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

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AN INTEGRATIVE VIEW OF OA PATHOPHYSIOLOGY
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

CIRCADIAN PACEMAKER: THE SUPRACHIASMATIC NUCLEUS

BRAIN OSCILLATORS

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

The Molecular Organization of the Circadian Clock

(Autoregulatory feedback loop)

Asher & Sassone-Corsi, Cell 2015

- HPA axis
- Parasympathetic nervous system
- Sympathetic-adrenal-medullary axis
The Inflammatory reflex

Abboud FM. Am J Physiol Regul Integr Comp Physiol 2010
the cholinergic anti-inflammatory pathway

Tracey KJ. Nature Rev Immunol 2009
How could the NS influence the OA process directly?
Desynchronization of chondrocyte clocks

(Period close to 24h)

Gossan et al. Biogerontology 2014
Masterclock deregulation with Met S
Clock-controlled genes

Insulin Adipokines

Circadian release of hormones and neuromediators

Locomotor activity

Masterclock deregulation with mechanical stress

Metabolic OA
Aging OA
Post-trauma OA

Berenbaum F. Arthritis Rheum 2013
PROTECTIVE EFFECT OF NICOTIN, A MUSCARINIC RECEPTOR LIGAND, IN THE MONOIODOACETATE RAT MODEL

α7 nAChR expression  MIA 1mg  MIA + Nic 1mg/kg
EFFECT OF ADRENALINE ON CHONDROCYTE DIFFERENTIATION

ATDC5 cells

(Effect through β2-AR +++)

Takarada et al. Bone 2009
Effect of norepinephrine (NE), a AR agonist, on the chondrogenesis of mesenchymal stem cells

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*?
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*

Body Weight (g)

Weeks on Diet
Kondratov et al. Genes Dev 2006
Can OA influence the brain?
IMPACT OF PRO-INFLAMMATORY CYTOKINES ON NEURONAL CIRCUITS
Levels of inflammatory cytokines are higher in OA compared to healthy sera

Sohn et al. AR&T 2012
Osteoarthritis accelerates and exacerbates Alzheimer’s disease pathology in mice

Stephanos Kyrkanides, Ross H Tallents, Jen-nie H Miller, Mallory E Olschowka, Renee Johnson, Meixiang Yang, John A Olschowka, Sabine M Brouxhon and M Kerry O’Banlon

![Graph showing transcript levels of IL-1β and TNFα in AD and AD+OA groups.](image)
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
THANK YOU!