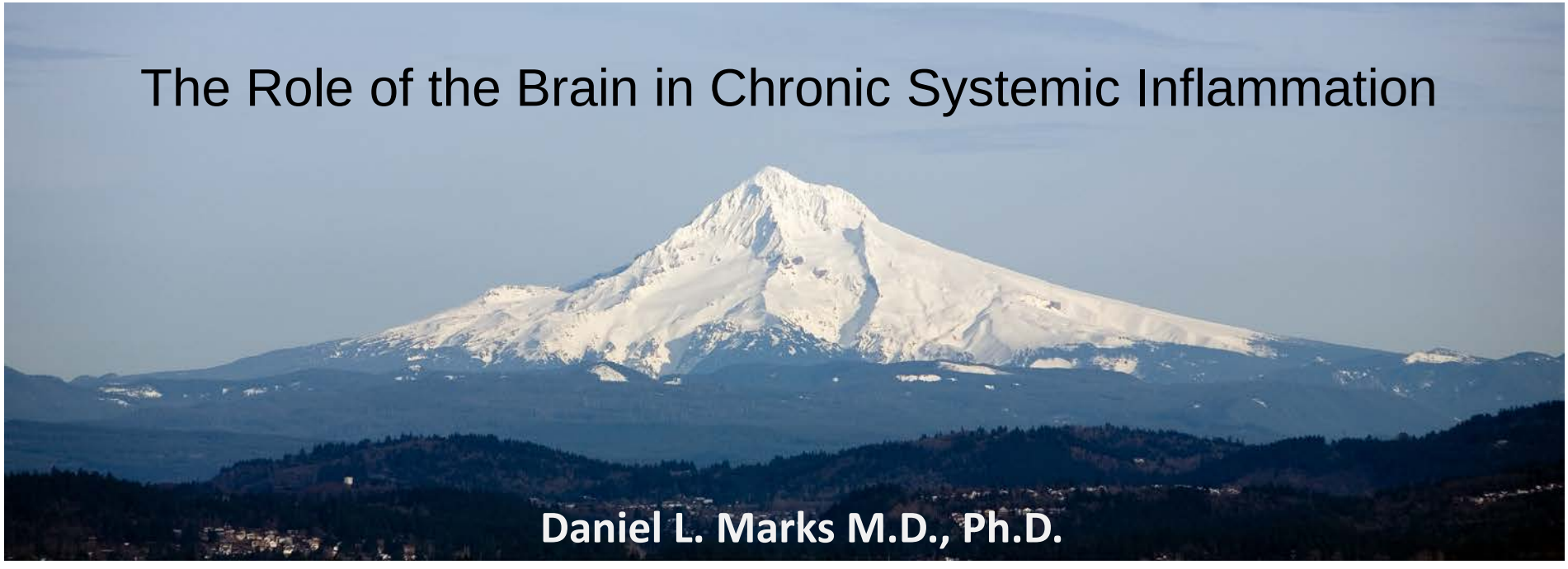
The Role of the Brain in Chronic Systemic Inflammation



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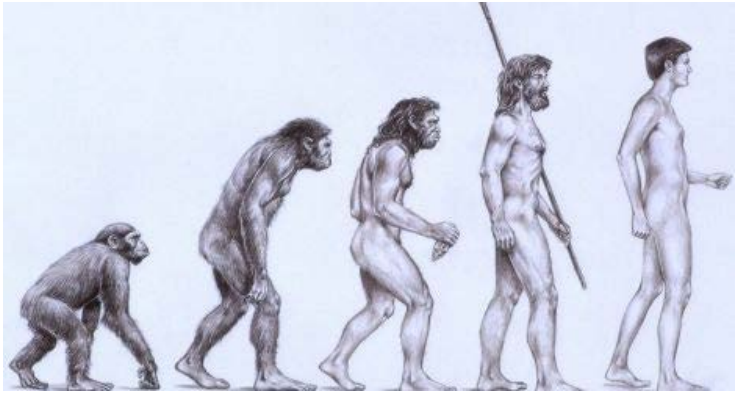
OHSU

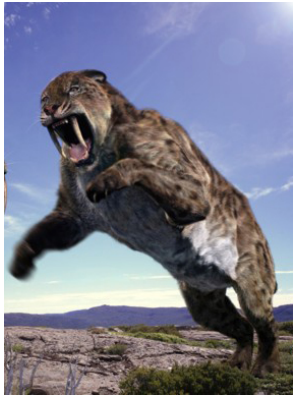
General Principles

- Chronic inflammation produces a complex multi-system disorder with metabolic and behavioral components
- Inflammation produces prolonged and dysfunctional activation of evolutionarily conserved sickness responses
- Even trivial peripheral inflammation produces a profound stress response due to multiple levels of bioamplification
- The CNS is a primary director of the behavioral and metabolic responses and provides therapeutic targets for reversing dysfunctional sickness responses to chronic inflammation

Acute Survival Challenges Throughout Evolution



Predation

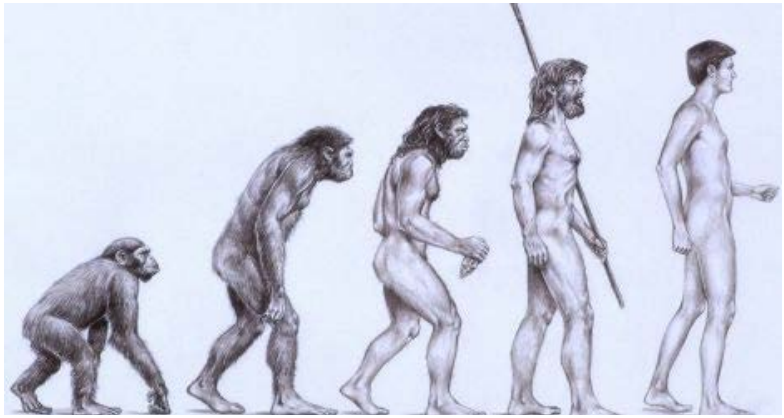


“Fight or Flight”

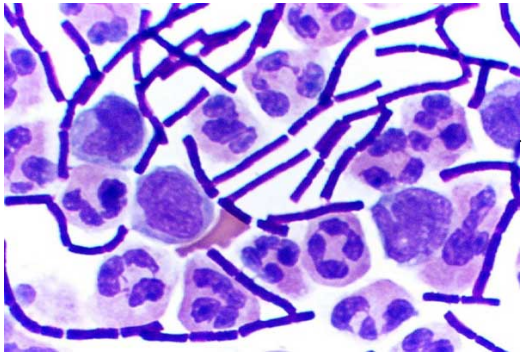
- HPA activation
- Epinephrine
- Glycolysis
- Cardiac Output
- Anesthesia
- Fear/Aggression

This response cannot be sustained.

Acute Survival Challenges Throughout Evolution



Infection



Coordinated
Behavioral and
Metabolic Response

This response also cannot be sustained

Illustration of St. Elizabeth from around 1380, as she gives a patient nutrition, on an altar of a Cologne master.

Sickness behavior:

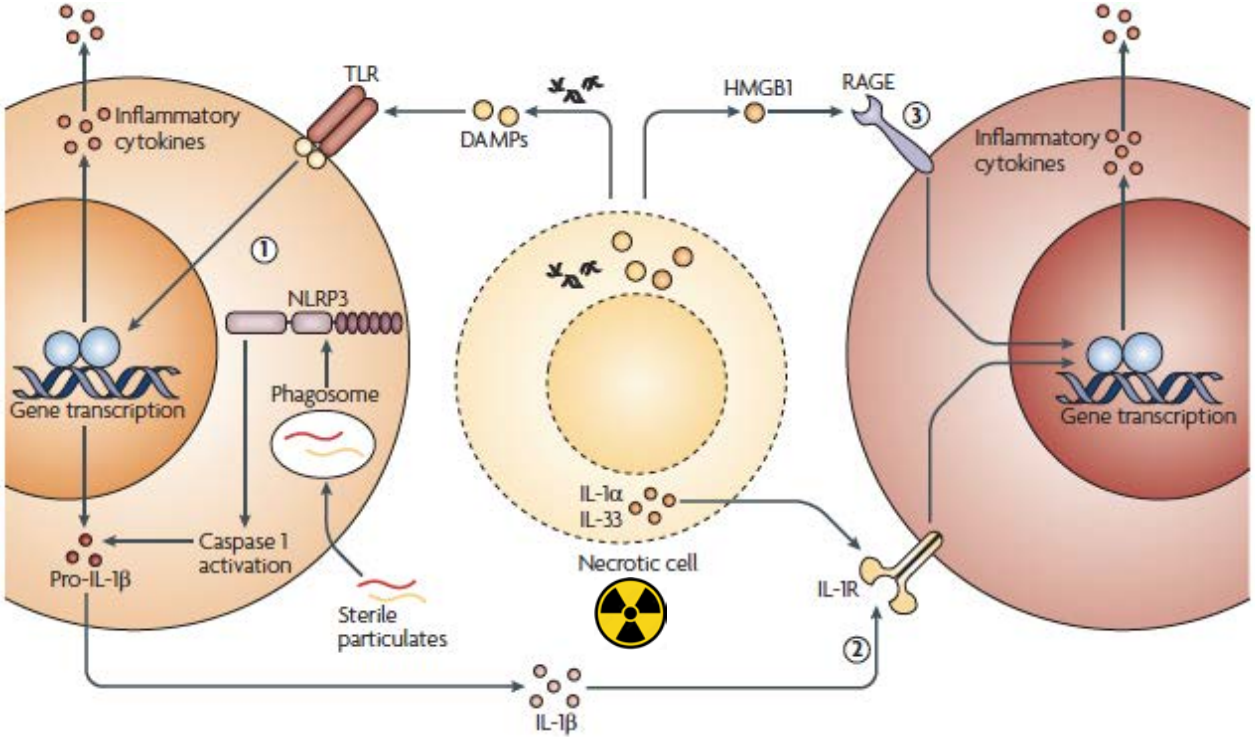
An adaptive response to infection

Minimize energy expenditure

Divert resources to fight “infection”

- Anorexia
- Lethargy
- Somnolence
- Anhedonia
- Muscle Catabolism
- Hyperalgesia

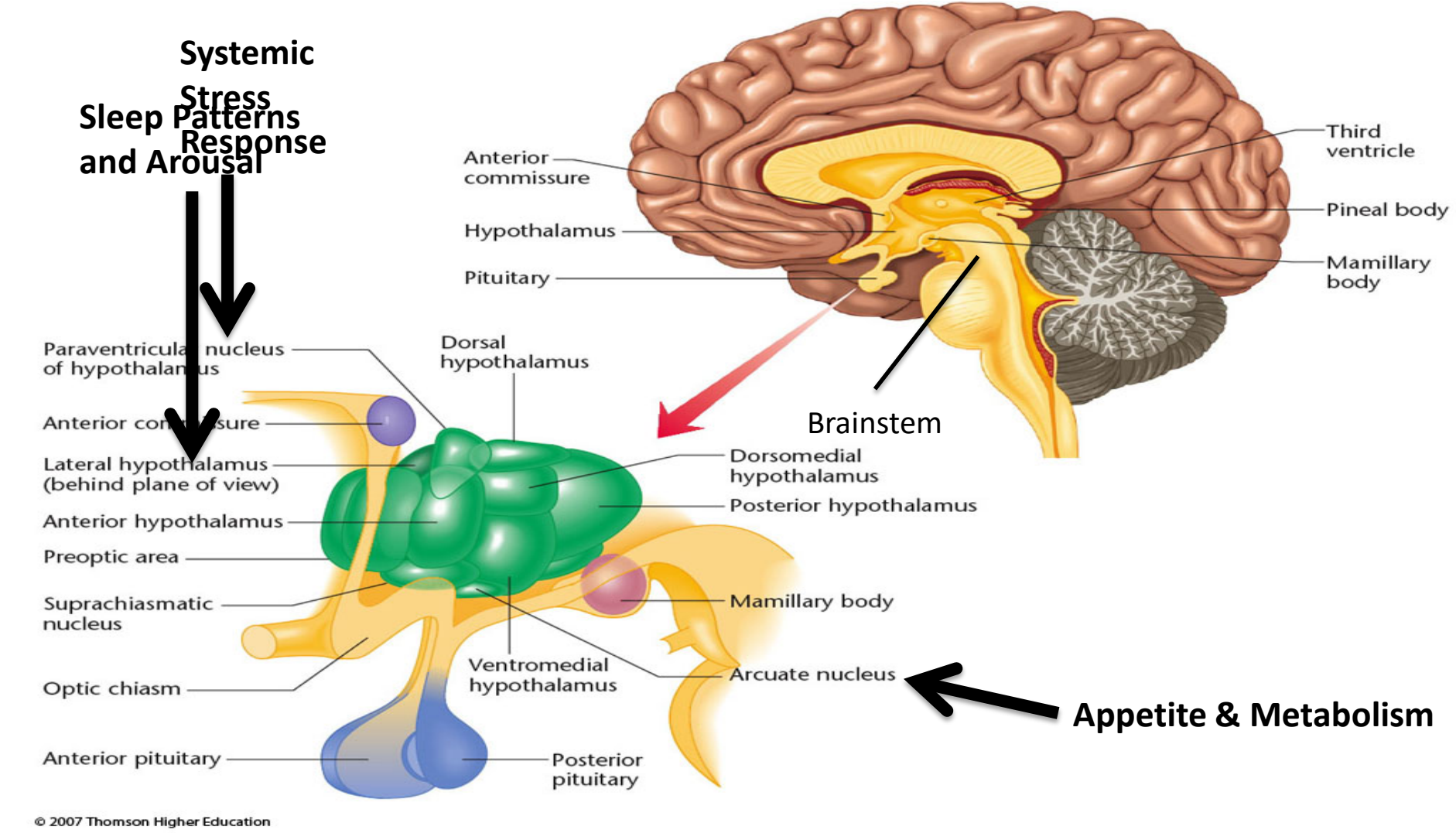
Radiation-Induced Bioamplification of Inflammation by DAMP Signaling



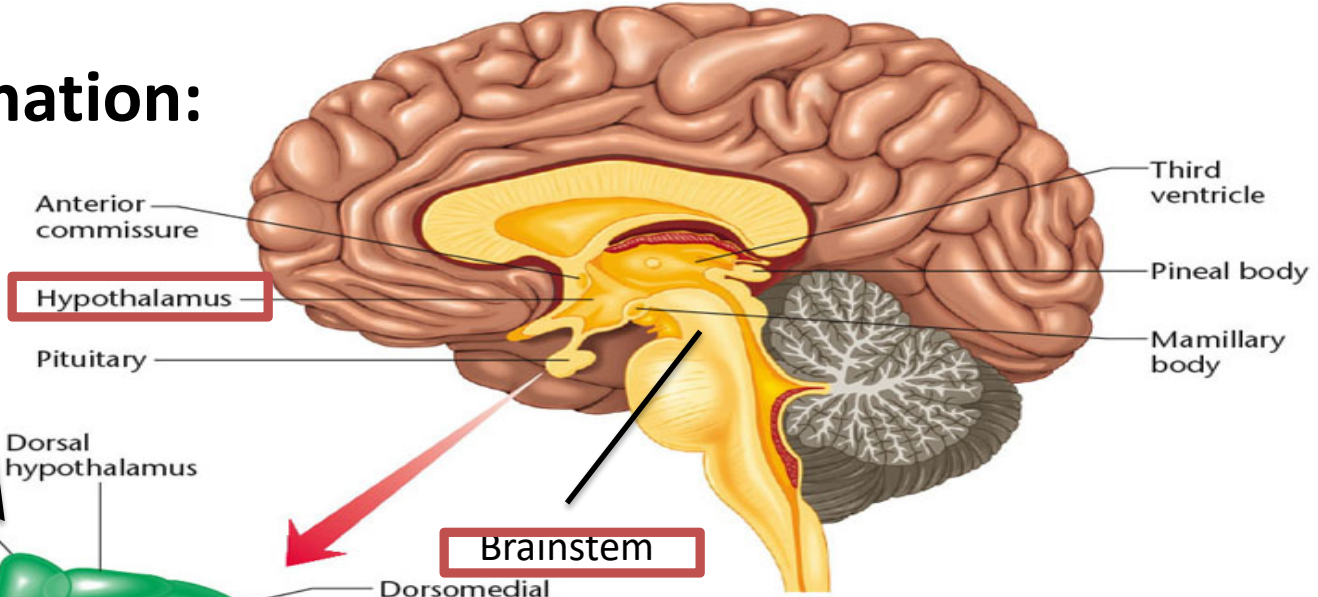
Adapted from Chen et al, Nat. Rev. Immun. 2010

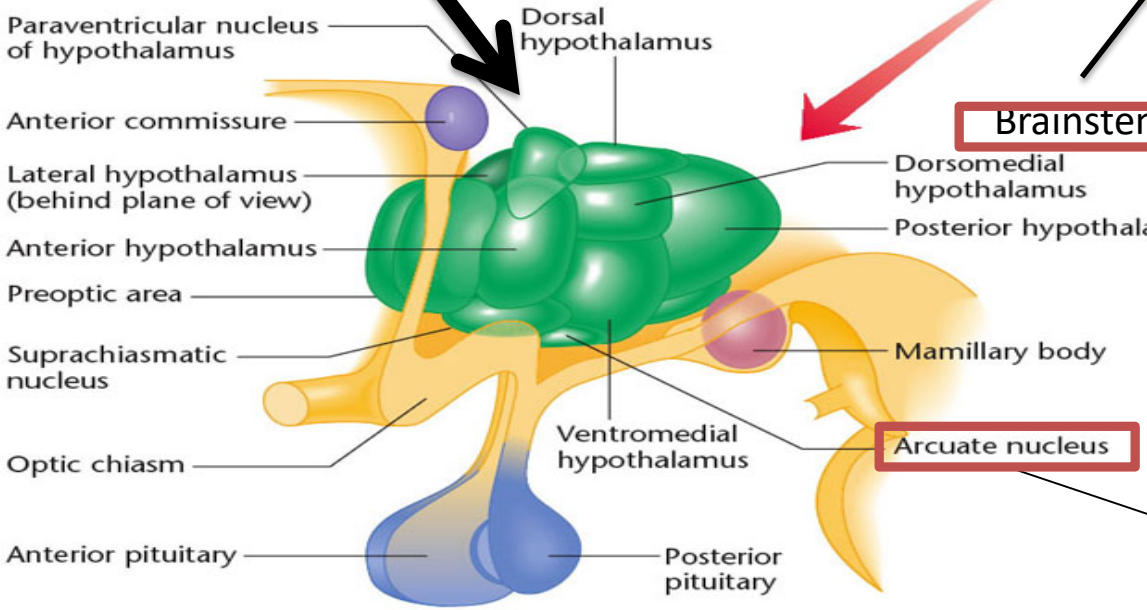
Systemic Stress Response

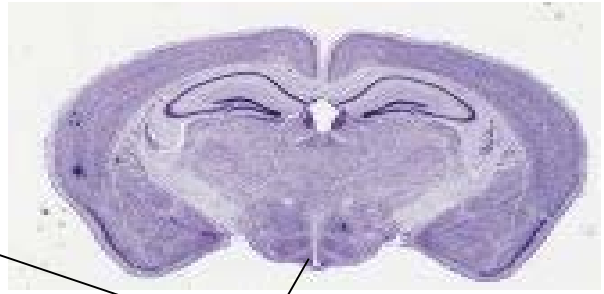
Sleep Patterns and Arousal



Systemic Inflammation: DAMP, PAMP

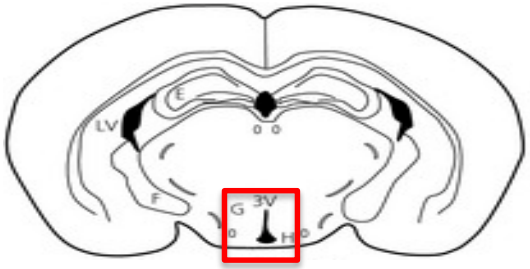


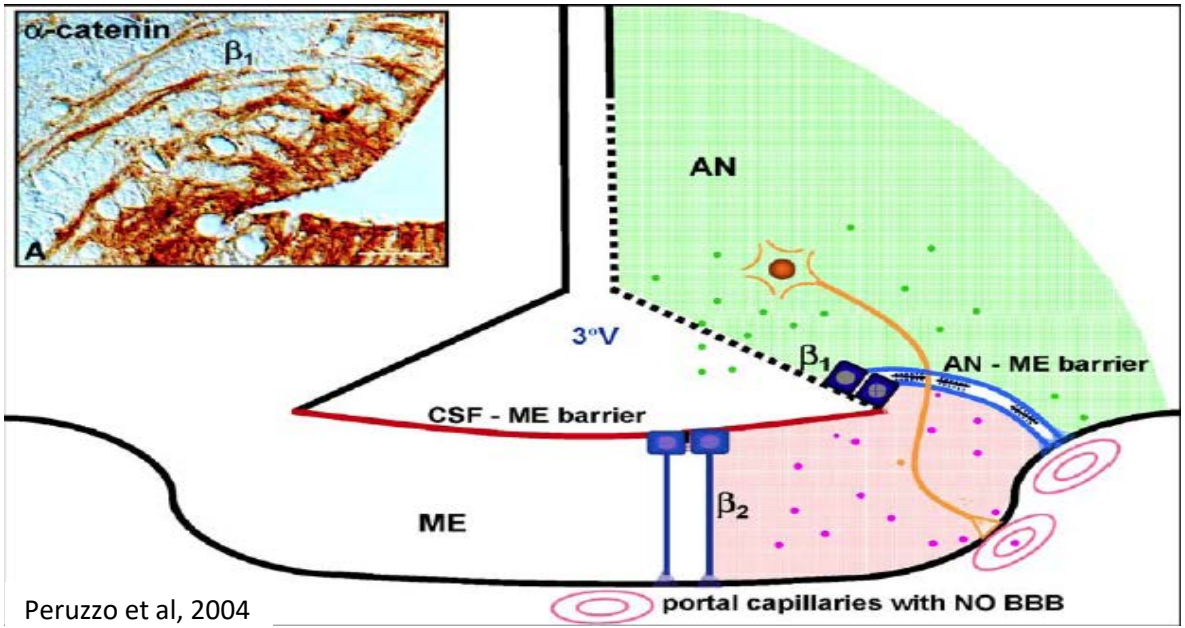




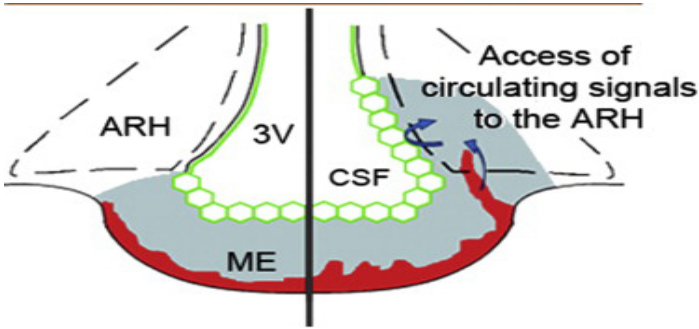
Complex BBB in the Hypothalamus

- Access to the medial basal hypothalamus is regulated, and the BBB is highly attenuated.
- Unique vasculature, microglia, tanycytes, etc.





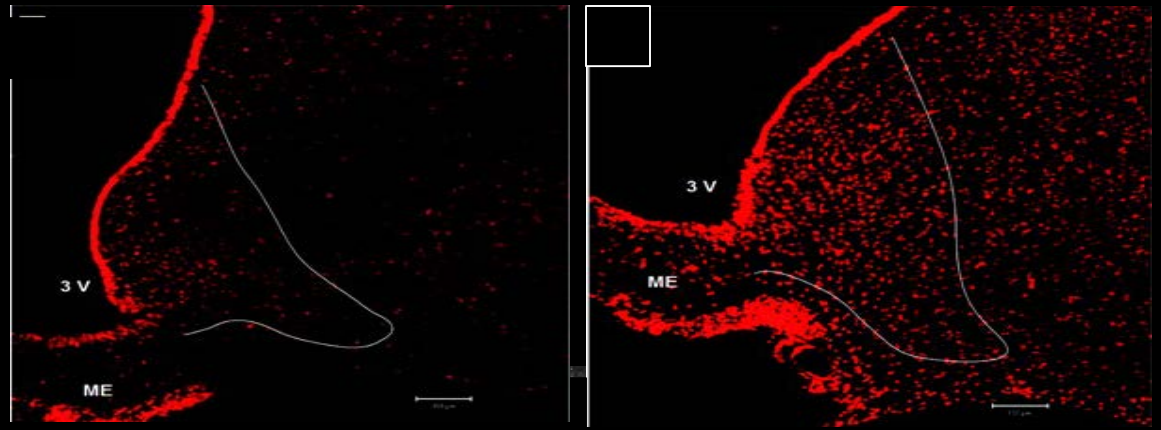
Peruzzo et al, 2004



Adapted from Langlet et al, 2014

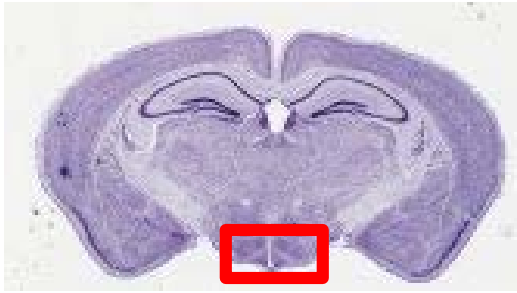
Baseline

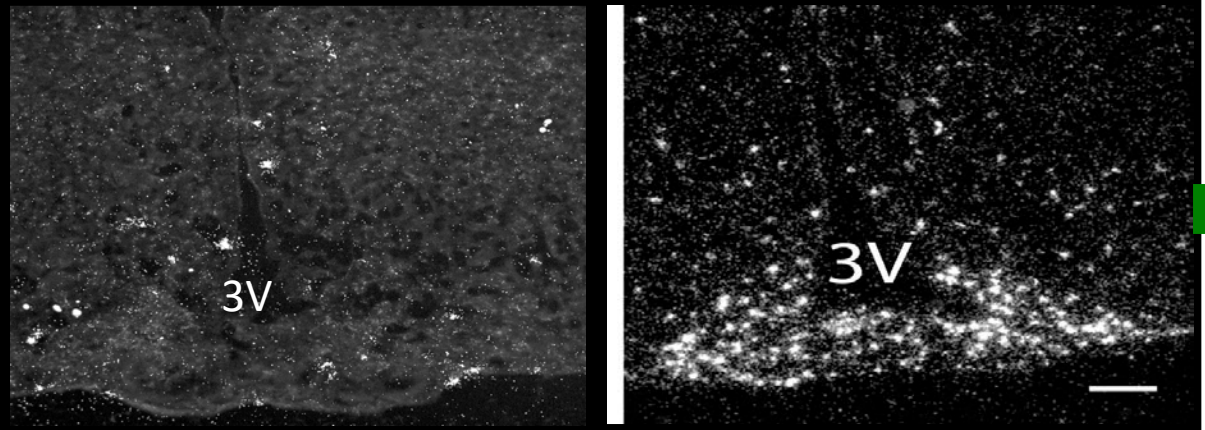
Inflammation (PAMP, DAMP)



Hypothalamic Neuronal Activation

RECEIVER

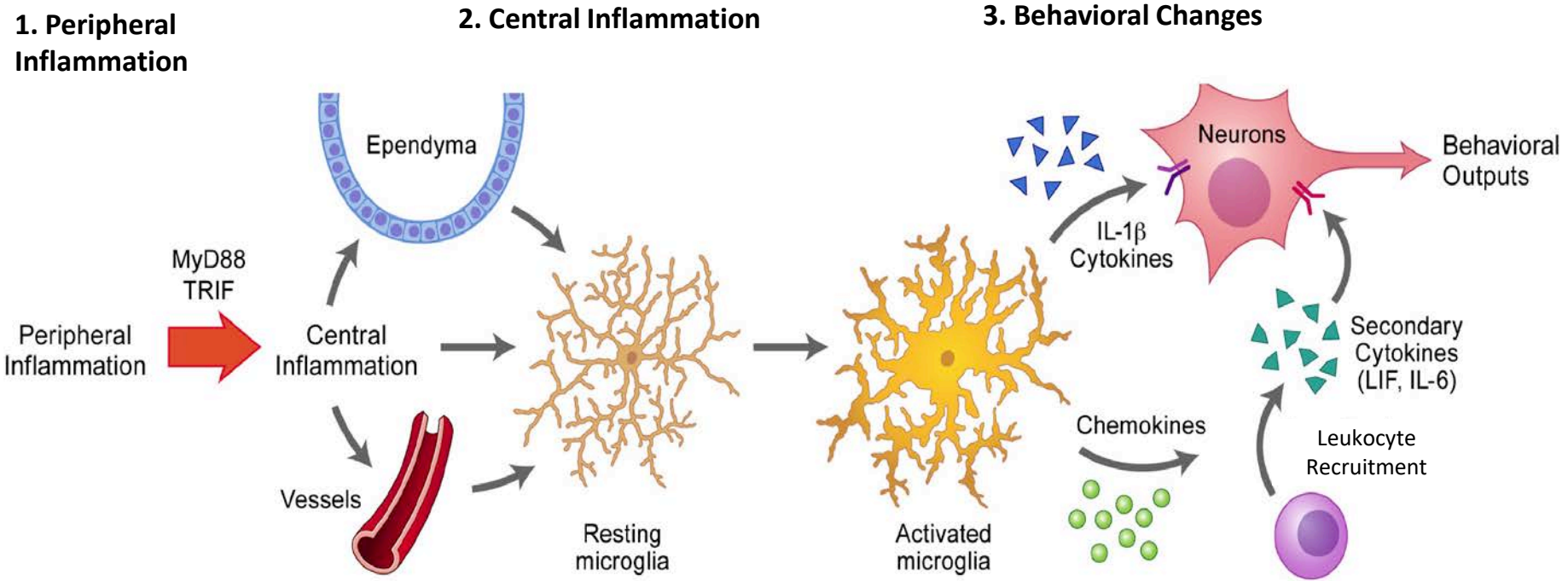




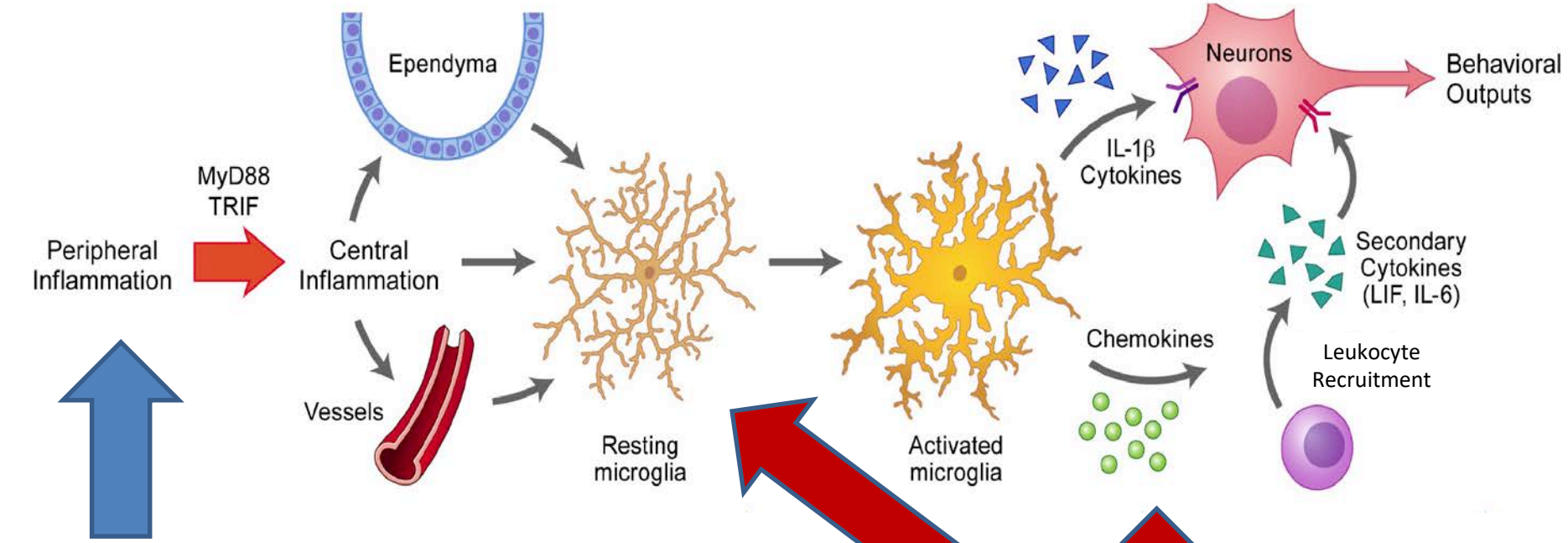
Hypothalamic Cytokine Production (IL-1b)

Bioamplifier

Amplification of Inflammation in the Hypothalamus



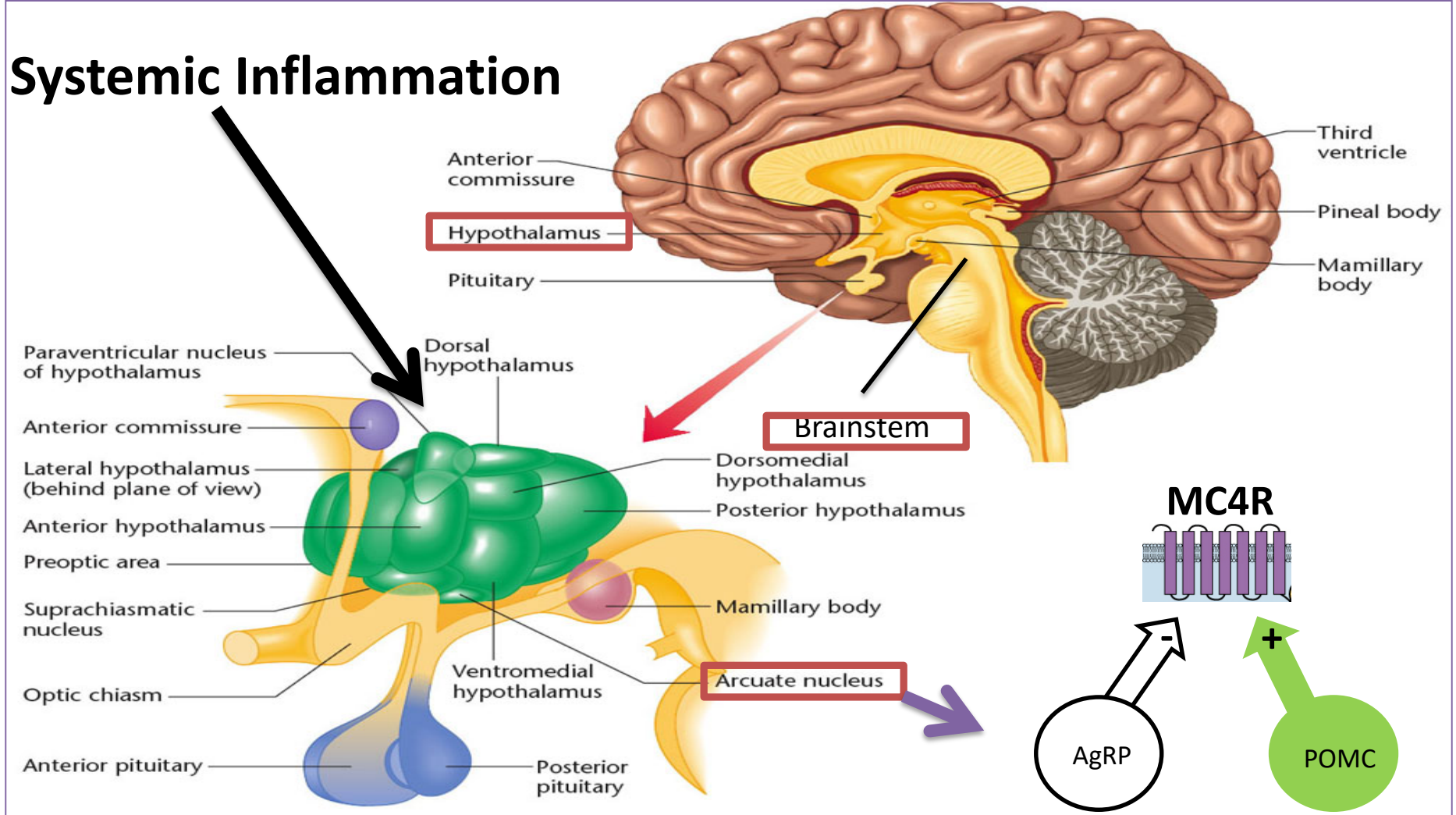
Burfeind, Michaelis and Marks, *Semin Cell Dev Biology*, 2016.



Action at a distance

Bioamplification

Systemic Inflammation



Jarrad Scarlett MD PhD

- Direct cytokine action on POMC neurons *causes* anorexia
- Support MC4R antagonism as Tx
- POMC activation *necessary* to suppress feeding

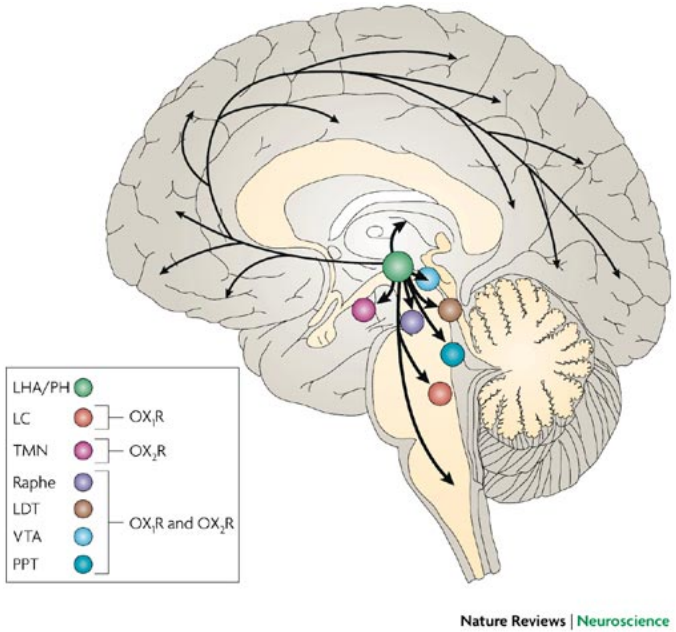
DISEASE → Inflammation → POMC

↓ Food Intake ← MC4-R ← α-MSH

DK062207, DK70333, CA150703

Orexin (hypocretin) Neurons

Sakurai *Nature Reviews Neuroscience* **8**, 171–181 (March 2007)

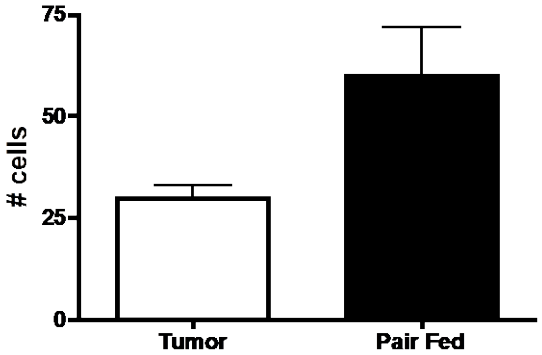


~~Orexin~~ = narcolepsy, with arousal not linked to energy status

- Active during wakefulness; silent during sleep
- Stabilize Wakefulness
- Integrate energy balance with physiologic arousal

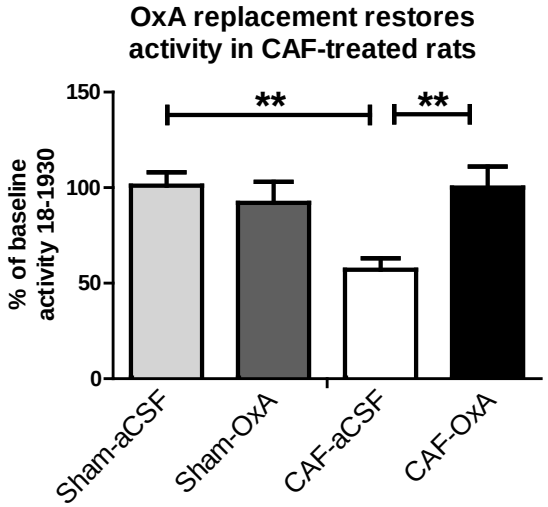
Inflammation-Induced Lethargy Is Mediated by Suppression of Orexin Neuron Activity

Aaron J. Grossberg,[1,2] XinXia Zhu,[2] Gina M. Leinninger,[3] Peter R. Levasseur,[2] Theodore P. Braun,[2] Martin G. Myers Jr,[3,4] and Daniel L. Marks[2]



Tumor Bearing Animals Lose Orexin Signaling

The Journal of Neuroscience, August 3, 2011 • 31(31):11376–11386



A role for orexin in cytotoxic chemotherapy-induced fatigue

K.B. Weymann [a], L.J. Wood [a,b], X. Zhu [a], D.L. Marks [a,*]

Brain Behav. Immun. , 2014

DISEASE or ChemoRx

Brain inflammation

Aaron Grossberg MD, PhD

Kris Weymann RN, PhD

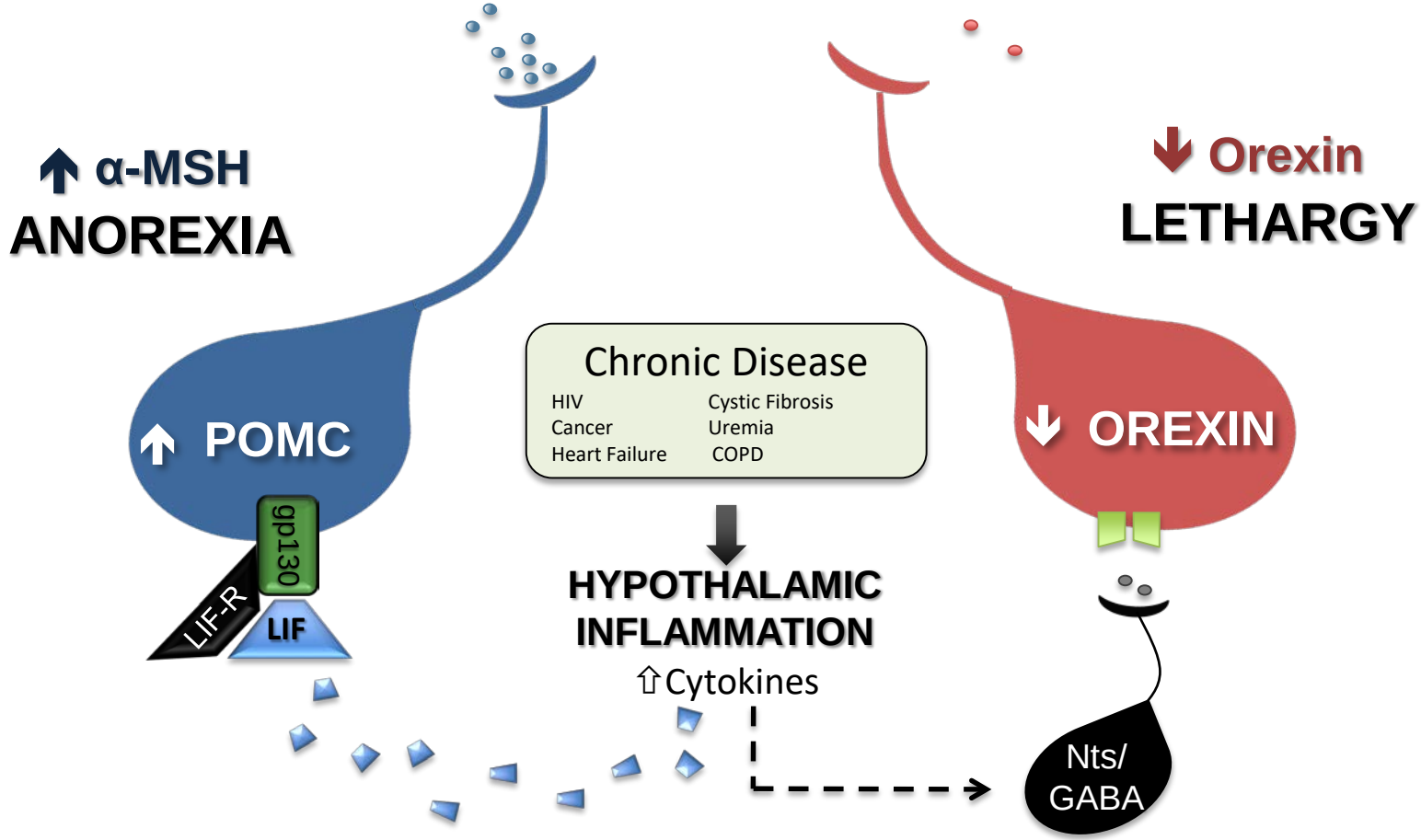
↓ OREXIN

↓ Arousal

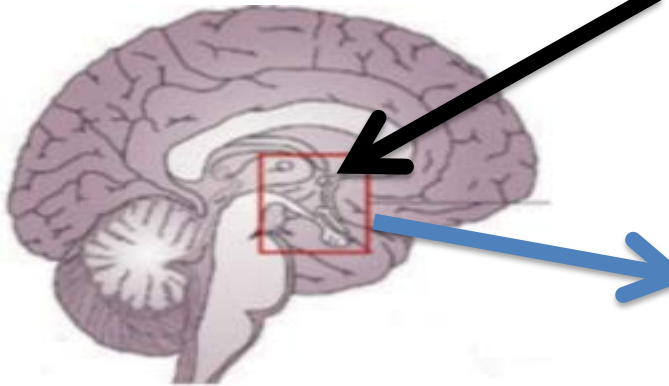
↓Orexin

DK084711, DK 70333, GM109835

Impact of CNS Cytokines on Neuronal Populations

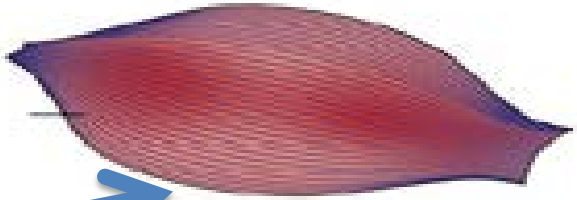


CNS inflammation contributes to muscle catabolism in a corticosterone-dependent manner



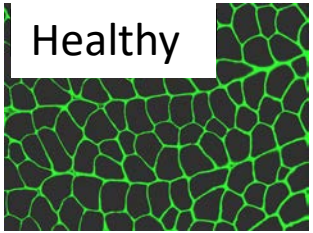
Inflammatory Cytokines

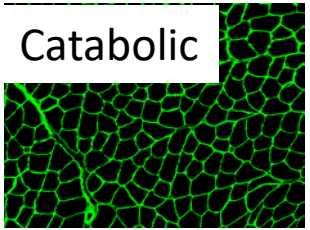
Corticosterone
(Humoral)



Muscle Catabolism

Braun et al.
J Ex Med 2011
FASEB J 2013



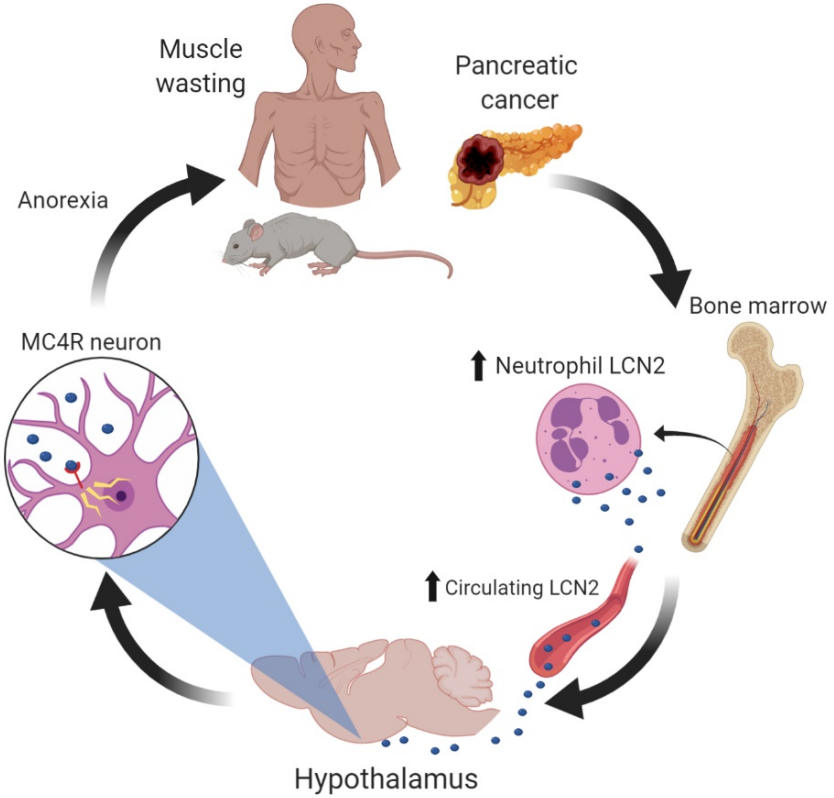


Summary

- **Chronic radiation-induced inflammation produces an understandable pathophysiological state with multiple avenues for treatment, not an inevitable side effect.**
- **The MBH functions as a receiver and an amplifier of peripheral inflammatory signals.**
- **The translation of peripheral inflammatory signals into local paracrine inflammation in the MBH is complex and involves multiple unique cell types.**
- **Orexin signaling is lost early during onset of inflammation. Actigraphy is the most sensitive signal for inflammation onset.**


Thank You!

Lipocalin-2 is an endogenous bioamplification signal that produces anorexia via binding to MC4R in the CNS



Brennan Olson

Olson et al, Nature Comm. 2021

Starvation

- Appetite ↑
- Metabolic Rate ↓
- No Lethargy
- Lean Mass Spared
- Normal Adipose Function

Cachexia

- Appetite ↓
- Metabolic Rate ↑
- Lethargy
- Lean Mass Wasting
- Adipose tissue ‘browning’