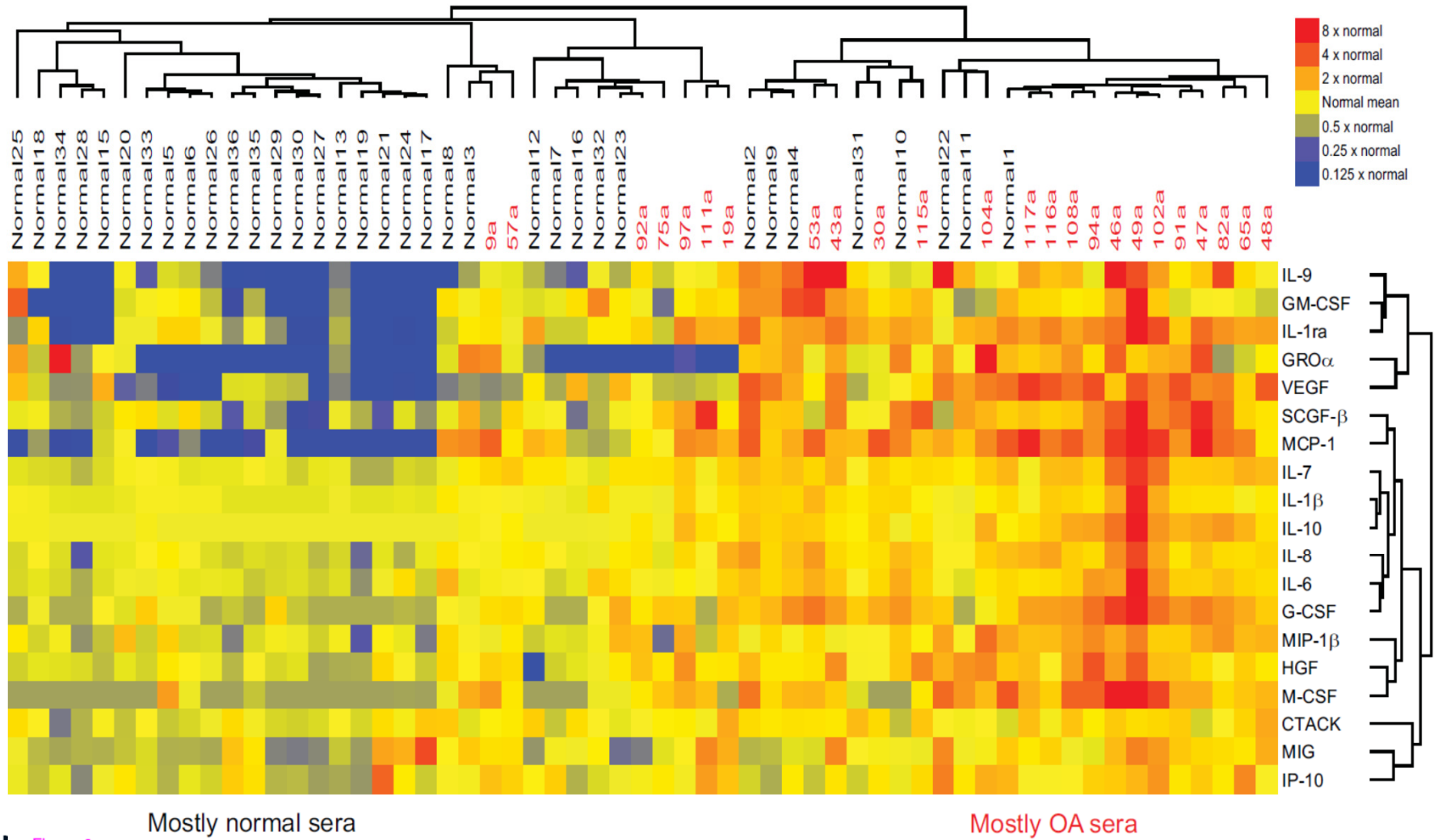
IMPACT OF PRO-INFLAMMATORY CYTOKINES ON NEURONAL CIRCUITS



Inserm
Institut national de la santé et de la recherche médicale

UPMC SORBONNE UNIVERSITÉS

Levels of inflammatory cytokines are higher in OA compared to healthy sera



Sohn et al. AR&T 2012

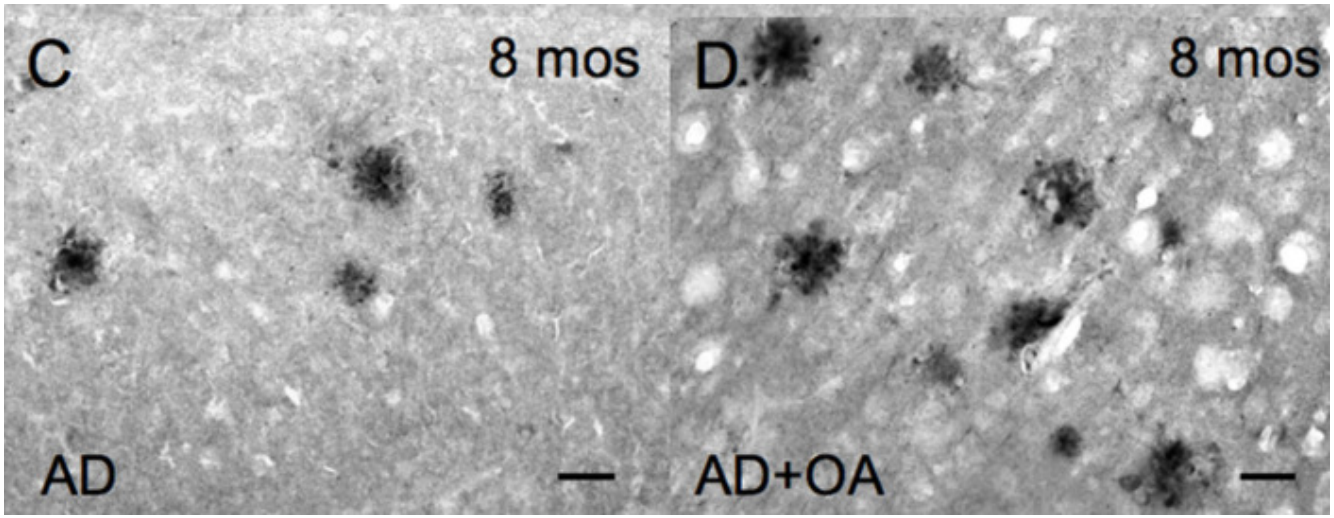
Kyrkanides *et al. Journal of Neuroinflammation* 2011, **8**:112
http://www.jneuroinflammation.com/content/8/1/112

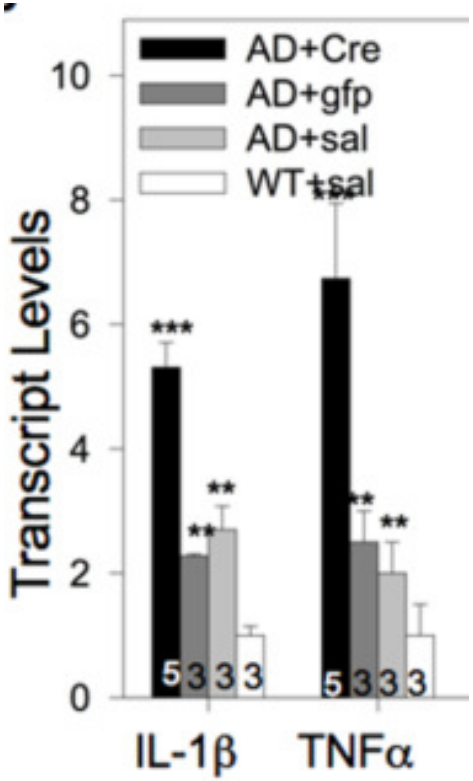
JOURNAL OF NEUROINFLAMMATION

RESEARCH Open Access

Osteoarthritis accelerates and exacerbates Alzheimer's disease pathology in mice

Stephanos Kyrkanides[1*], Ross H Tallents[4], Jen-nie H Miller[4], Mallory E Olschowka[4,5], Renee Johnson[5], Meixiang Yang[1], John A Olschowka[5], Sabine M Brouxhon[2,3] and M Kerry O'Banion[5]

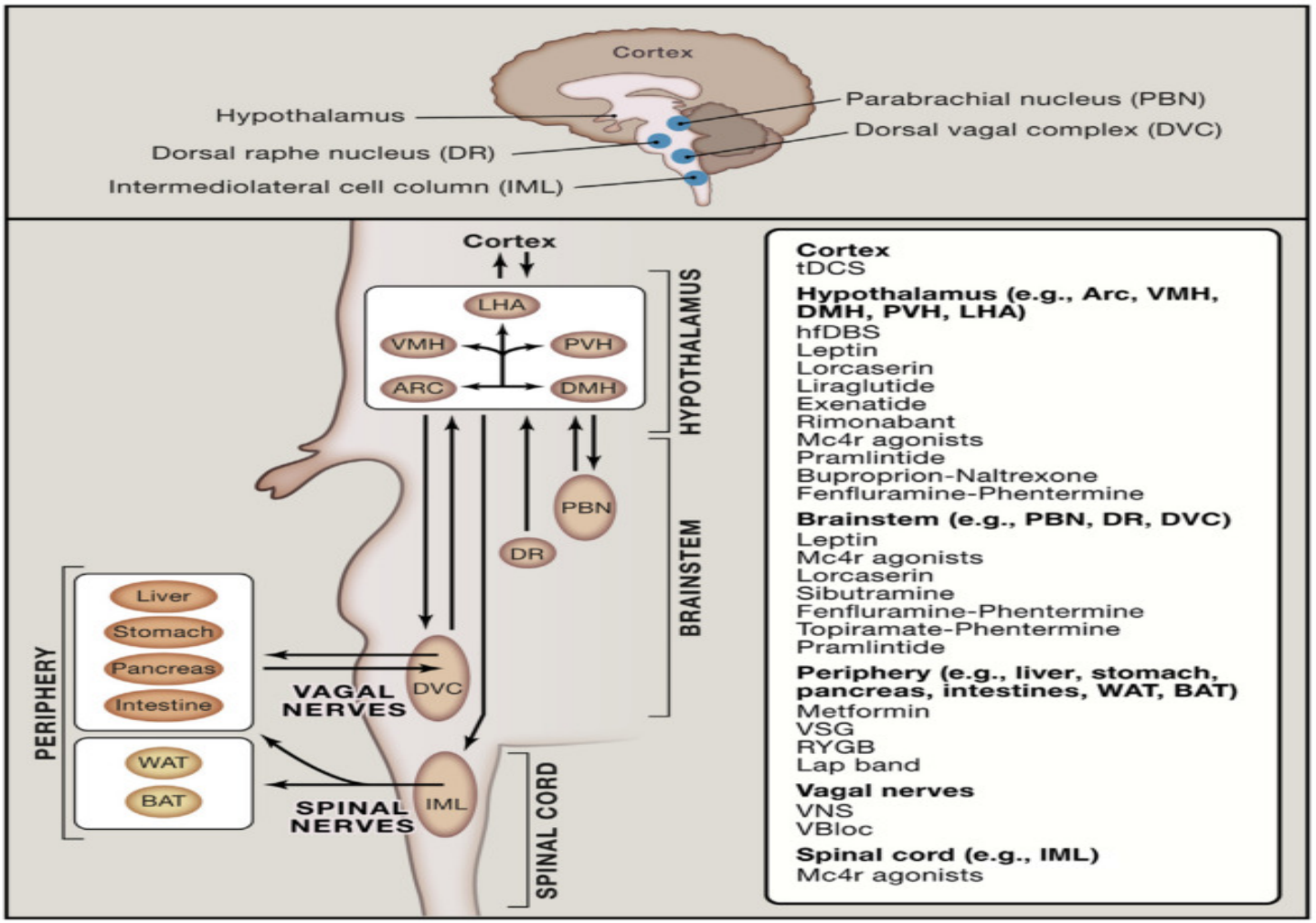




Inserm
Institut national de la santé et de la recherche médicale

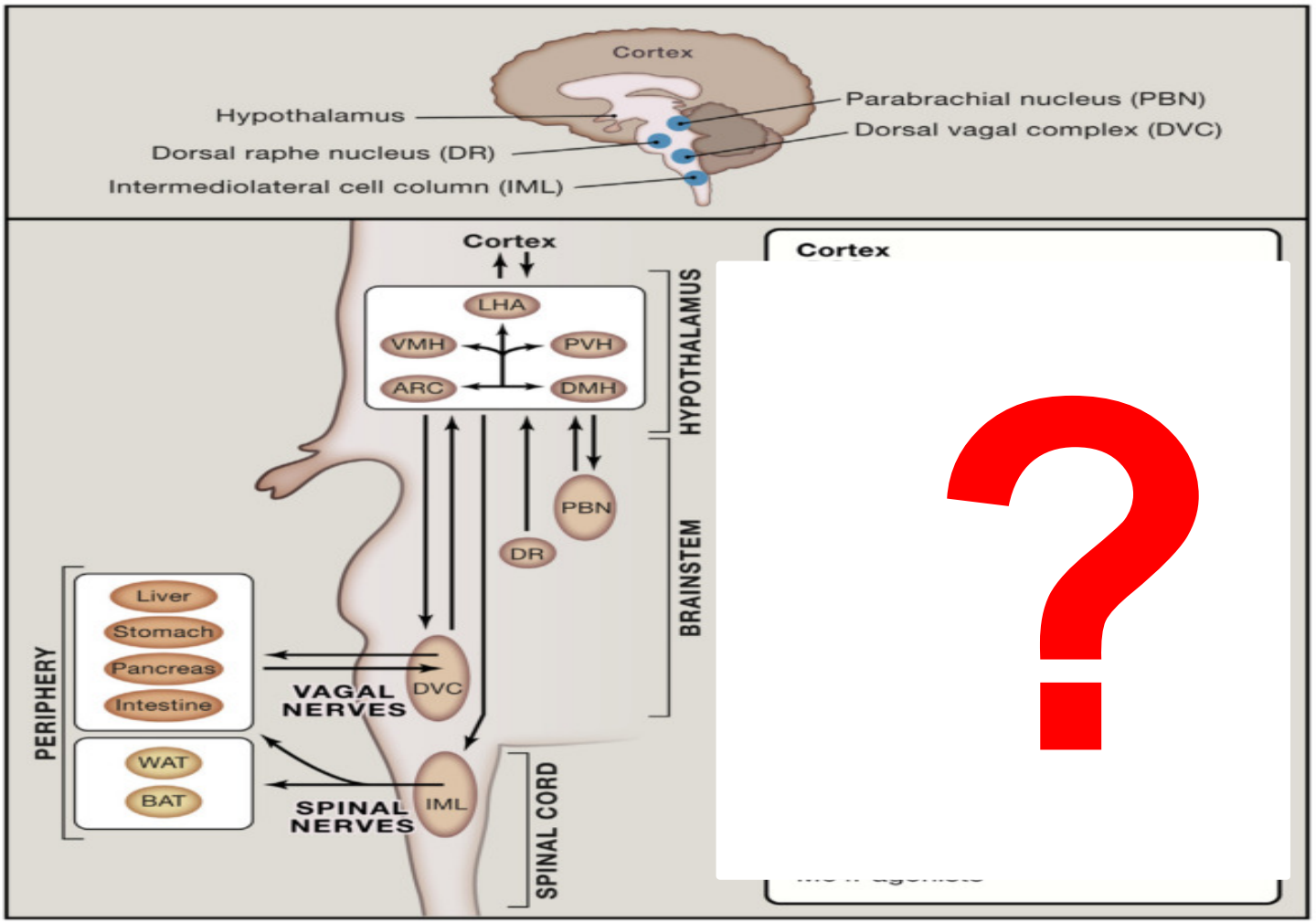
UPMC SORBONNE UNIVERSITÉS

Selected Therapeutic Options for Treating Obesity and Diabetes by Targeting the Brain



Gautron et al. Cell 2015

Selected Therapeutic Options for Treating *OSTEOARTHRITIS* by Targeting the Brain



Inserm
Institut national de la santé et de la recherche médicale

UPMC SORBONNE UNIVERSITÉS

THANK YOU !

Inserm
Institut national
de la santé et de la recherche médicale

UPMC
SORBONNE UNIVERSITÉS