X ISNIM & III SIPNEI Congress - Neuroimmunomodulation at brain levels - Rome - 27th May 2017

Chemokines in the brain: beneficial or detrimental?

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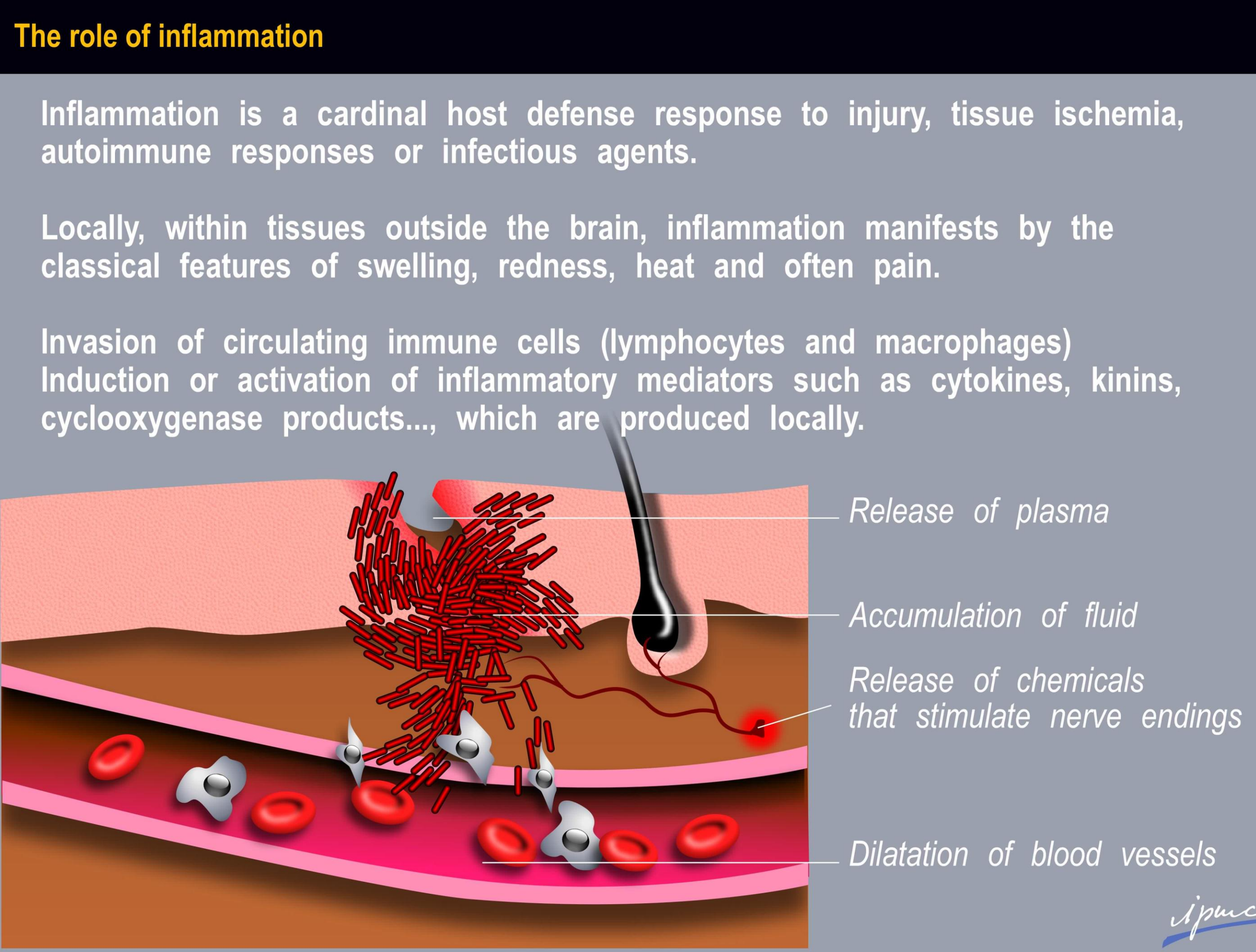
The role of inflammation

Inflammation is a cardinal host defense response to injury, tissue ischemia, autoimmune responses or infectious agents.

Locally, within tissues outside the brain, inflammation manifests by the classical features of swelling, redness, heat and often pain.

Invasion of circulating immune cells (lymphocytes and macrophages)
Induction or activation of inflammatory mediators such as cytokines, kinins, cyclooxygenase products..., which are produced locally.



The inflammatory response: a beneficial process

Local and generalized inflammatory responses to limit proliferation pathogens:

- have clear benefits in infectious states when activated in a regular manner for a defined period of time.

- localize and eradicate the irritant and repair the surrounding tissue.

Production of acute phase proteins in the liver
Activation of the sympathic nervous system
Changes in cardiovascular function
Altered neuroendocrine status

And behavioural changes which lead to energy conservation (fever...)

...which can limit bacterial proliferation

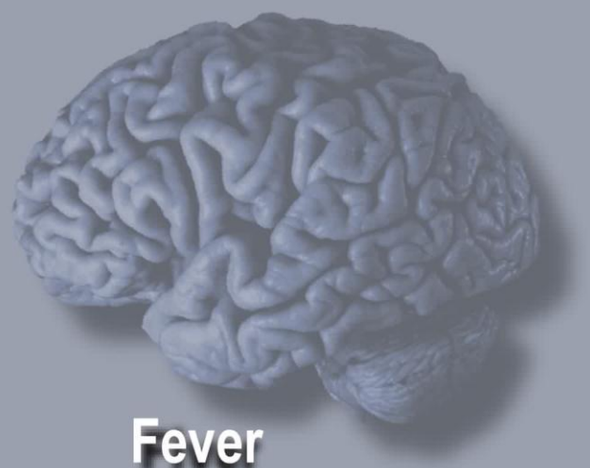
The inflammatory response: a deleterious process

- Excessive and inappropriate (in time, place and magnitude) inflammation increasingly implicated in diverse states including:
  cancer, anorexia/cachexia, diabetes, obesity, atherosclerosis, heart diseases and CNS diseases.

- Acute and chronic inflammation is involved in energy balance deregulations.

The inflammatory response and cytokines/chemokines production

CNS

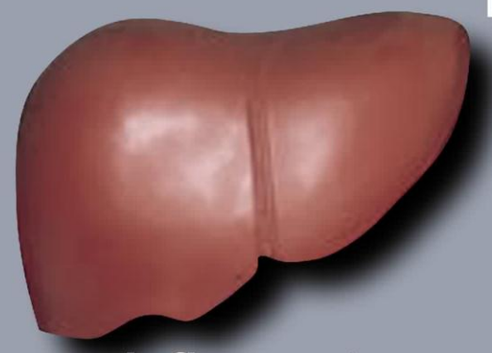


Fever

Pro-inflammatory
cytokines/ chemokines

Periphery

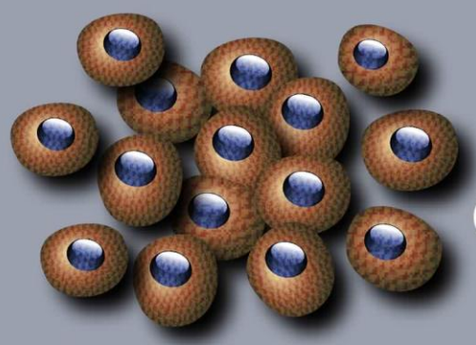
Liver



Inflammatory proteins
CRP, haptoglobin...

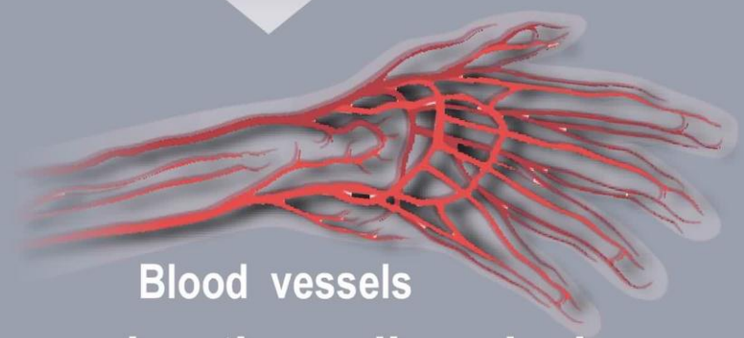
Bone marrow

leukocytosis



Cells

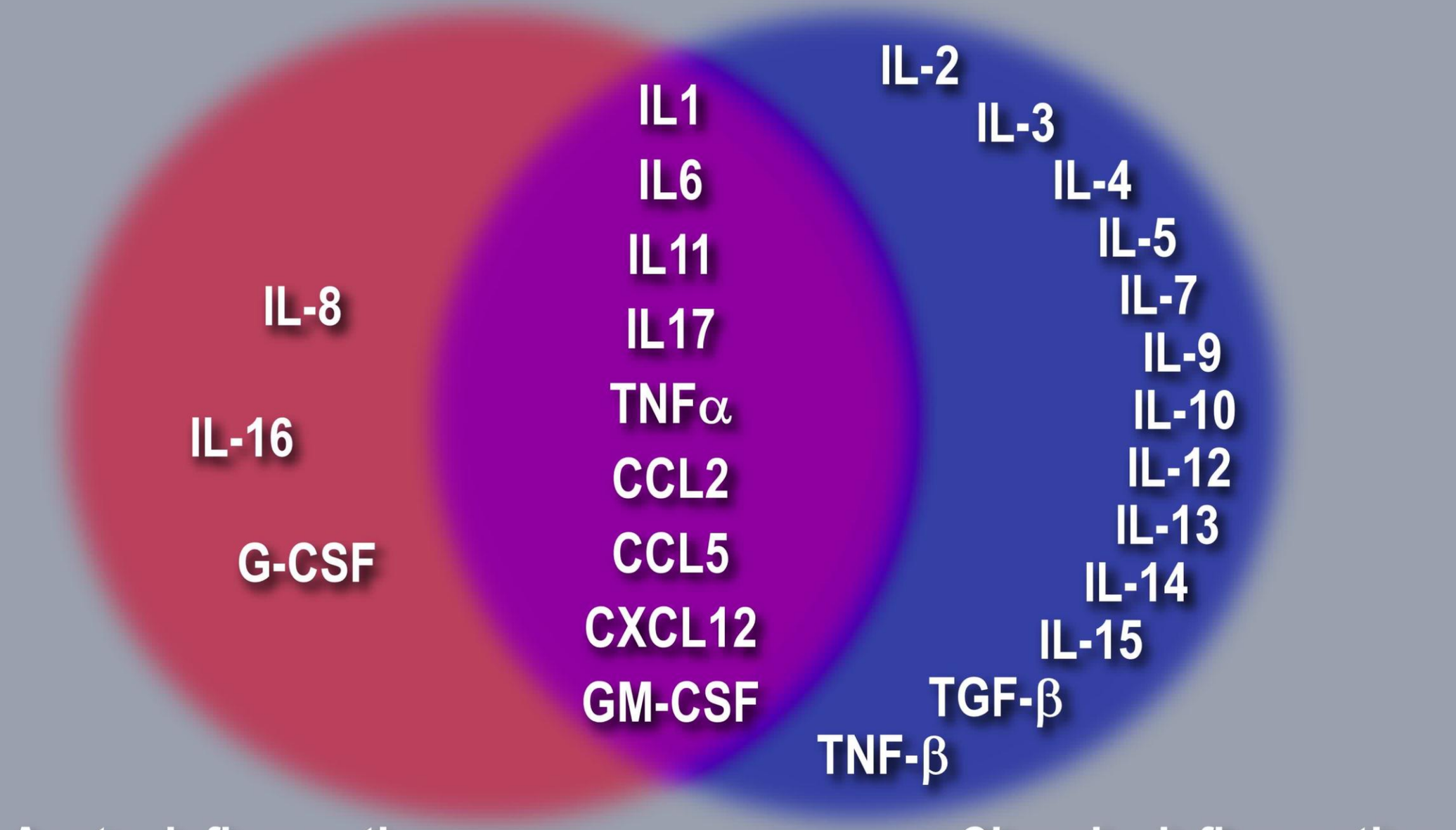
Chemotactism
Release of :
- cytokines/ chemokines
- proteases
- lipid mediators
- free radicals



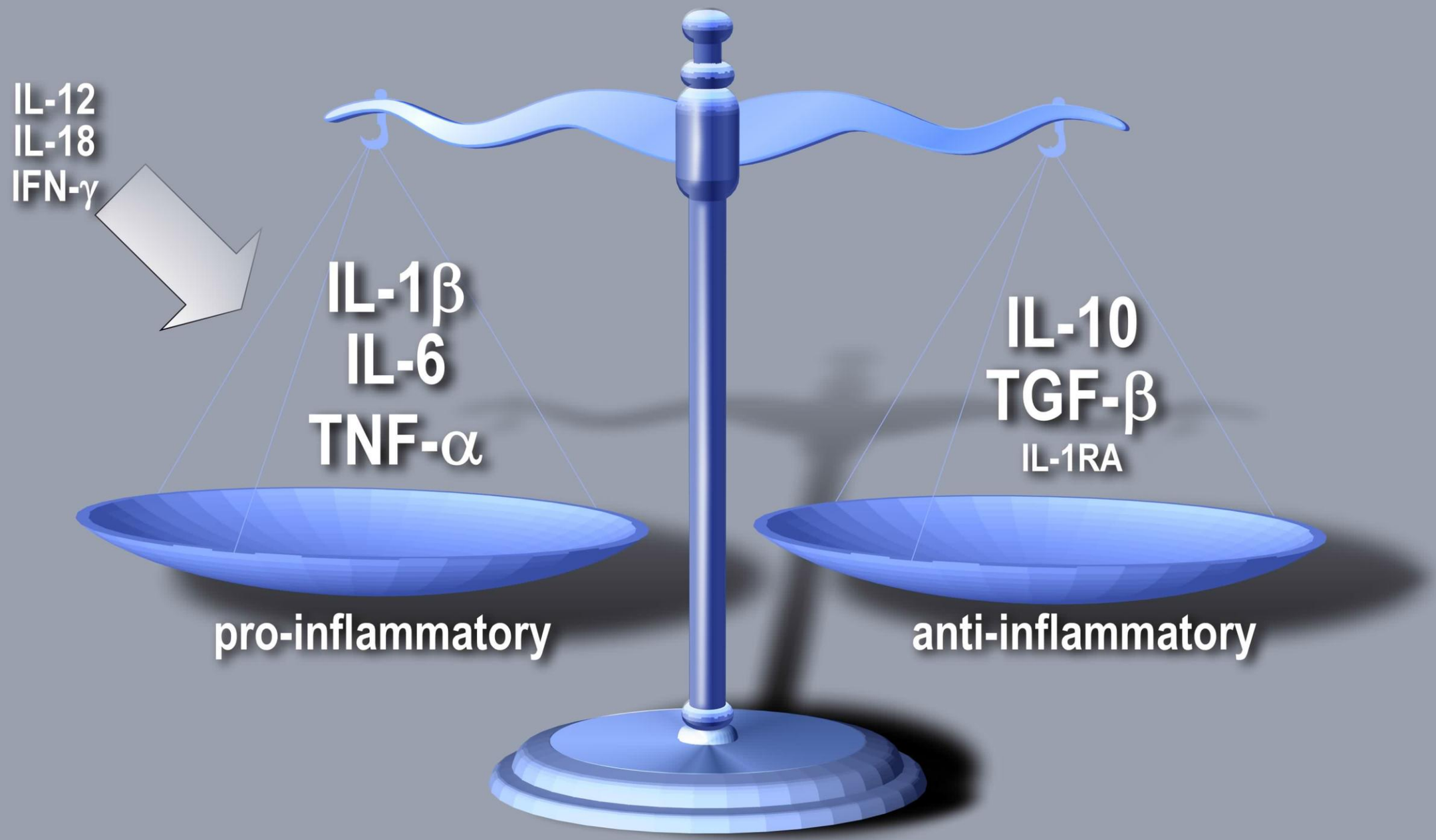
Blood vessels

migration, diapedesis,
cellular activation, cellular influx

Cytokines/chemokines involved in acute and chronic inflammatory responses



The inflammation: a balance between pro- and anti- inflammatory cytokines



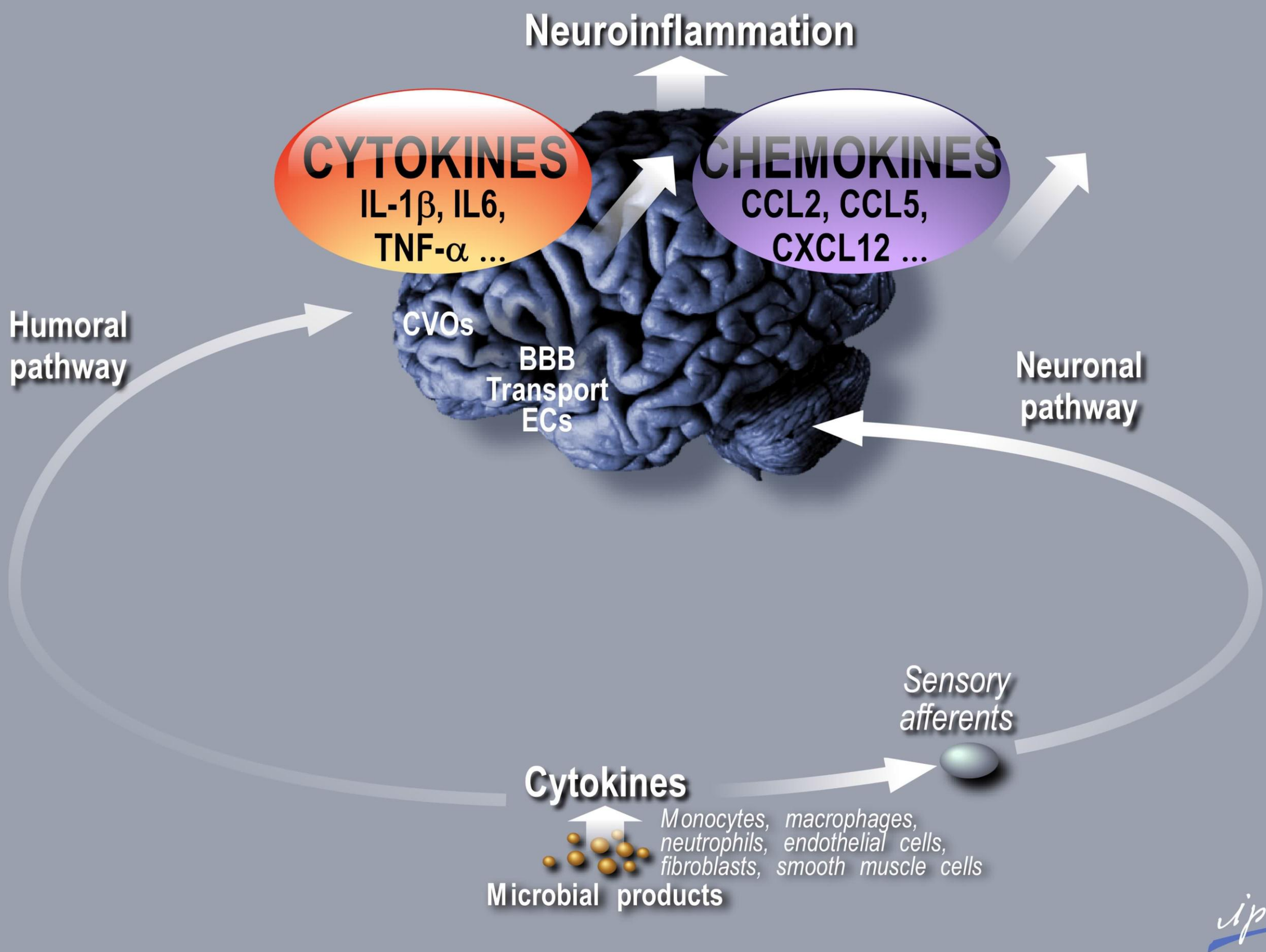
The brain as an immune privileged site

- *Old dogma:*
  Brain as an “immune privileged” organ which was not susceptible to inflammation or immune activation.

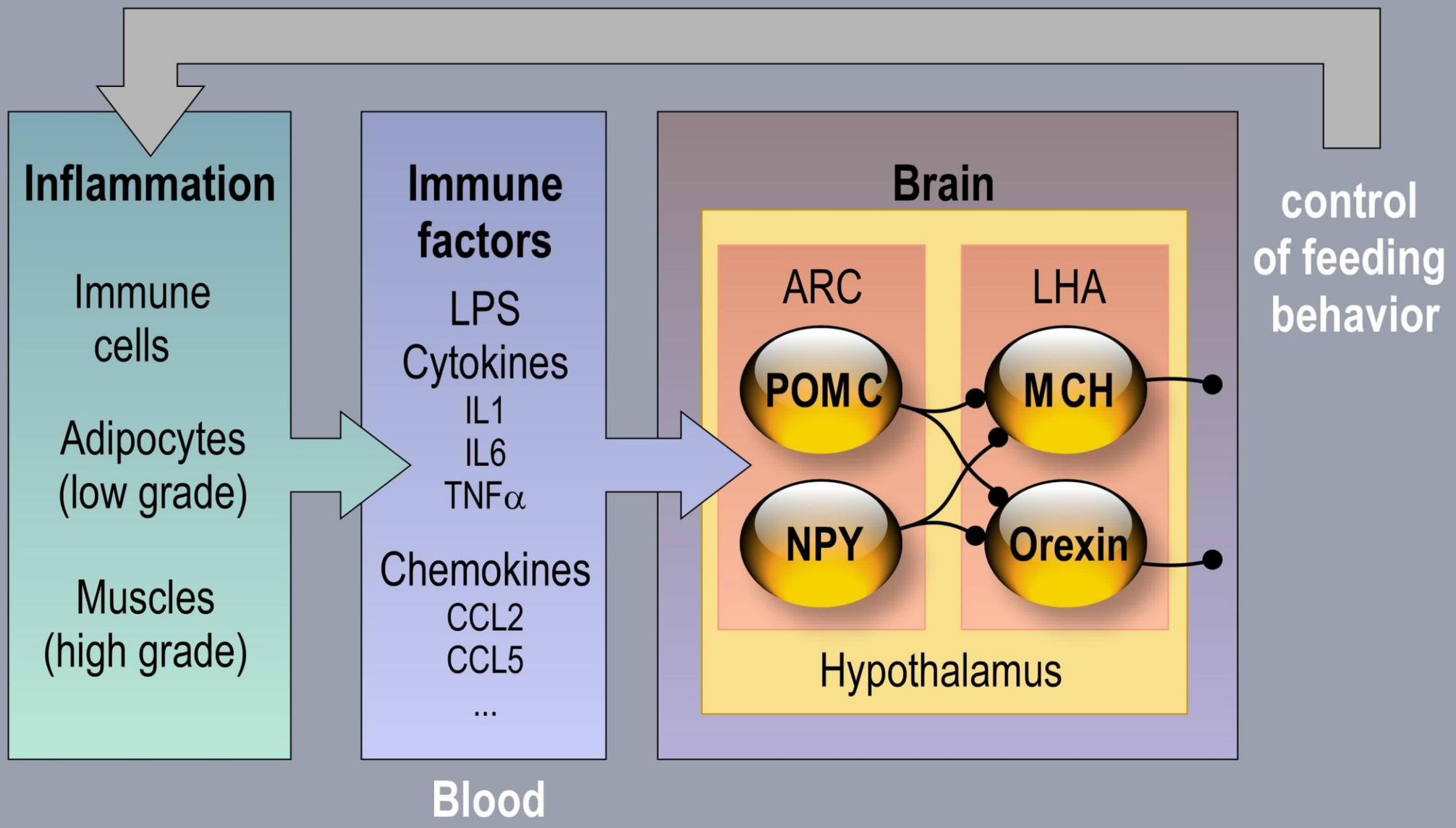
- *Actually:*
  Does exhibit key features of inflammation:
  Glial activation
  Oedema
  Systemic acute phase response with general inflammation
  Complement activation
  Synthesis of inflammatory mediators such as cytokines/chemokines
  Invasion of immune cells

CNS inflammation contributes to many acute and chronic neurodegenerative disorders and energy balance deregulations.

Expression of inflammatory mediators in the CNS



Inflammation can influence the control of feeding behavior



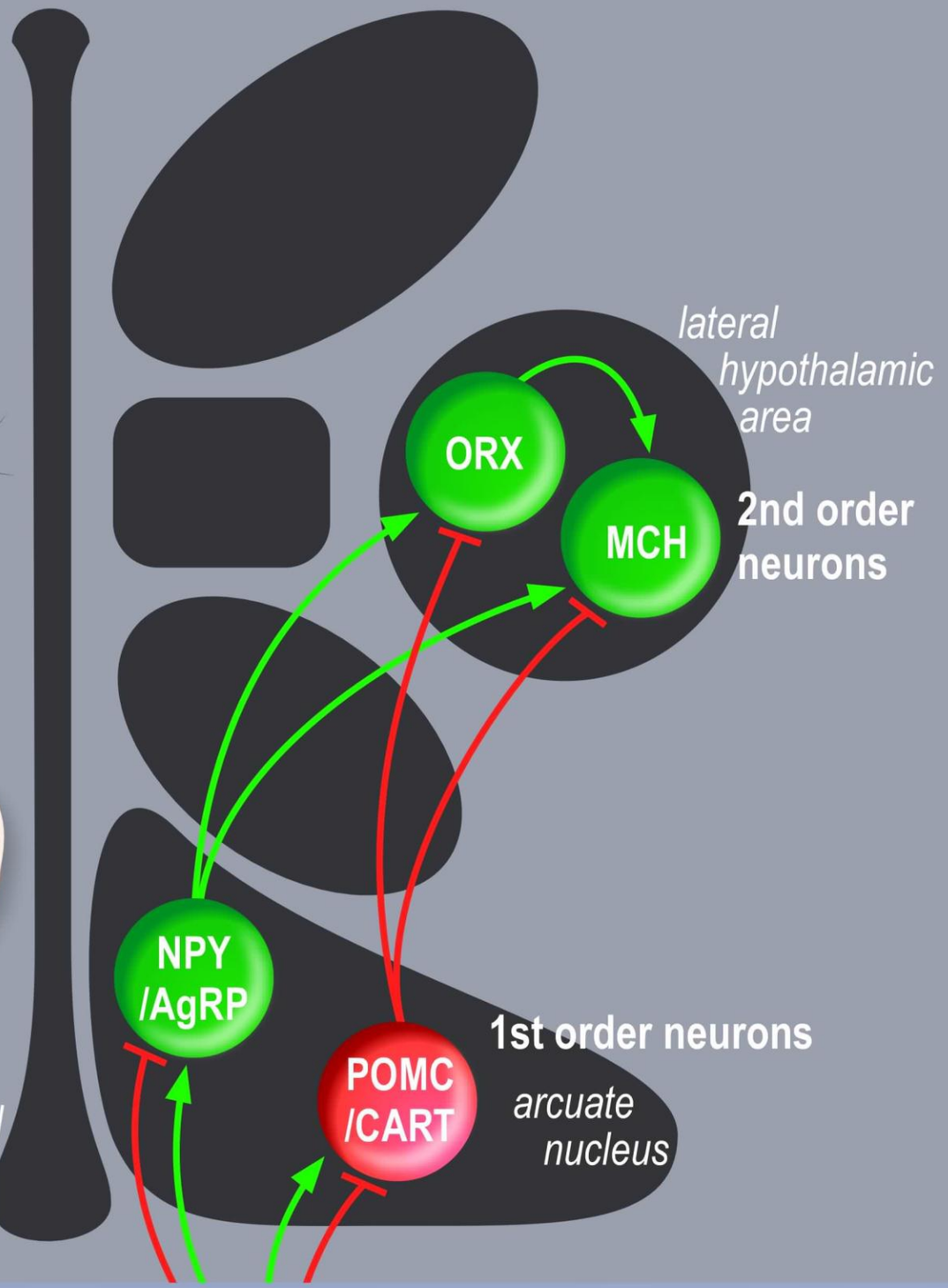
Release of immune factors in the blood which can reach the brain and modulate the neuronal circuits controlling food intake and metabolism

The energy balance

Energy intake

Energy expenditure

Hypothalamic networks involved in regulation of feeding behavior



Peripheral hormonal factors (leptin, insulin, ghrelin...)
Nutrients
Vagal afferences

appropriate food intake

orexigenic peptides:
↗ food intake

anorexigenic peptides:
↘ food intake

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Hypothalamic inflammation and energy balance deregulations

Anorexia / weight loss

Endogenous brain IL-1 mediates LPS-induced anorexia and hypothalamic cytokine expression

SOPHIE LAYÉ,[1] GILLES GHEUSI,[1] SANDRINE CREMONA,[1] CHANTAL COMBE,[1] KEITH KELLEY,[2] ROBERT DANTZER,[1] AND PATRICIA PARNET[1]

Central Nervous System Mechanisms Contributing to the Cachexia–Anorexia Syndrome

Carlos R. Plata-Salamán, MD, DSc

From the Division of Molecular Biology, School of Life and Health Sciences, University of Delaware, Newark, Delaware, USA

Evidence that Lipopolysaccharide-Induced Anorexia Depends upon Central, Rather than Peripheral, Inflammatory Signals

Brent E. Wisse, Kayoko Ogimoto, Jingjing Tang, Marvin K. Harris, Jr., Elaine W. Raines, and Michael W. Schwartz

NF-κB Activation in Hypothalamic Pro-opiomelanocortin Neurons Is Essential in Illness- and Leptin-induced Anorexia*

Received for publication, September 29, 2009, and in revised form, January 15, 2010 Published, JBC Papers in Press, January 22, 2010, DOI 10.1074/jbc.M109.070706

Pil-Geum Jang[‡1], Cherl Namkoong[‡1], Gil Myoung Kang[‡], Man-Wook Hur[§], Seung-Whan Kim[¶], Geun Hyang Kim[¶], Yeoungsup Kang[‡], Min-Jae Jeon[§], Eun Hee Kim[‖], Myung-Shik Lee[**], Michael Karin[‡‡], Ja-Hyun Baik[§§], Joong-Yeol Park[‖], Ki-Up Lee[‖], Young-Bum Kim[¶¶], and Min-Seon Kim[‡2]

Obesity

Consumption of a Fat-Rich Diet Activates a Proinflammatory Response and Induces Insulin Resistance in the Hypothalamus

Cláudio T. De Souza,* Eliana P. Araujo,* Silvana Bordin, Rika Ashimine, Ricardo L. Zollner, Antonio C. Boschero, Mário J. A. Saad, and Lício A. Velloso

Hypothalamic proinflammatory lipid accumulation, inflammation, and insulin resistance in rats fed a high-fat diet

Kelly A. Posey,[1] Deborah J. Clegg,[2] Richard L. Printz,[1] Jaeman Byun,[3] Gregory J. Morton,[4] Anuradha Vivekanandan-Giri,[3] Subramaniam Pennathur,[3] Denis G. Baskin,[5,6] Jay W. Heinecke,[7] Stephen C. Woods,[8] Michael W. Schwartz,[4] and Kevin D. Niswender[9,1,10]

MyD88 Signaling in the CNS Is Required for Development of Fatty Acid-Induced Leptin Resistance and Diet-Induced Obesity

André Kleinridders,[1,2,3,5] Dominik Schenten,[4,5] A. Christine Könner,[1,2,3,5] Bengt F. Belgardt,[1,2,3,5] Jan Mauer,[1,2,3] Tomoo Okamura,[1,2,3] F. Thomas Wunderlich,[1,2,3] Ruslan Medzhitov,[4] and Jens C. Brüning[1,2,3,*]

Obesity is associated with hypothalamic injury in rodents and humans

Joshua P. Thaler,[1,2] Chun-Xia Yi,[3] Ellen A. Schur,[2] Stephan J. Guyenet,[1,2] Bang H. Hwang,[1,2,4] Marcelo O. Dietrich,[5] Xiaolin Zhao,[1,2,6] David A. Sarruf,[1,2] Vitaly Izgur,[7] Kenneth R. Maravilla,[7] Hong T. Nguyen,[1,2] Jonathan D. Fischer,[1,2] Miles E. Matsen,[1,2] Brent E. Wisse,[1,2] Gregory J. Morton,[1,2] Tamas L. Horvath,[5,8] Denis G. Baskin,[1,2,4] Matthias H. Tschöp,[3] and Michael W. Schwartz[1,2]

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Actors of inflammation

Cellular actors

basophil

monocyte

macrophage

dendritic cell

eosinophil

« Natural Killer »

T lymphocyte

platelets

neutrophil

mast cell

B lymphocyte

astrocyte *in the CNS*

microglia

Molecular actors

histamin

serotonin

reactive oxygen species

nitric oxyde

kinins

factors of complement

lysosomal enzymes

prostaglandins

coagulation/ fibrinolys system

leucotrienes

cytokines (IL-1β, IL-6, TNF-α...)

chemokines (CCL2, CCL5...)

Actors of inflammation

Cellular actors

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prostaglandins

coagulation/ fibrinolys system

leucotrienes

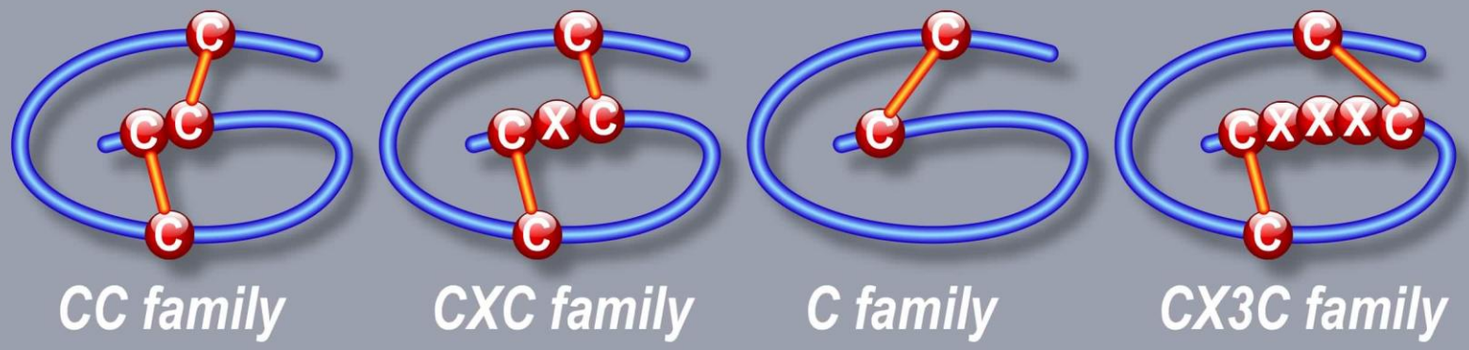
cytokines (IL-1β, IL-6, TNF-α...)

chemokines (CCL2, CCL5...)

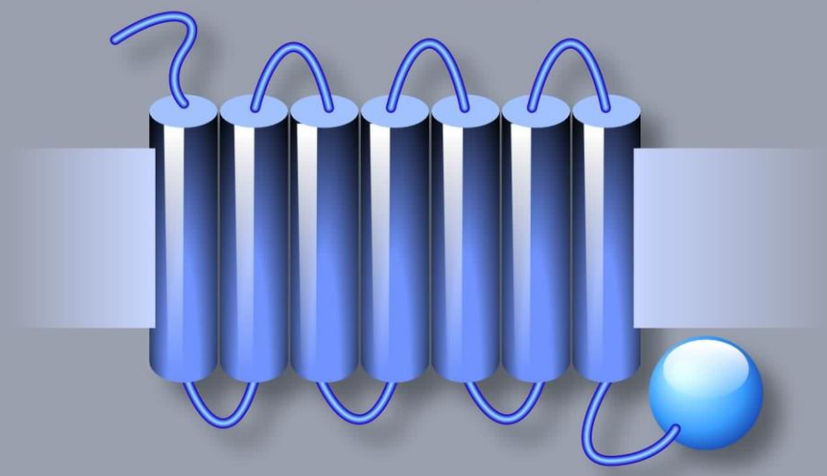
Chemokines and their receptors

Chemokines: chemoattractant cytokines
Known for attracting immune cells to infection/inflammed site

Chemokines families



Chemokines receptors



Redundant system

- **CCR2** ← **CCL2**, CCL6, CCL7, CCL8, CCL12, CCL13
- **CCL5** ← CCR1, CCR3, CCR5

Roles of chemokines in the brain

European Journal of Neuroscience, Vol. 21, pp. 701–710, 2005 © Federation of European Neuroscience Societies

Complex effects of stromal cell-derived factor-1α on melanin-concentrating hormone neuron excitability

A. Guyon,[1] G. Banisadr,[2] C. Rovère,[1] A. Cervantes,[1] P. Kitabgi,[2] S. Melik-Parsadaniantz[2] and J.-L. Nahon[1]

Are chemokines the third major system in the brain?

Martin W. Adler*,†,[1] and Thomas J. Rogers*,†,‡

*Center for Substance Abuse Research, ‡Fels Institute for Cancer Research and Molecular Biology, †Department of Pharmacology, Temple University School of Medicine, Philadelphia, Pennsylvania

The chemokine SDF-1/CXCL12 modulates the firing pattern of vasopressin neurons and counteracts induced vasopressin release through CXCR4

Céline Callewaere*†‡, Ghazal Banisadr*†‡, Michel G. Desarménien§¶‖, Patricia Mechighel*†, Patrick Kitabgi*†, William H. Rostène*†**, and Stéphane Mélik Parsadaniantz*†

Chemokines in and out of the central nervous system: much more than chemotaxis and inflammation

Astrid E. Cardona,[1] Meizhang Li,[1] Liping Liu,[1] Carine Savarin,[1] and Richard M. Ransohoff[2]

Neuroinflammation Research Center, Department of Neurosciences, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA

OPINION

Chemokines: a new class of neuromodulator?

William Rostène, Patrick Kitabgi and Stéphane Mélik Parsadaniantz

Some facts about chemokines in the CNS

- Regulation of leukocyte infiltration into the brain
- Immune-glial cell communication
- Physiological intracellular communications
- Neurotoxicity/Neuronal survival
- Brain development
- Constitutively expressed in the brain
- **Neuromodulation**
- etc

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For each pathology, an inflammation state

Anorexia / weight loss

High-grade inflammation with high levels of pro-inflammatory mediators

Acute, often limited in time

Inflammation by systemic infection, lesion, cancer ...

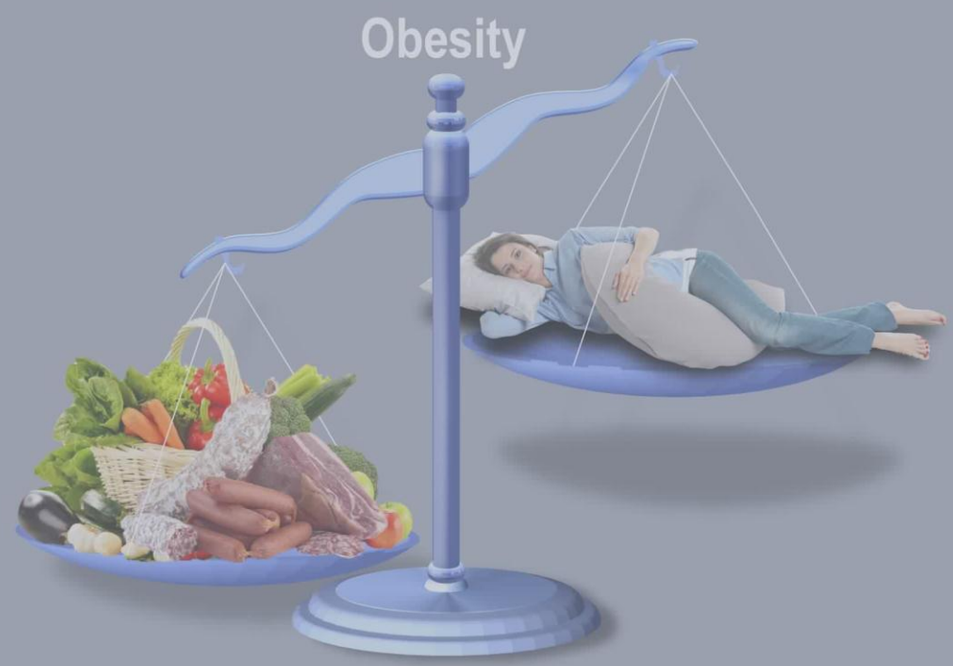
Obesity

Low-grade inflammation with low levels of pro-inflammatory mediators

Chronic

Aseptic inflammation, metabolic inflammation

For each pathology, an inflammation state



High-grade inflammation with high levels of pro-inflammatory mediators	Low-grade inflammation with low levels of pro-inflammatory mediators
Acute, often limited in time	Chronic
Inflammation by systemic infection, lesion, cancer ...	Aseptic inflammation, metabolic inflammation

Weight loss and inflammation

illness
(high-grade inflammation)

overexpression
of pro-inflammatory mediators
(cytokines, chemokines...)

sickness behavior

fever
malaise
lassitude
muscle and joint pain
loss of appetite and
weight-loss...

our question?

which inflammatory factor(s) can mediate this energy balance deregulation at the central level?

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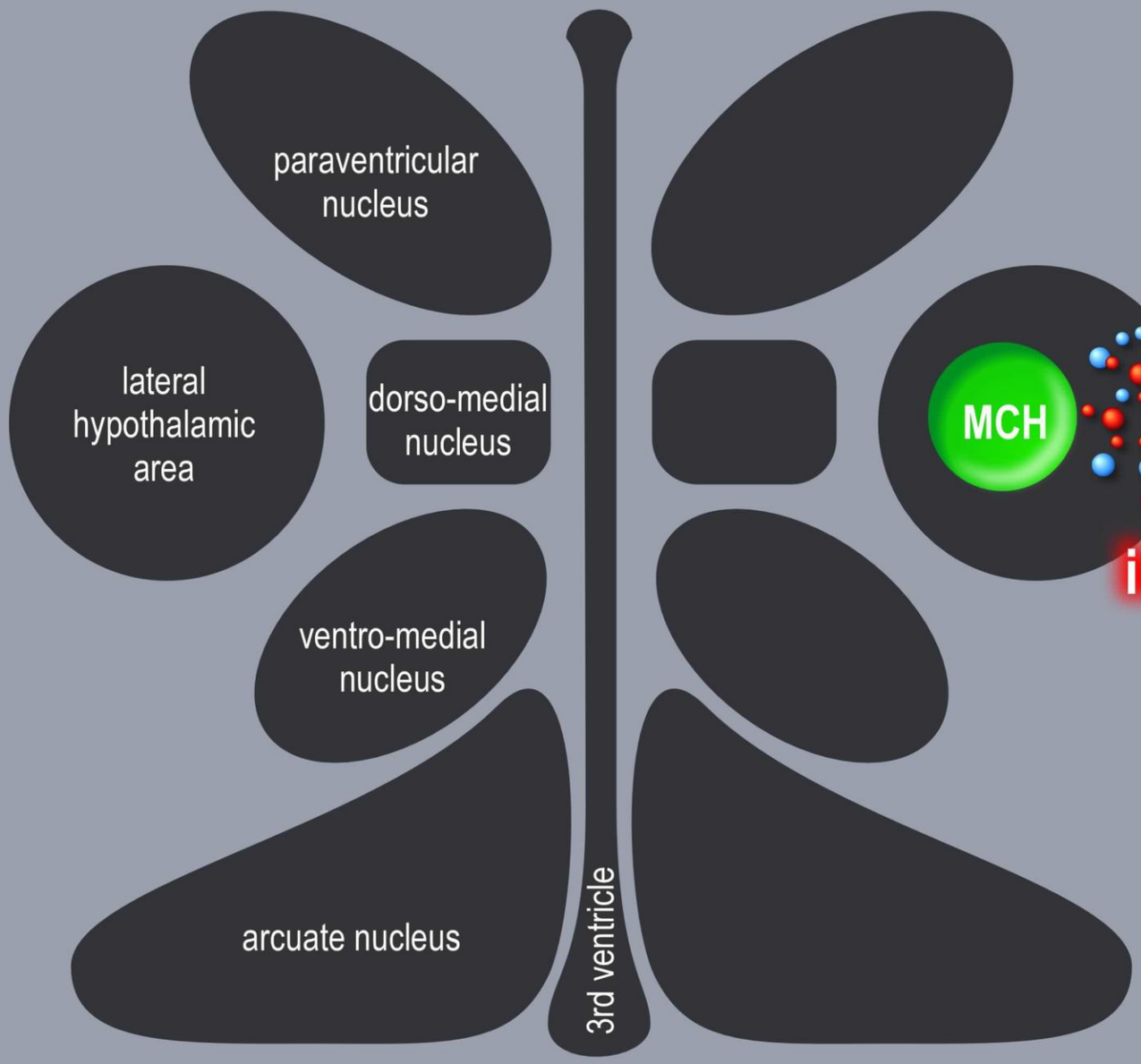
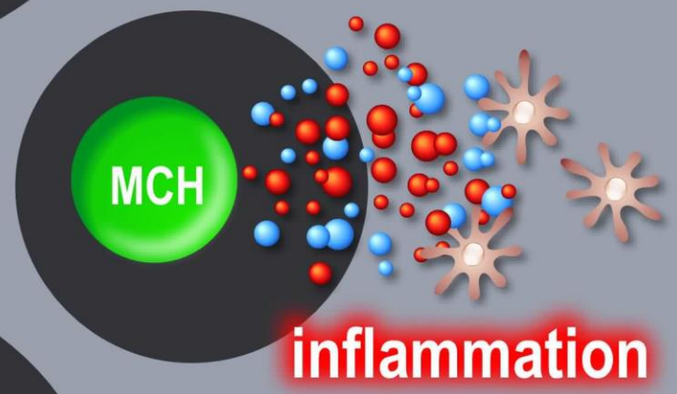
Hypothesis

high-grade inflammation in the hypothalamus





↘ of production and secretion of orexigenic peptides (MCH)

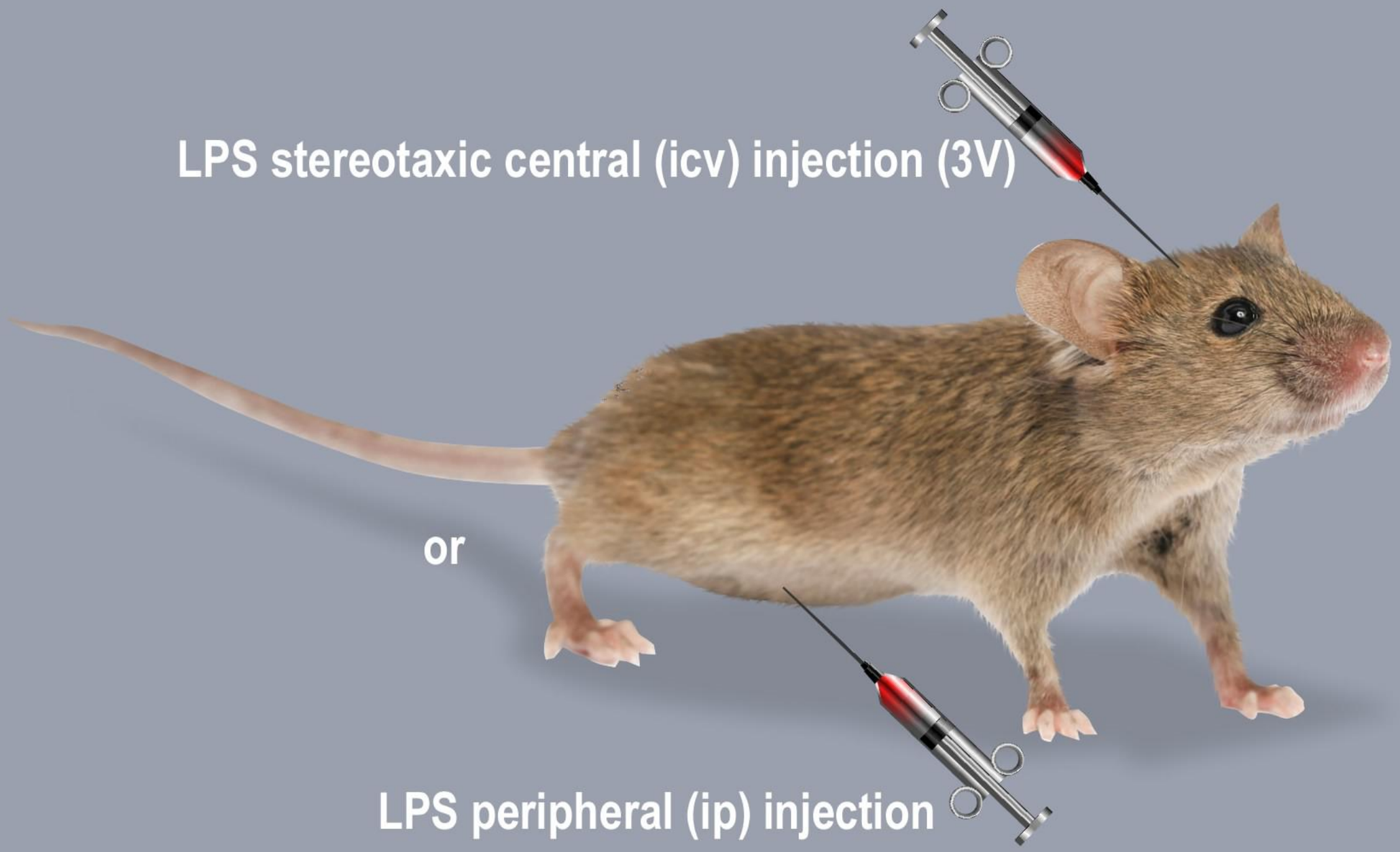
→ anorexia + ↘ body weight

Our model: LPS-induced inflammation

LPS stereotaxic central (icv) injection (3V)

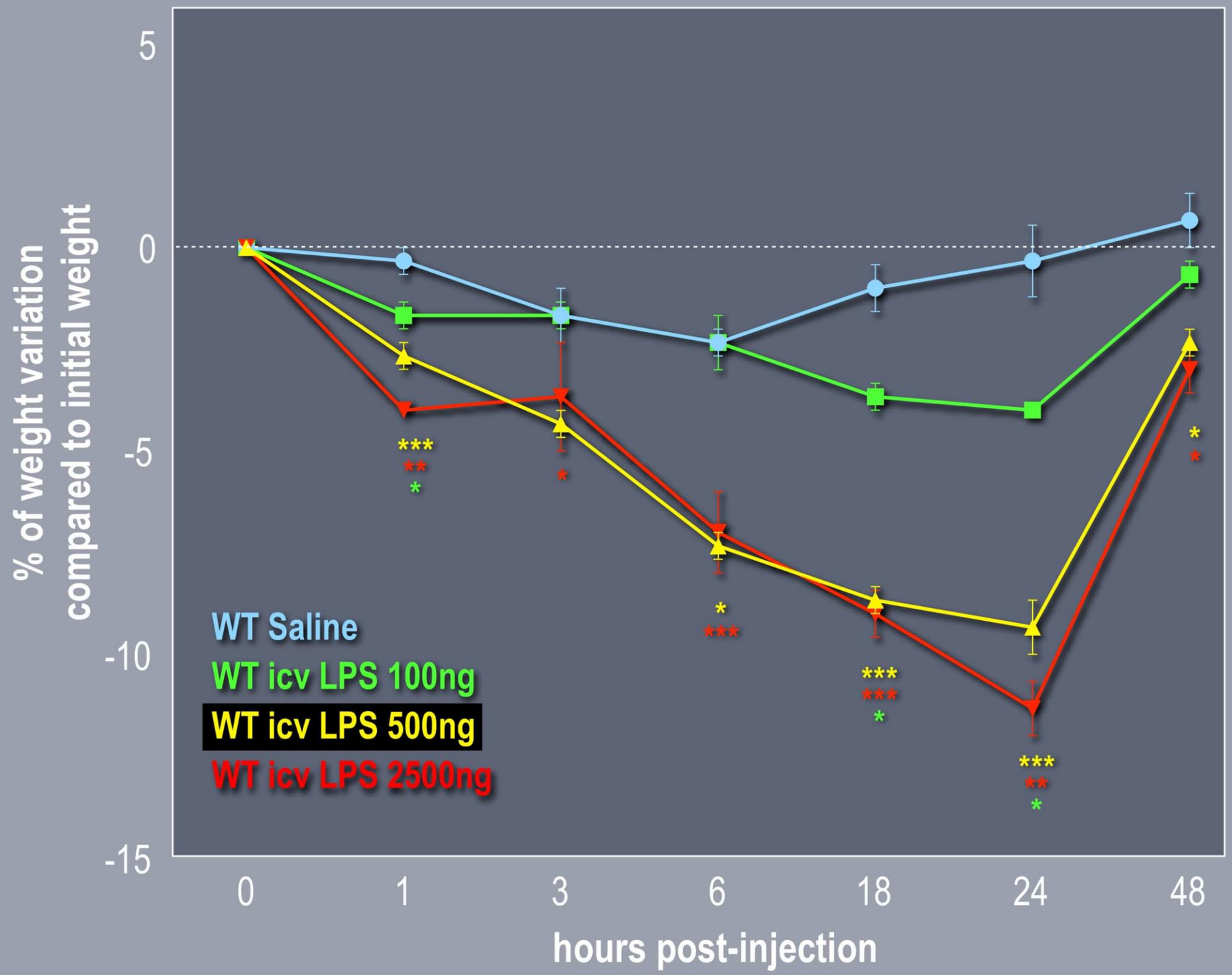
or

LPS peripheral (ip) injection



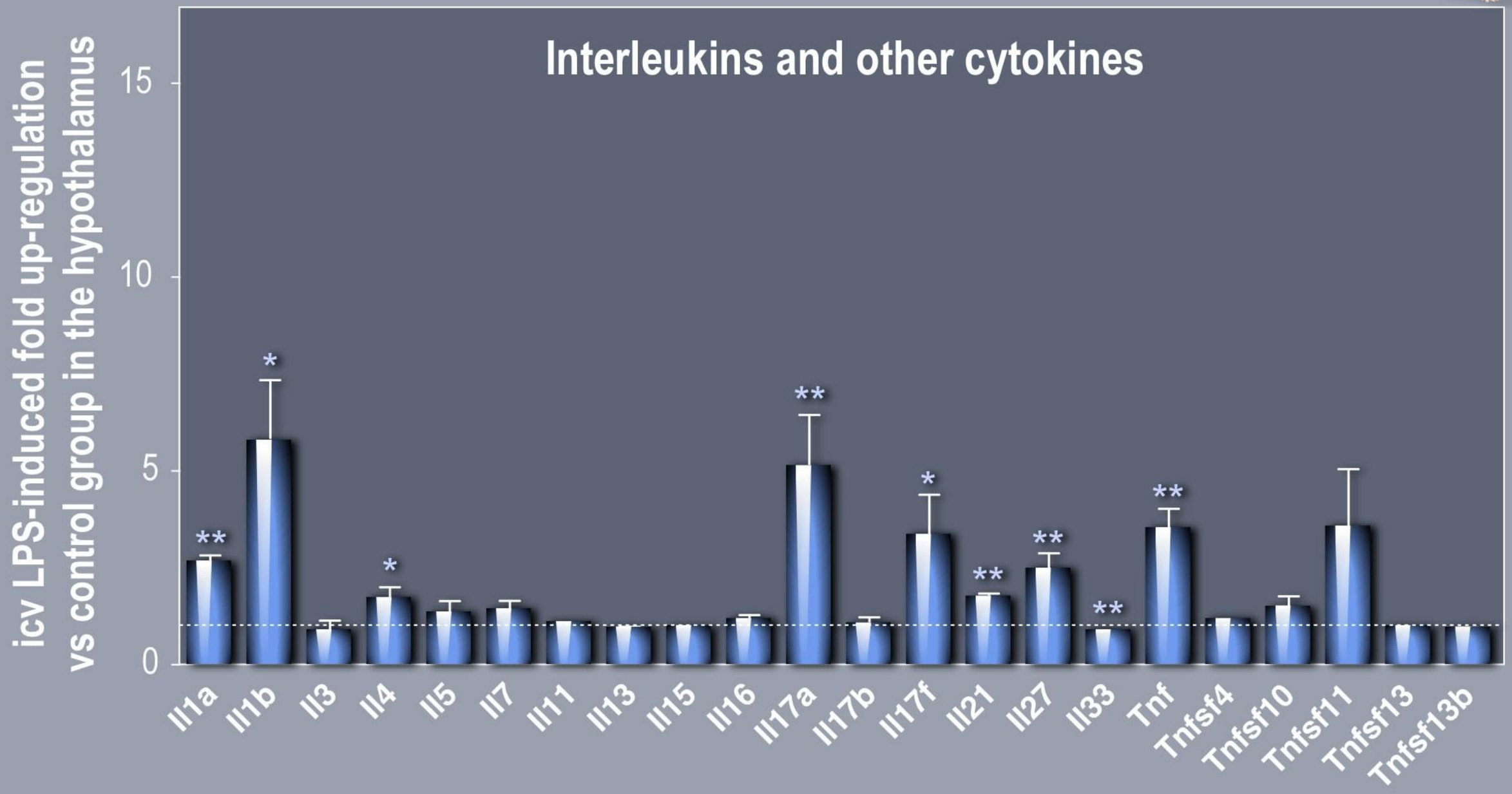
Le Thuc et al., EMBO Reports, 2016

LPS injection induces weight loss



Le Thuc et al., EMBO Reports, 2016

LPS injection induces inflammation in the hypothalamus



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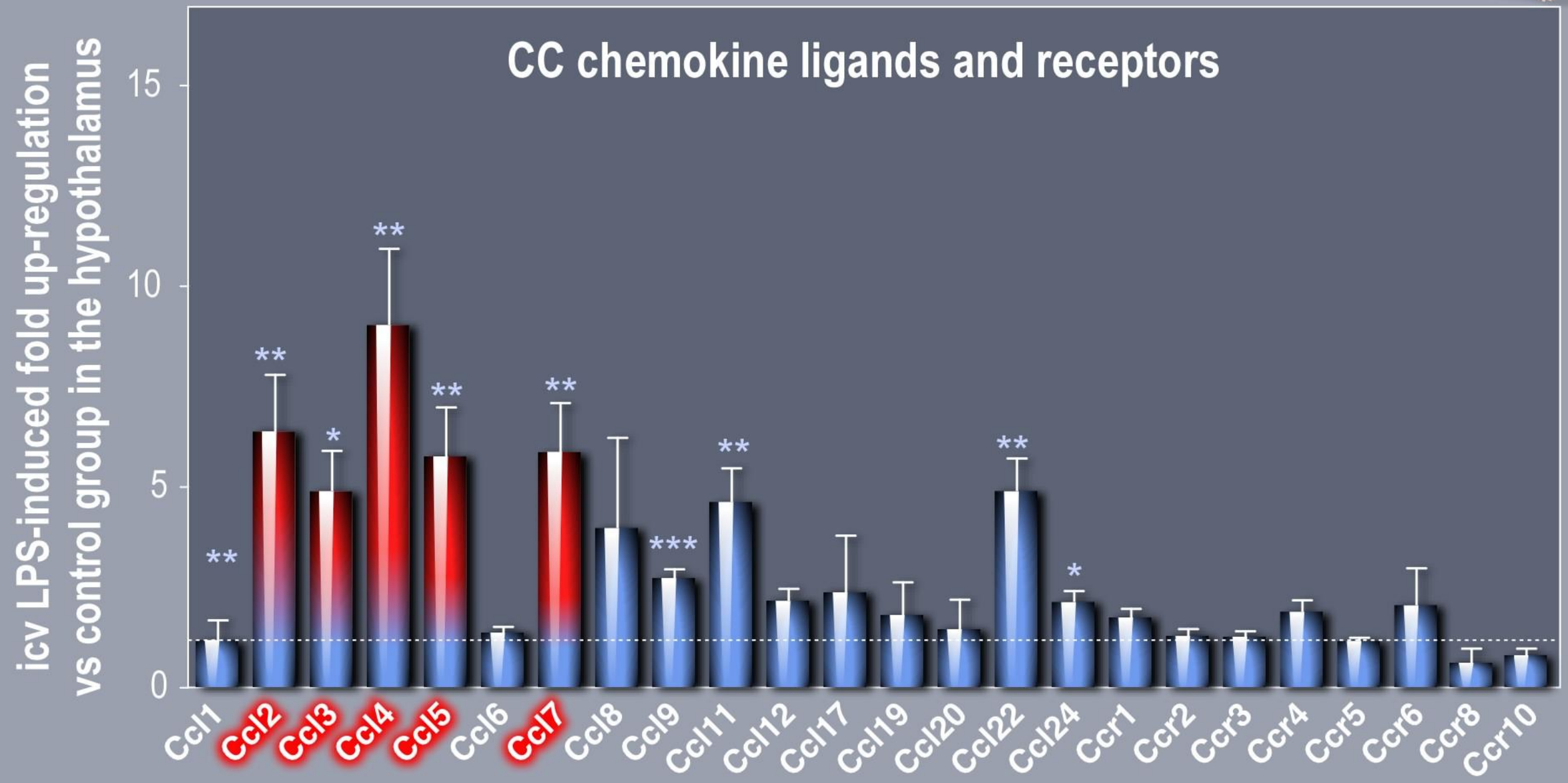
LPS injection induces inflammation in the hypothalamus



CCL2 is primarily involved in brain inflammation after ip LPS injection

(Thompson et al., 2008; Cazareth et al., 2014)

Can CCL2 mediate inflammation-induced weight-loss?

Le Thuc et al., EMBO Reports, 2016

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Central CCR2 signalling is required for metabolic and behavioural changes associated with inflammation

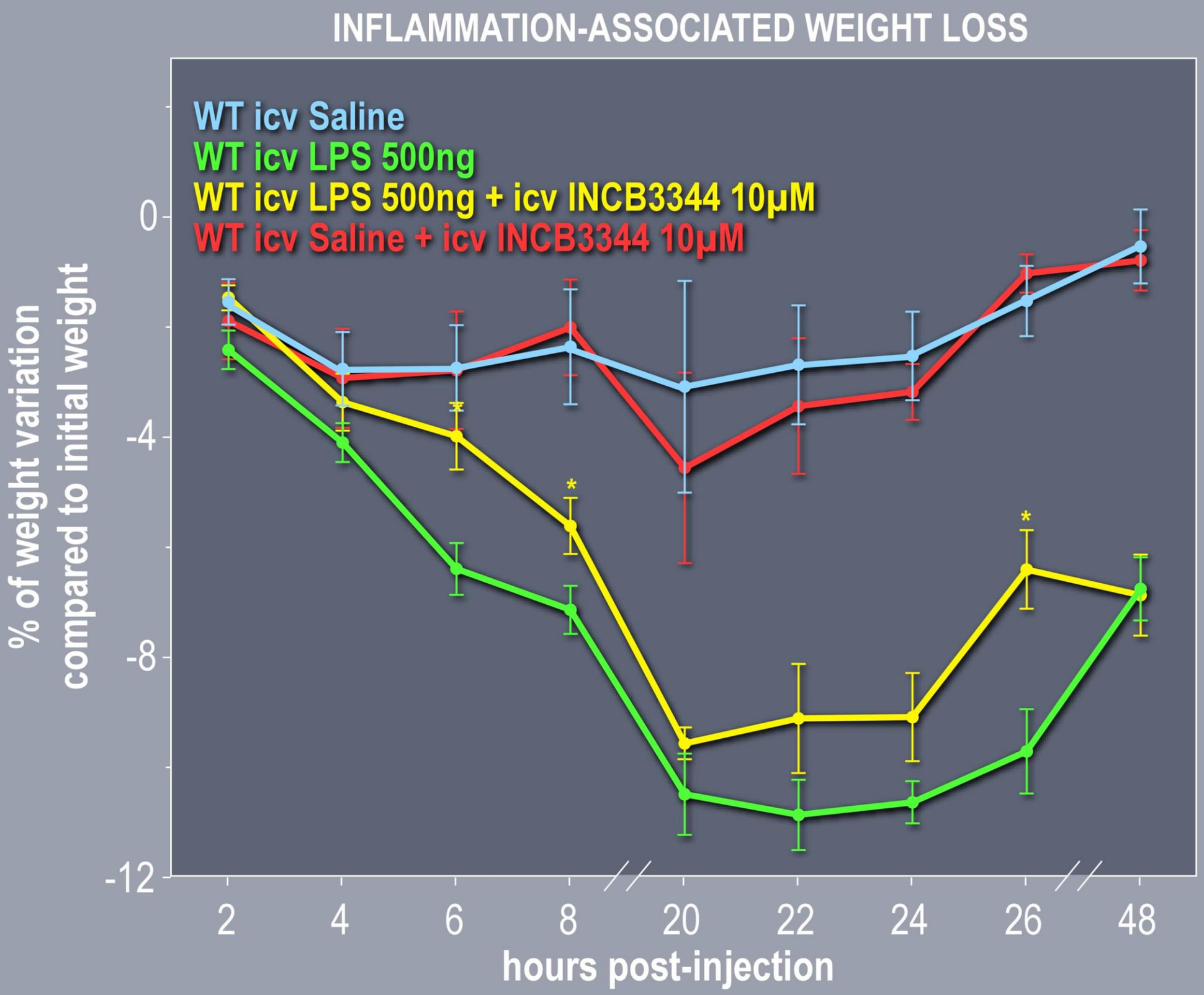
Strategy:
block central CCR2 signalling pharmacologically and by use of transgenic animals

icv injection of INCB3344 (inhibitor of CCR2)

CCR2 KO mice

Le Thuc et al., EMBO Reports, 2016

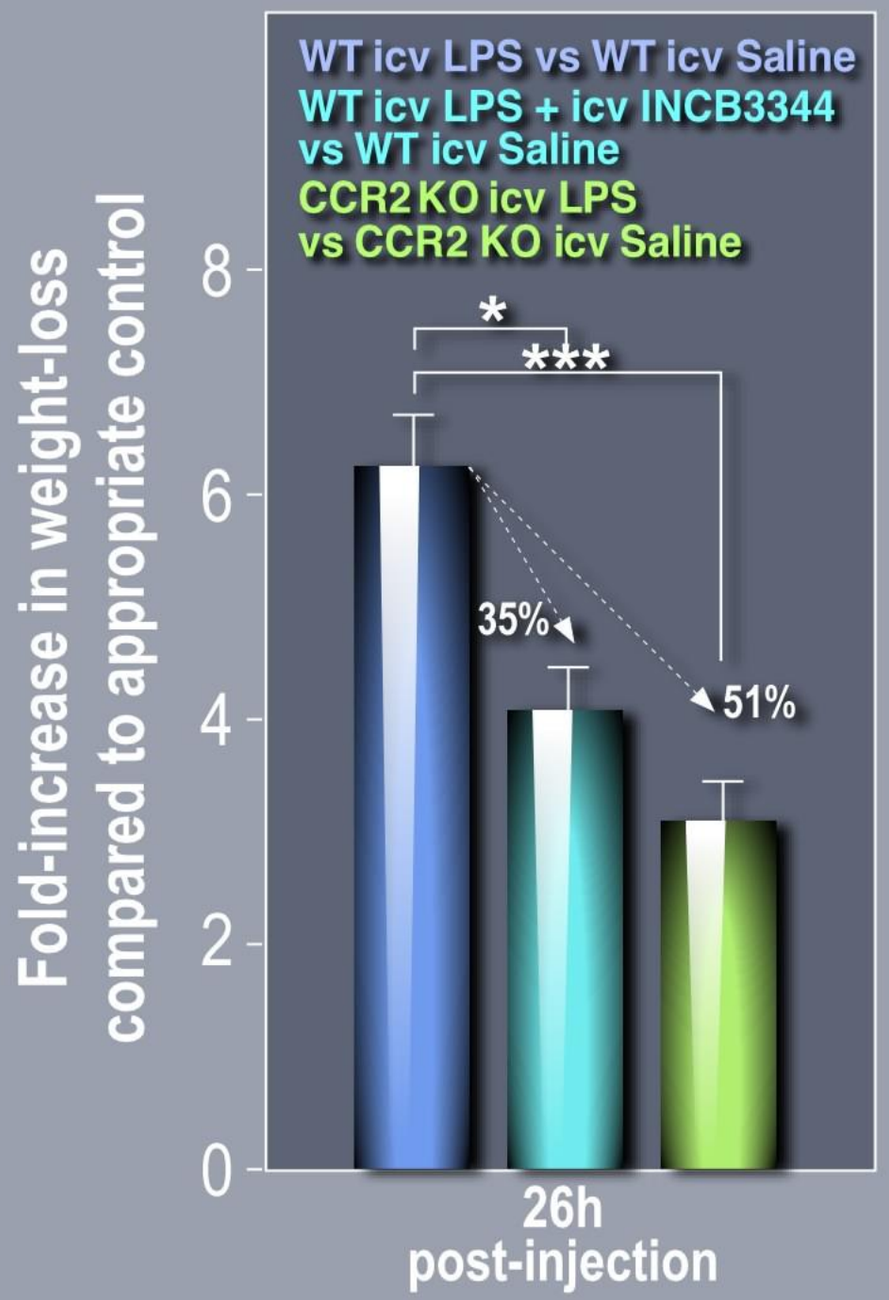
Central CCR2 signalling is required for metabolic and behavioural changes associated with inflammation

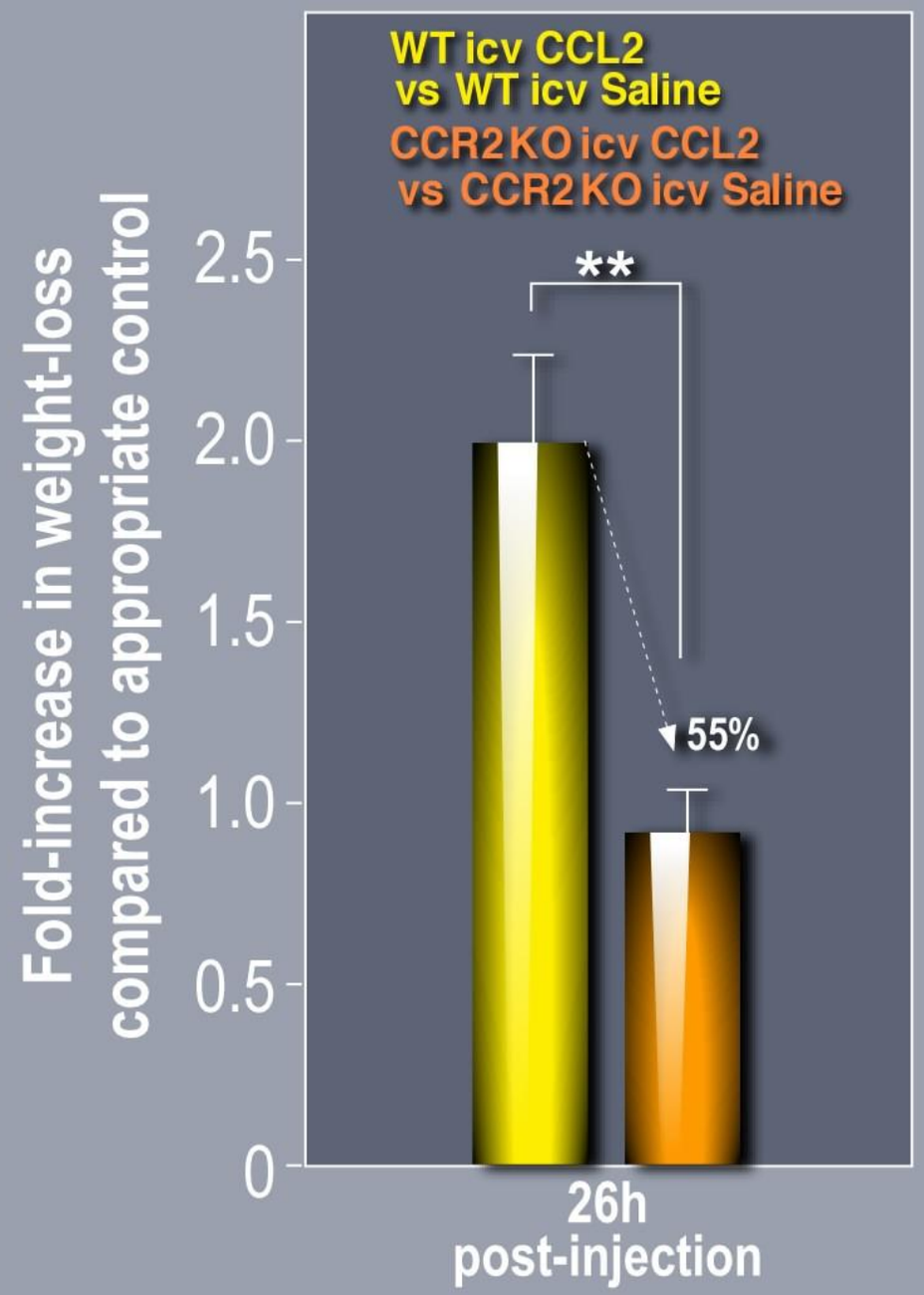


Le Thuc et al., EMBO Reports, 2016

Central CCR2 signalling is required for metabolic and behavioural changes associated with inflammation

INFLAMMATION-ASSOCIATED WEIGHT LOSS



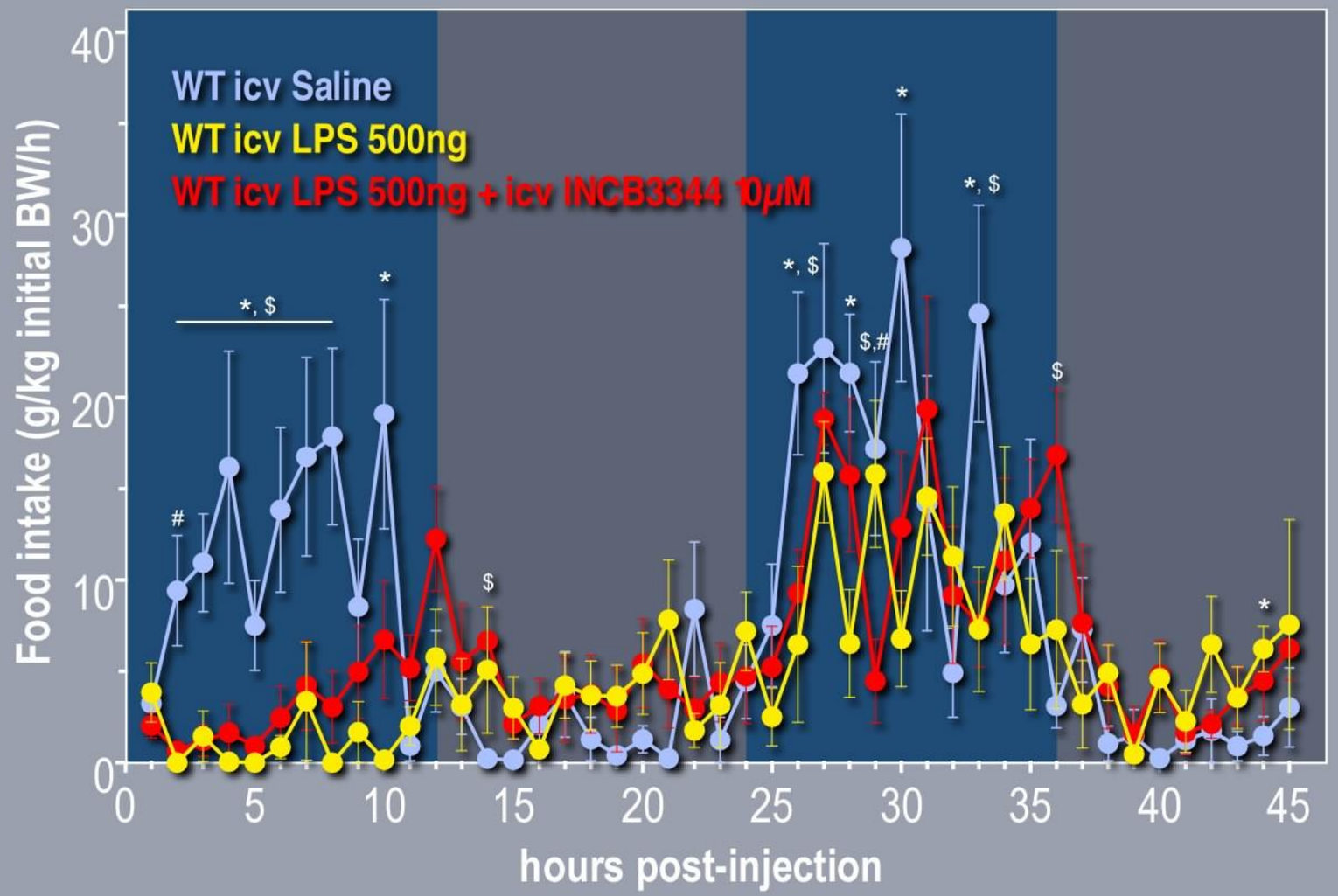


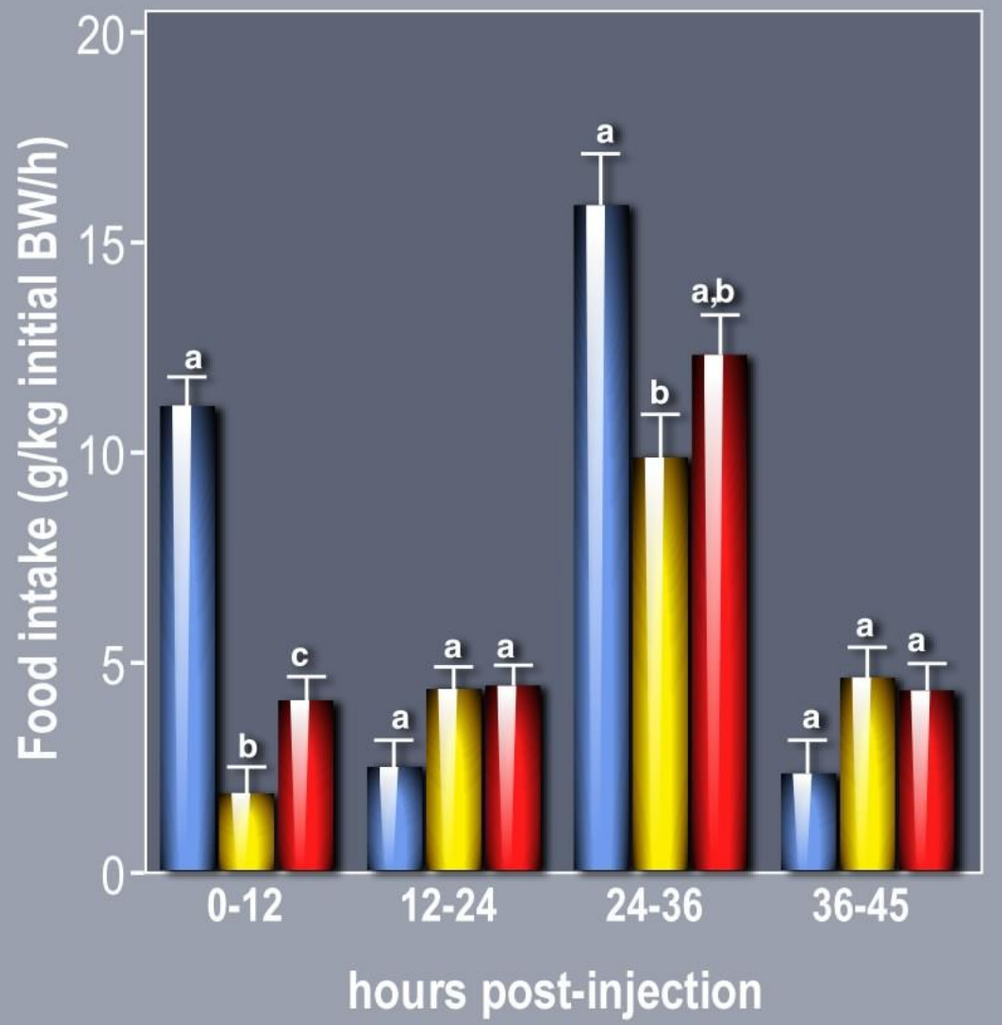
Blocking central CCR2 signalling reduces LPS-induced weight loss in mice

Le Thuc et al., EMBO Reports, 2016

Central CCR2 signalling is required for metabolic and behavioural changes associated with inflammation

FOOD INTAKE



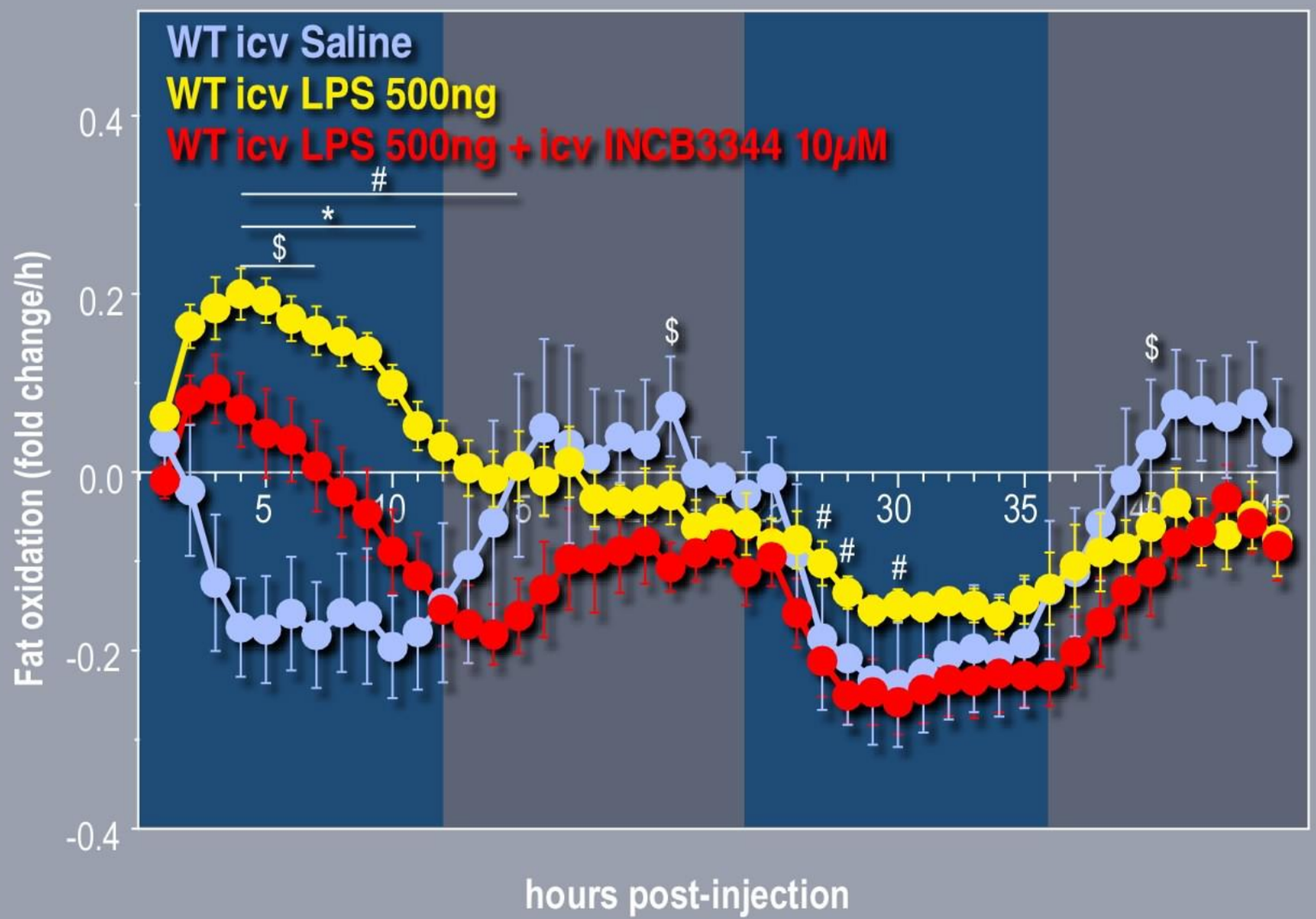


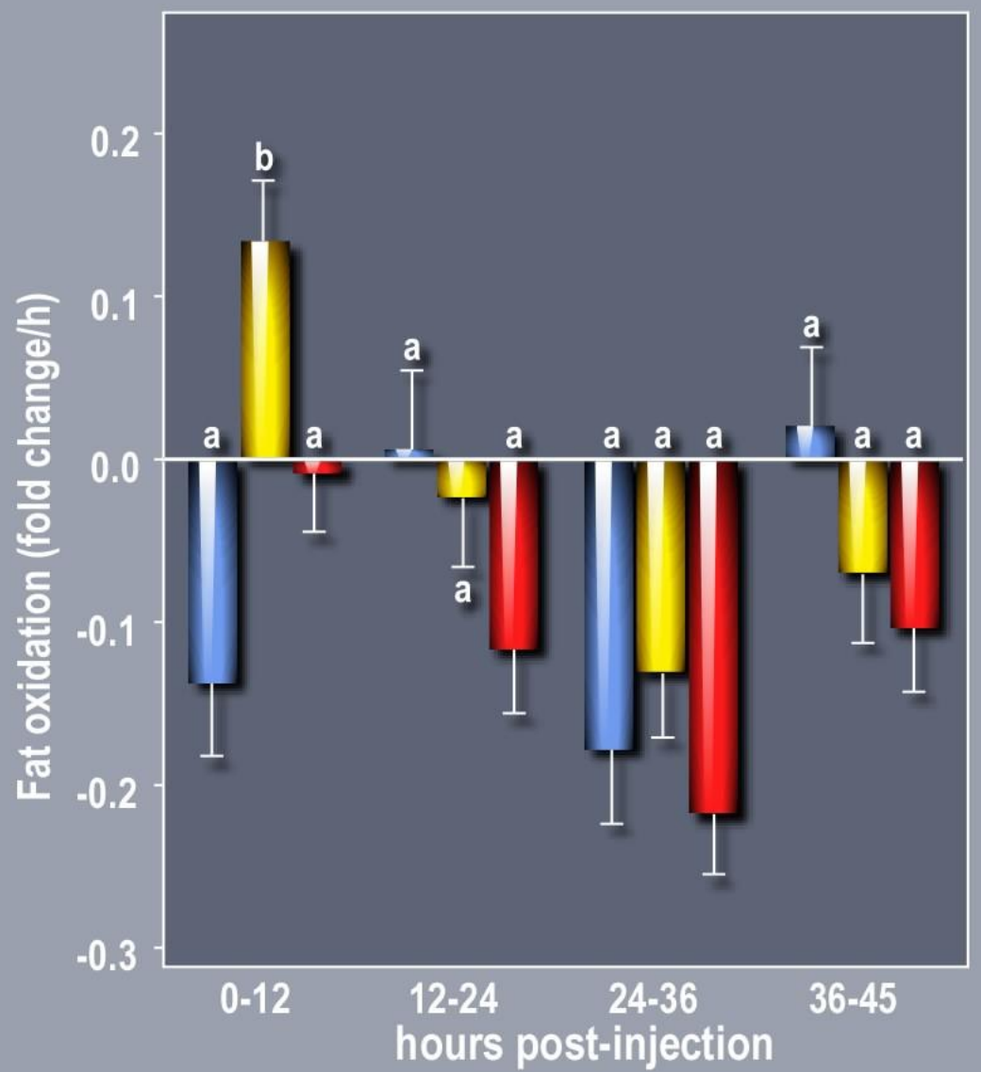
Blocking central CCR2 signalling partially rescues the LPS-induced decrease in food intake

Le Thuc et al., EMBO Reports, 2016

Central CCR2 signalling is required for metabolic and behavioural changes associated with inflammation

FAT OXIDATION



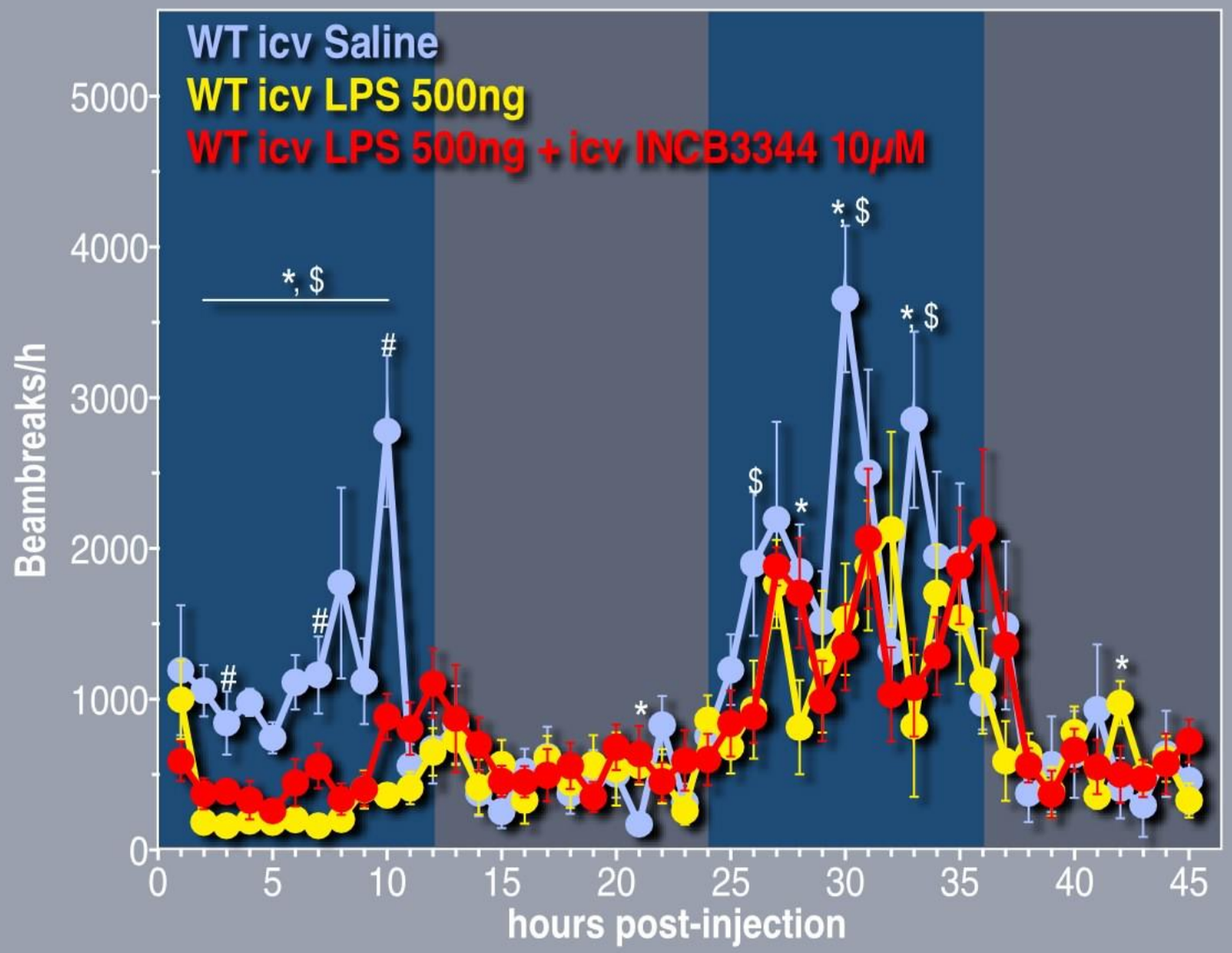


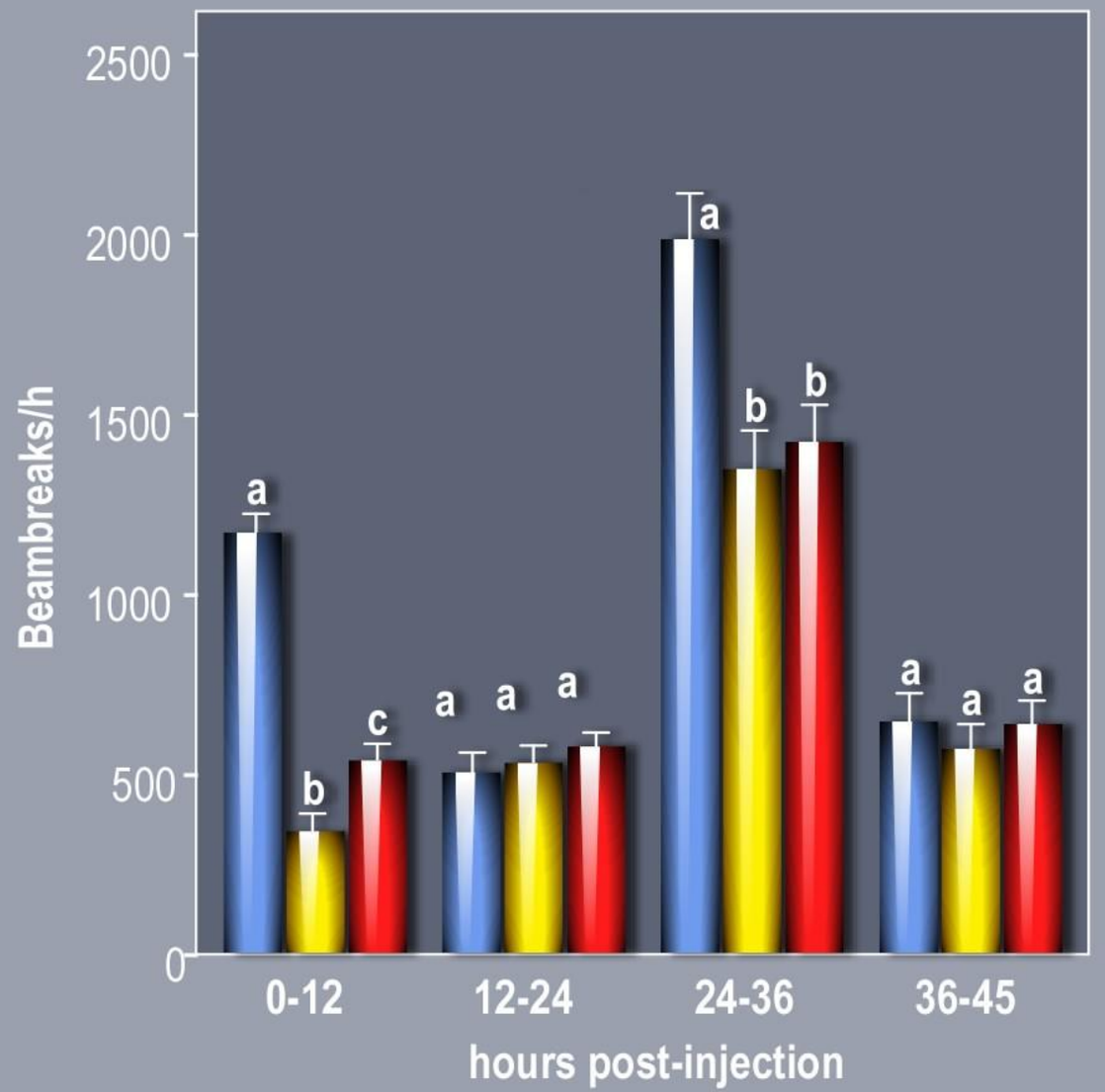
Blocking central CCR2 signalling partially rescues the LPS-induced increase in fat oxidation and energy stores consumption

Le Thuc et al., EMBO Reports, 2016

Central CCR2 signalling is required for metabolic and behavioural changes associated with inflammation

ACTIVITY

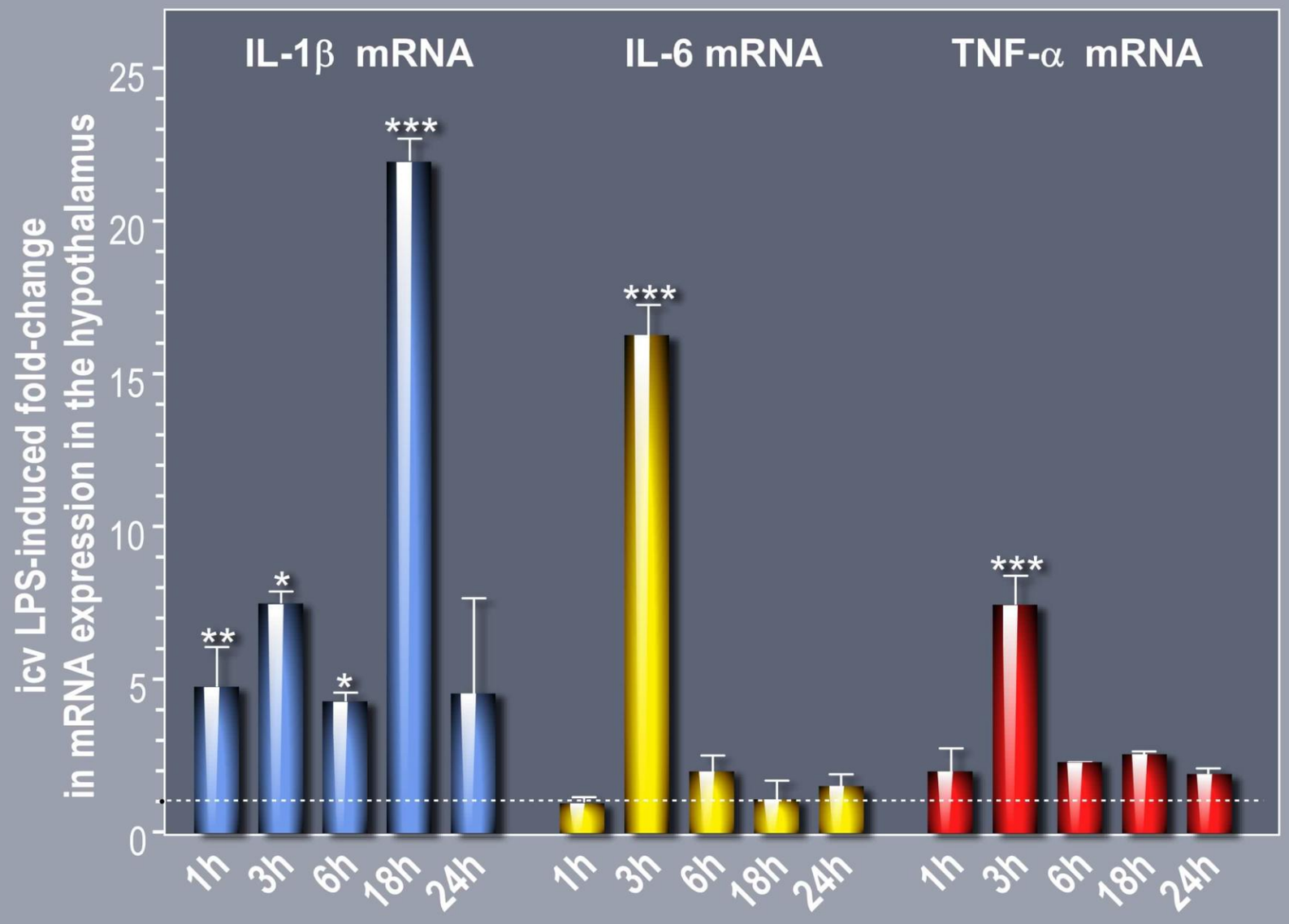




Blocking central CCR2 signalling partially rescues the LPS-induced decrease in locomotor activity

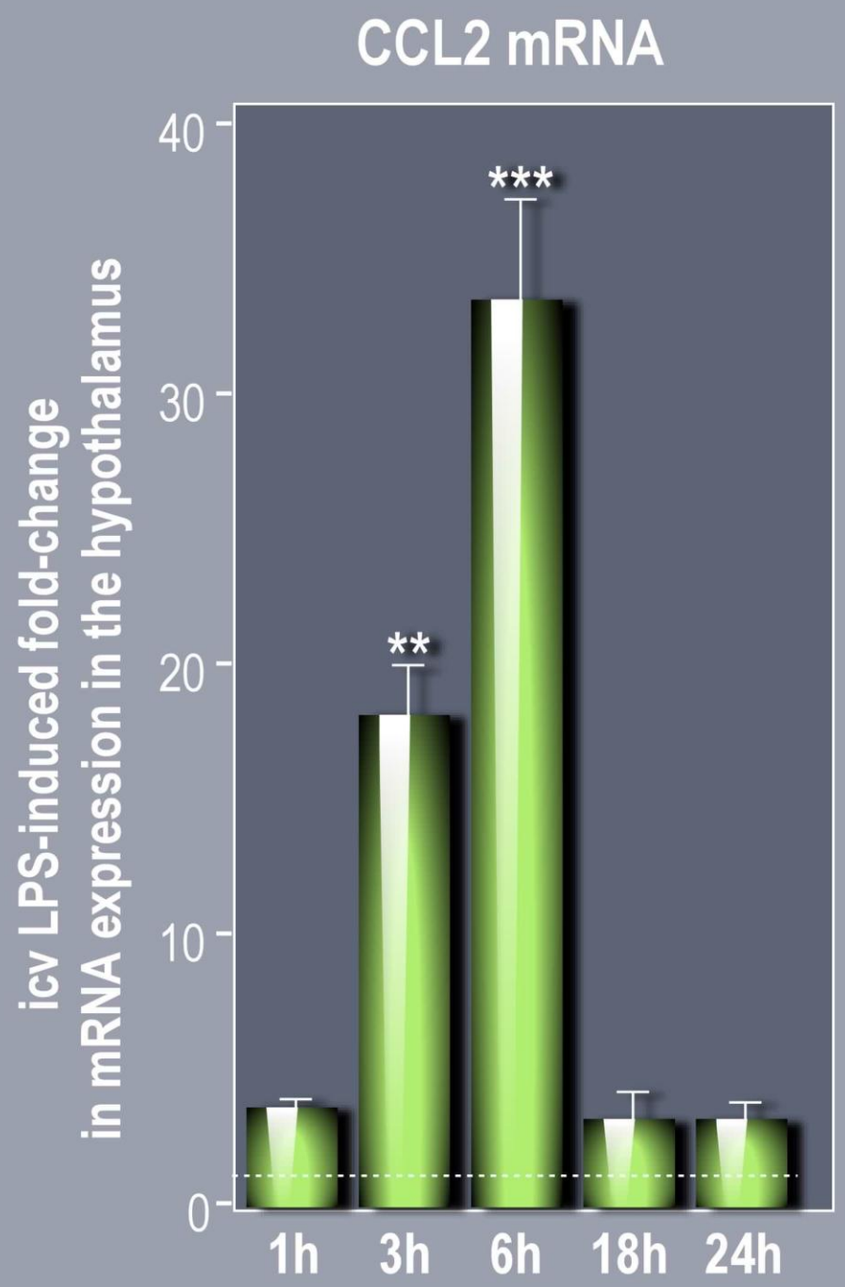
Le Thuc et al., EMBO Reports, 2016

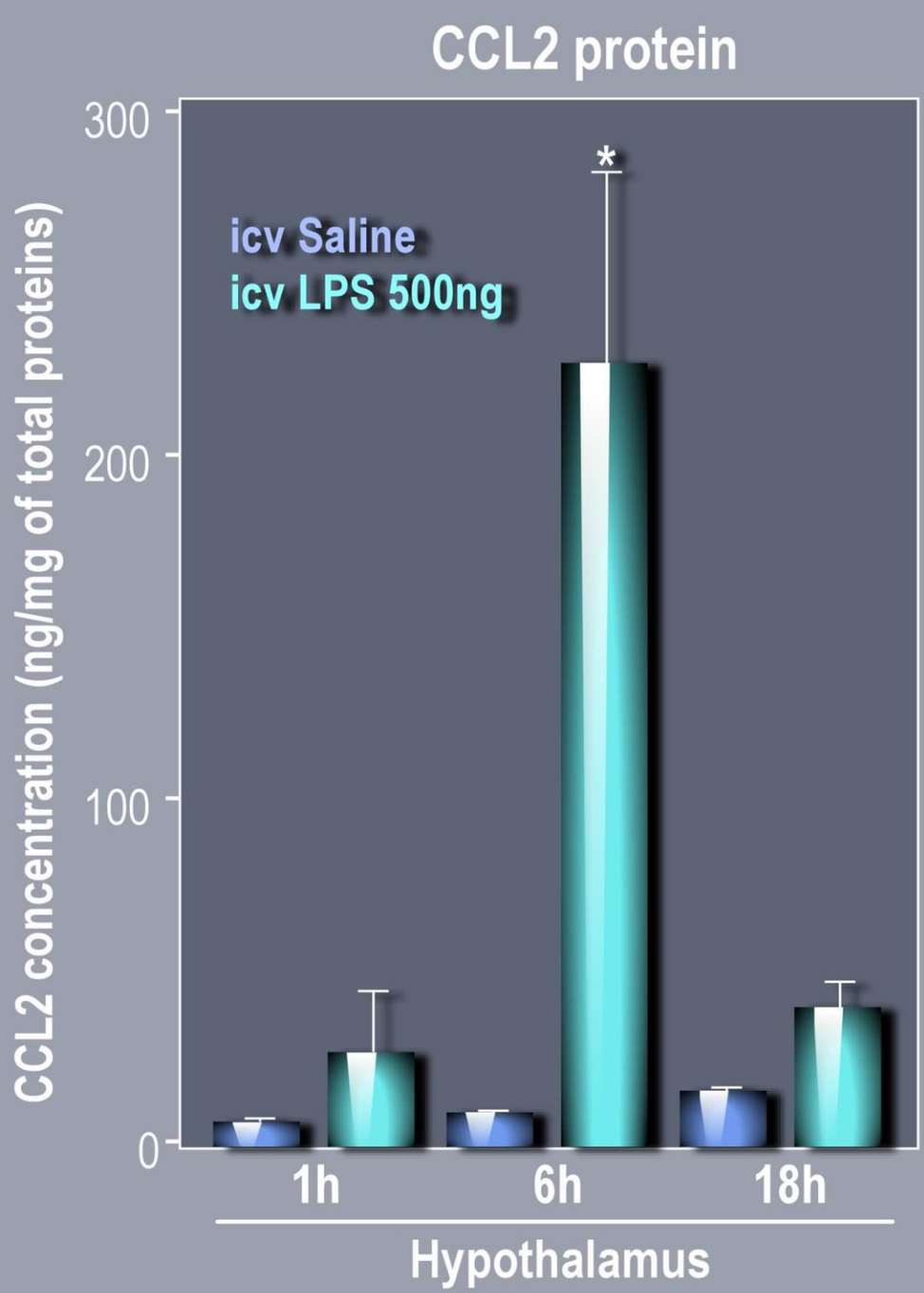
icv injected LPS activates the expression of pro-inflammatory cytokines



Le Thuc et al., EMBO Reports, 2016

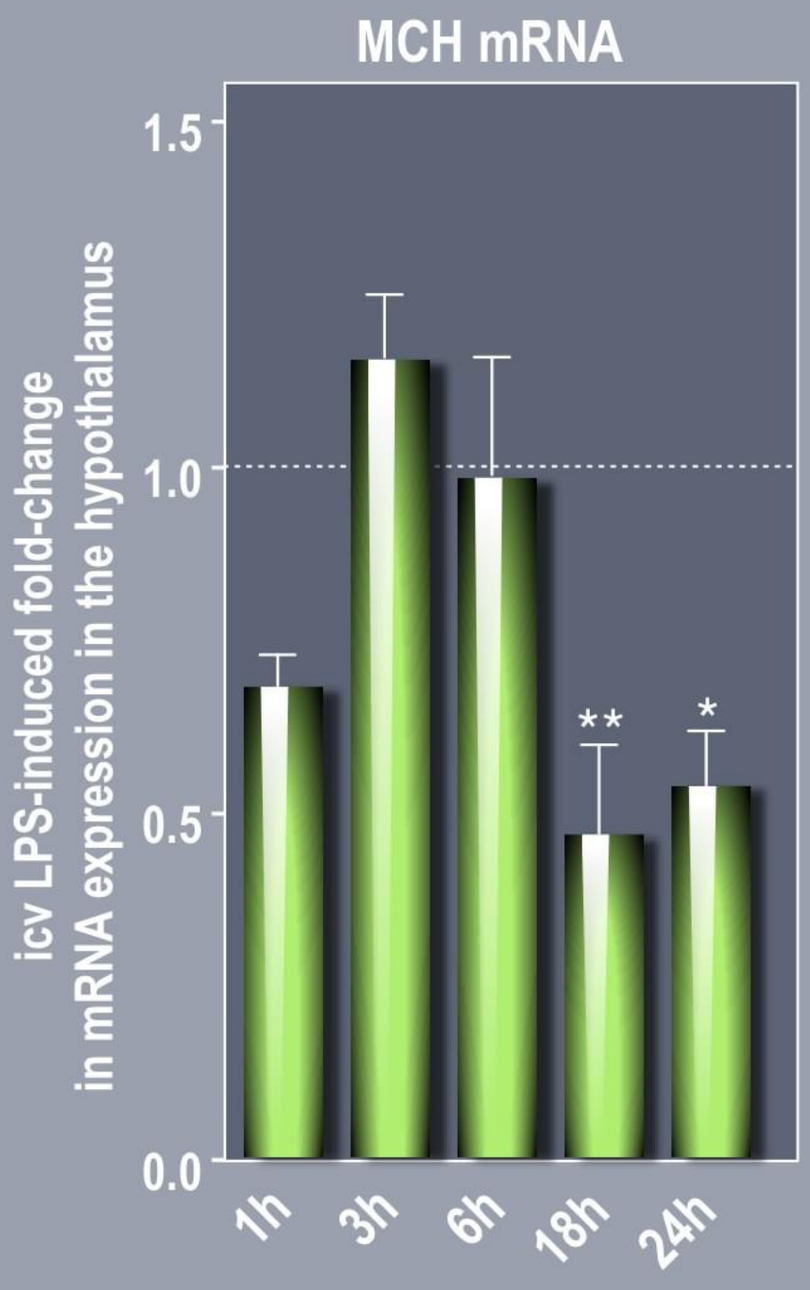
icv injected LPS increases CCL2 expression

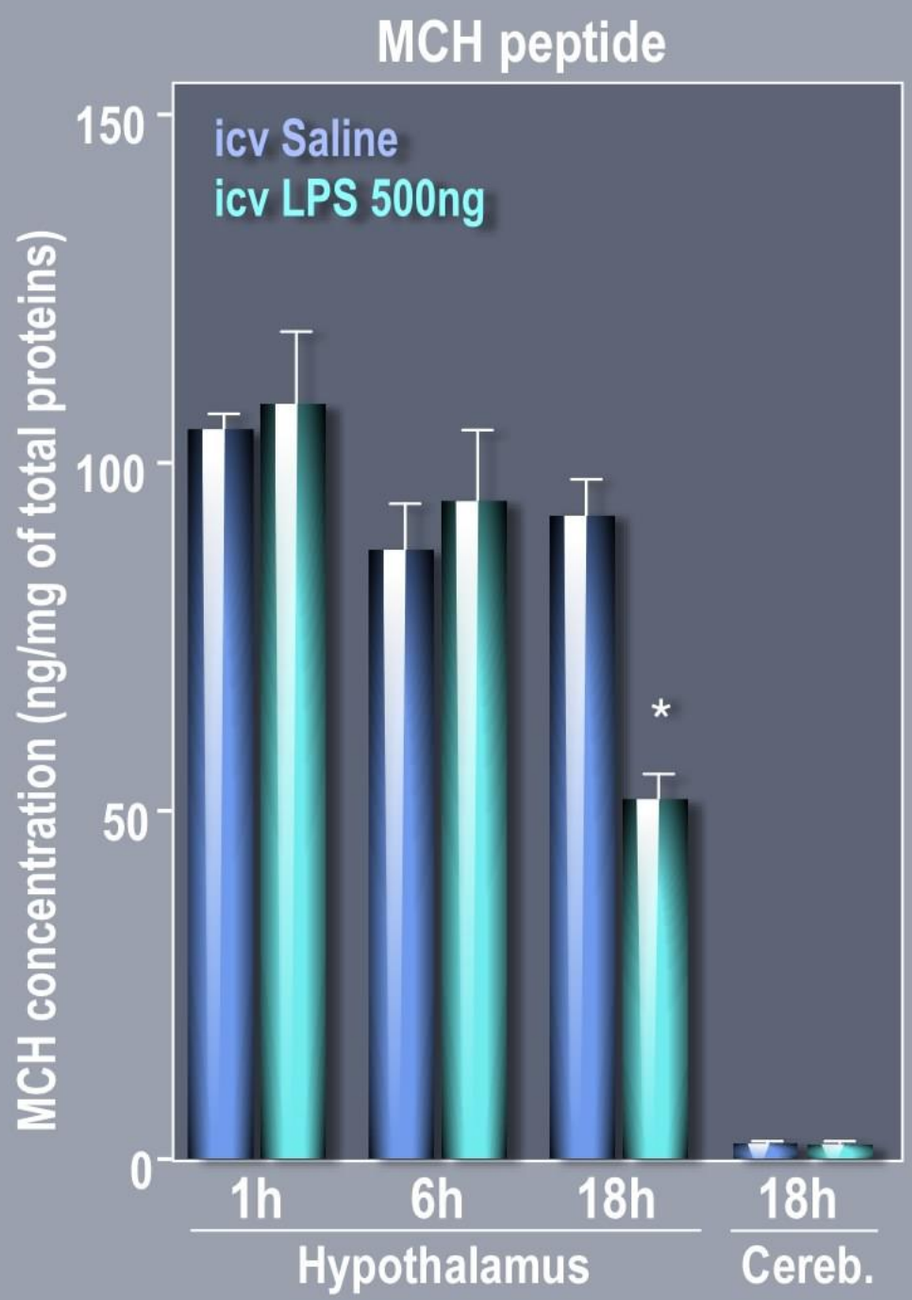


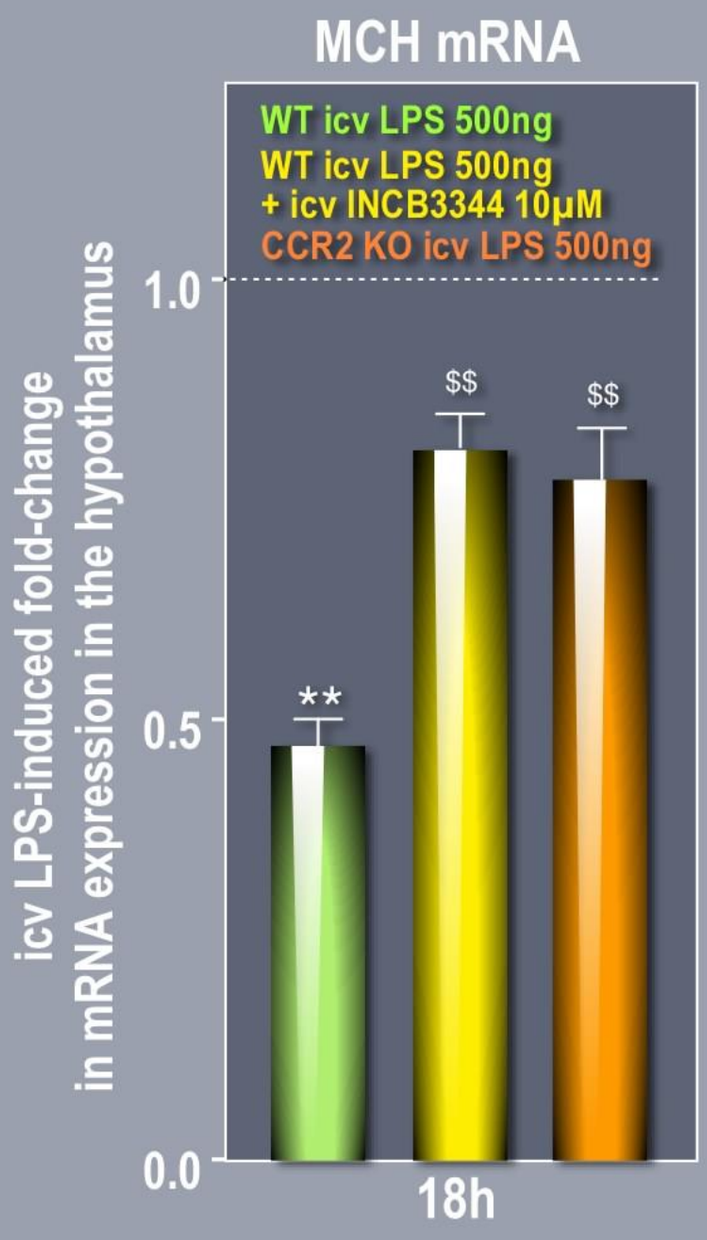


Le Thuc et al., EMBO Reports, 2016

icv injected LPS decreases MCH levels through CCR2 signalling







LPS injection induces hypothalamic CCL2 overexpression, thus over activation of central CCR2 signalling, which in turn mediates decrease in MCH expression

Le Thuc et al., EMBO Reports, 2016

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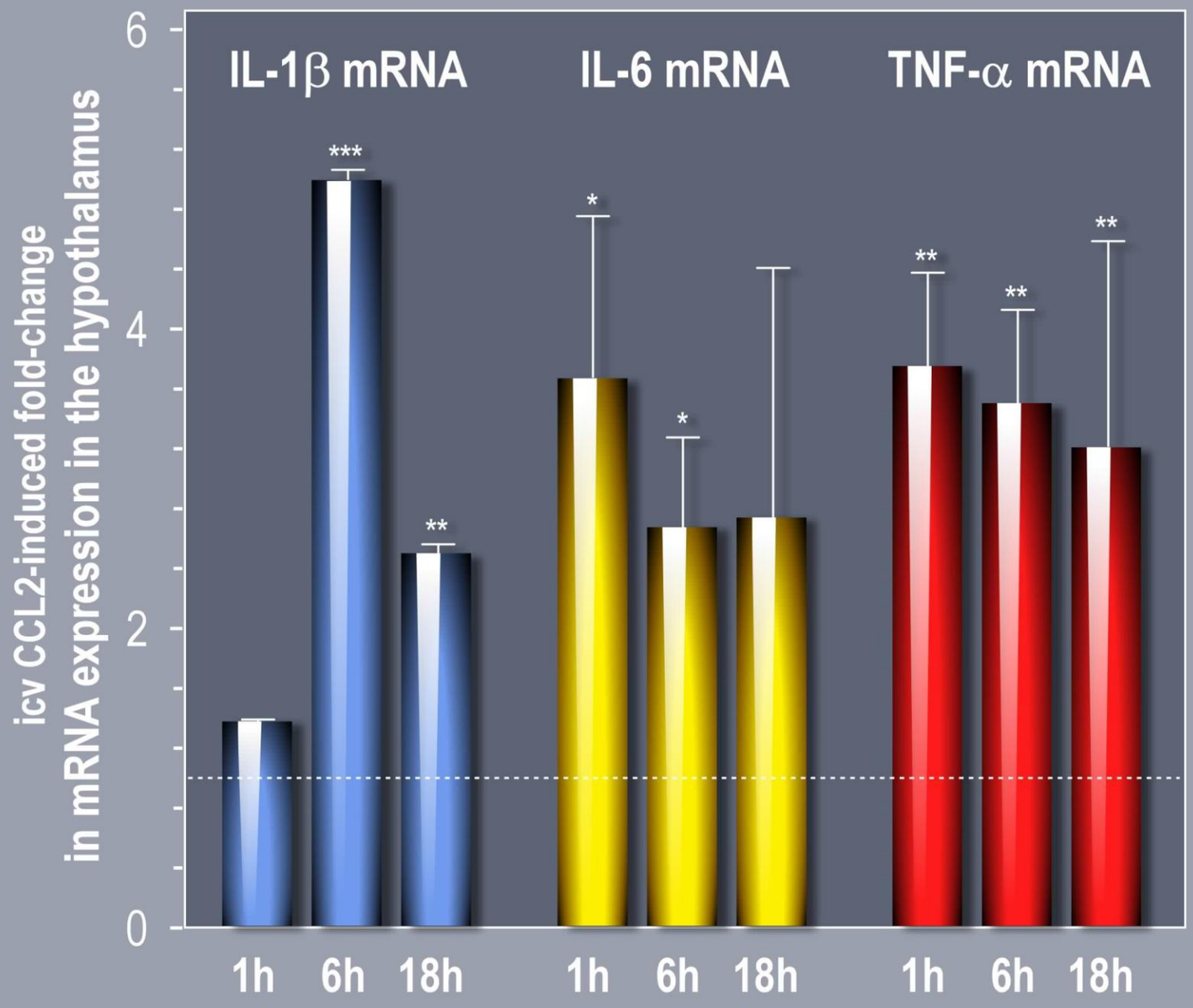
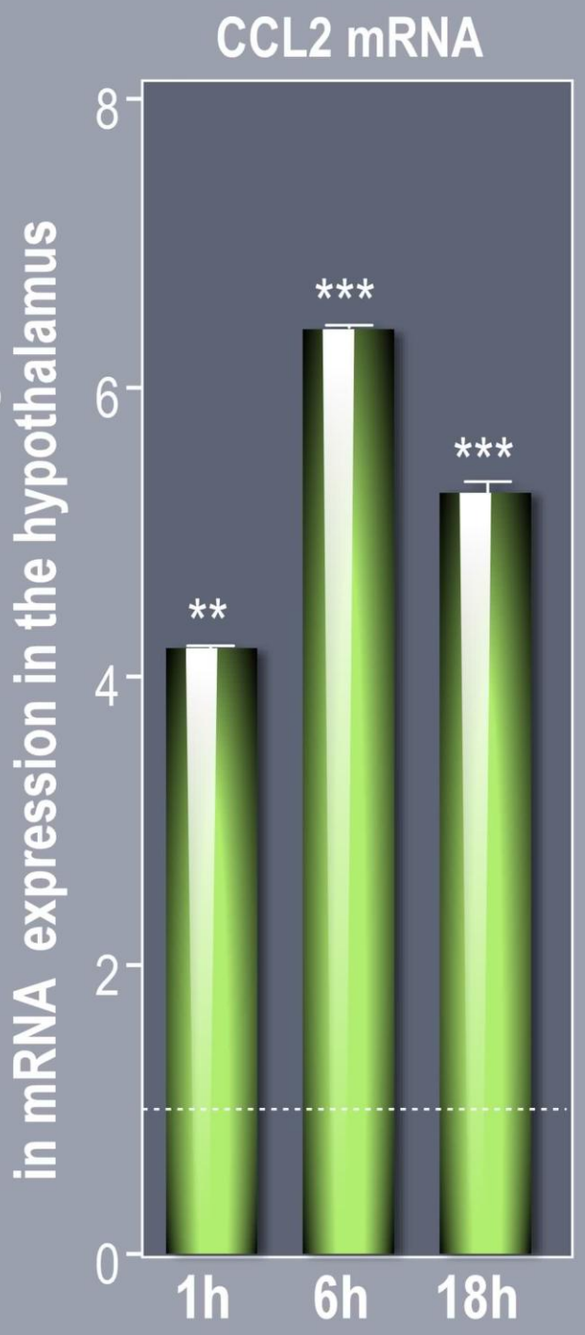
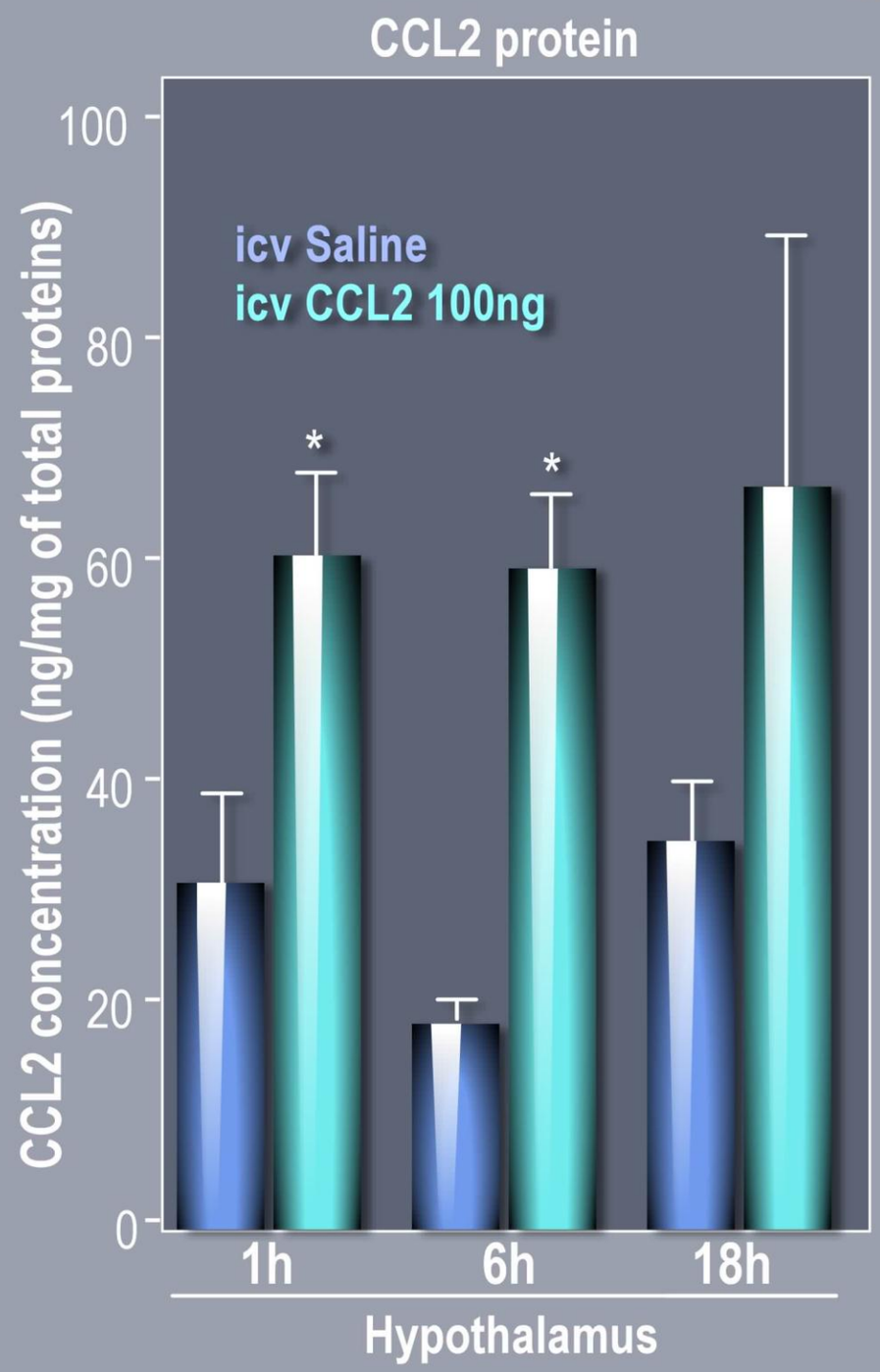
icv injected CCL2 activates the expression of pro-inflammatory cytokines



Le Thuc et al., EMBO Reports, 2016

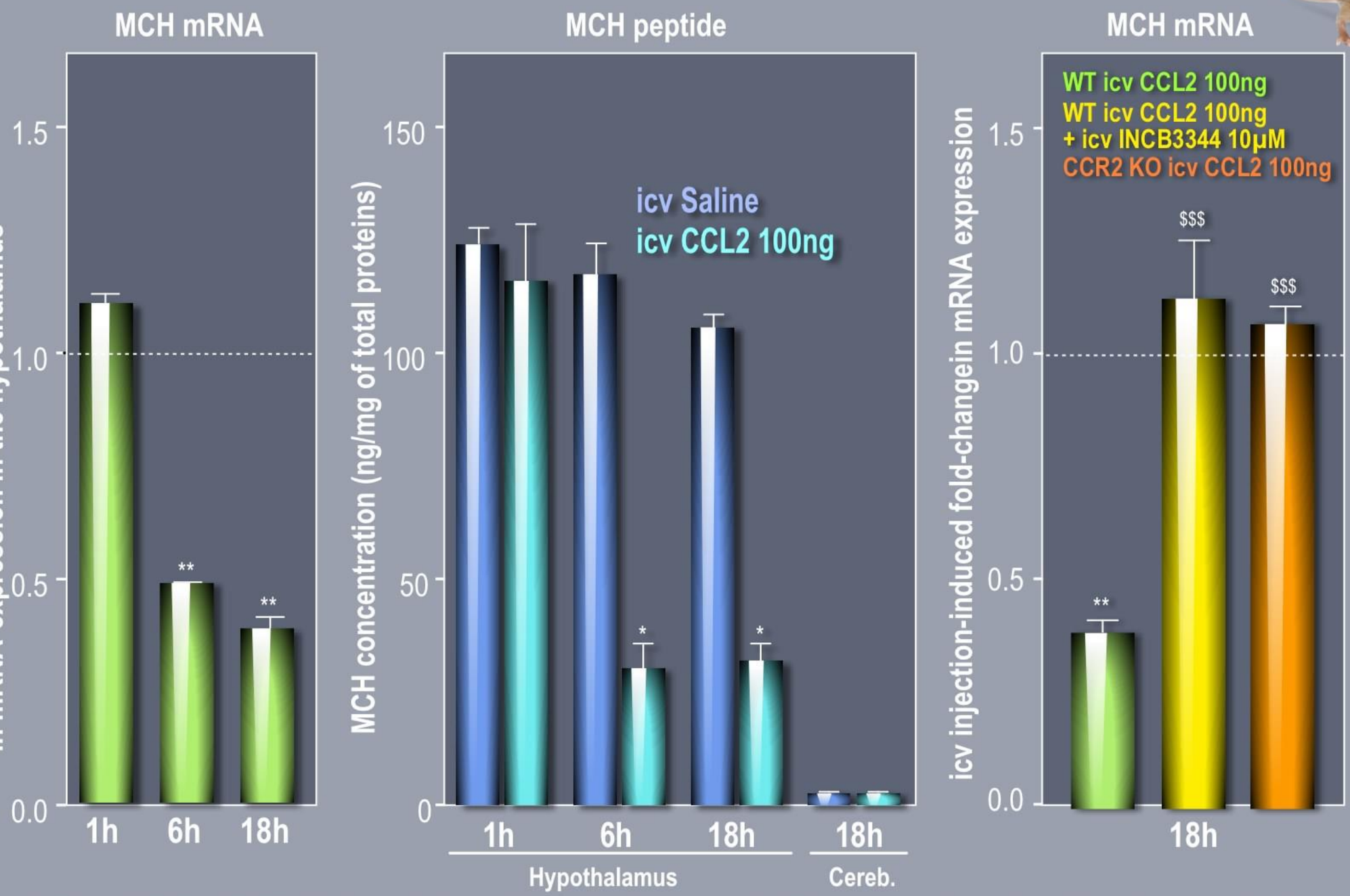
icv injected CCL2 increases its own expression





Le Thuc et al., EMBO Reports, 2016

icv injected CCL2 also decreases MCH levels through CCR2 signalling



Like LPS, CCL2 icv injection induces inflammation in the hypothalamus with CCL2 overexpression and a decrease in MCH expression. This decrease totally depends on CCR2 central signalling.

Le Thuc et al., EMBO Reports, 2016

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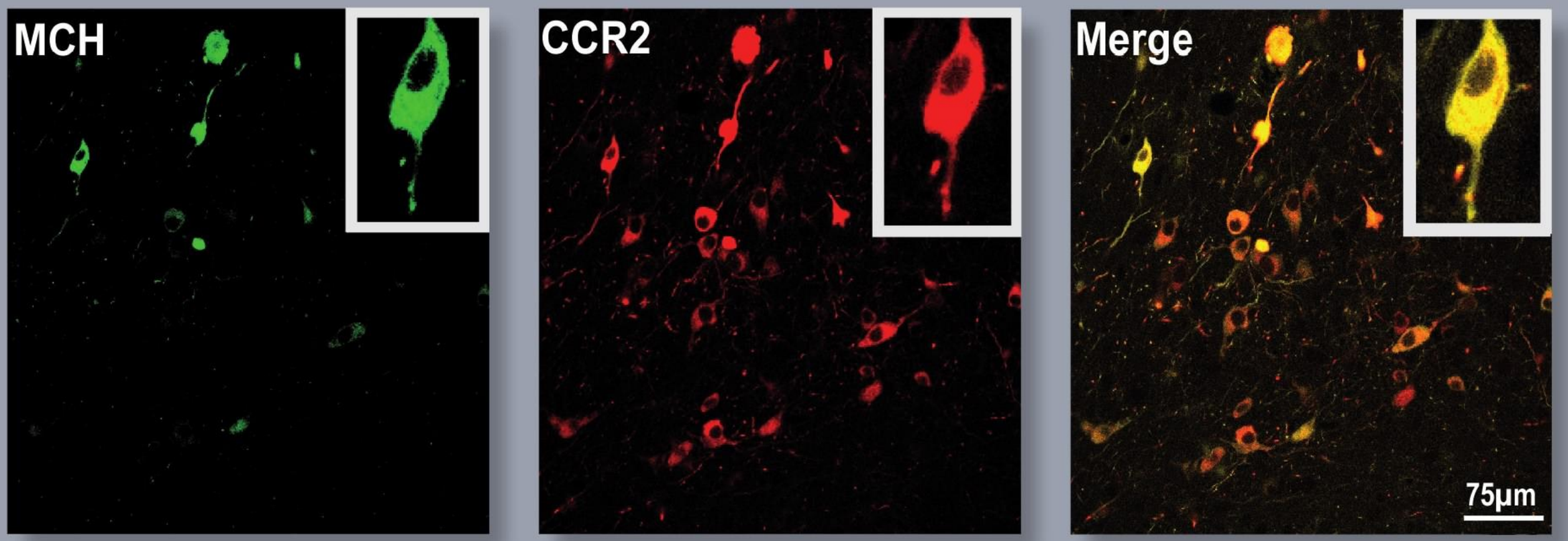
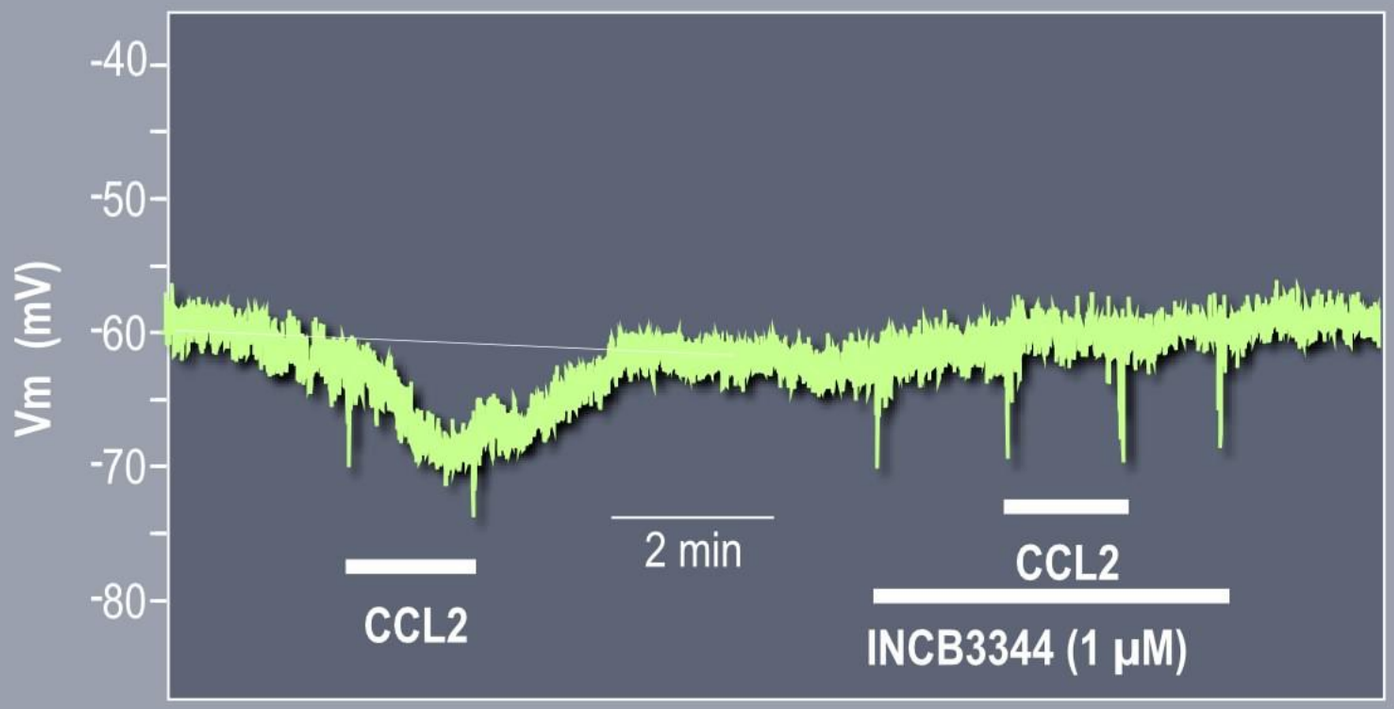
CCL2 can directly modulate the activity of MCH neurons

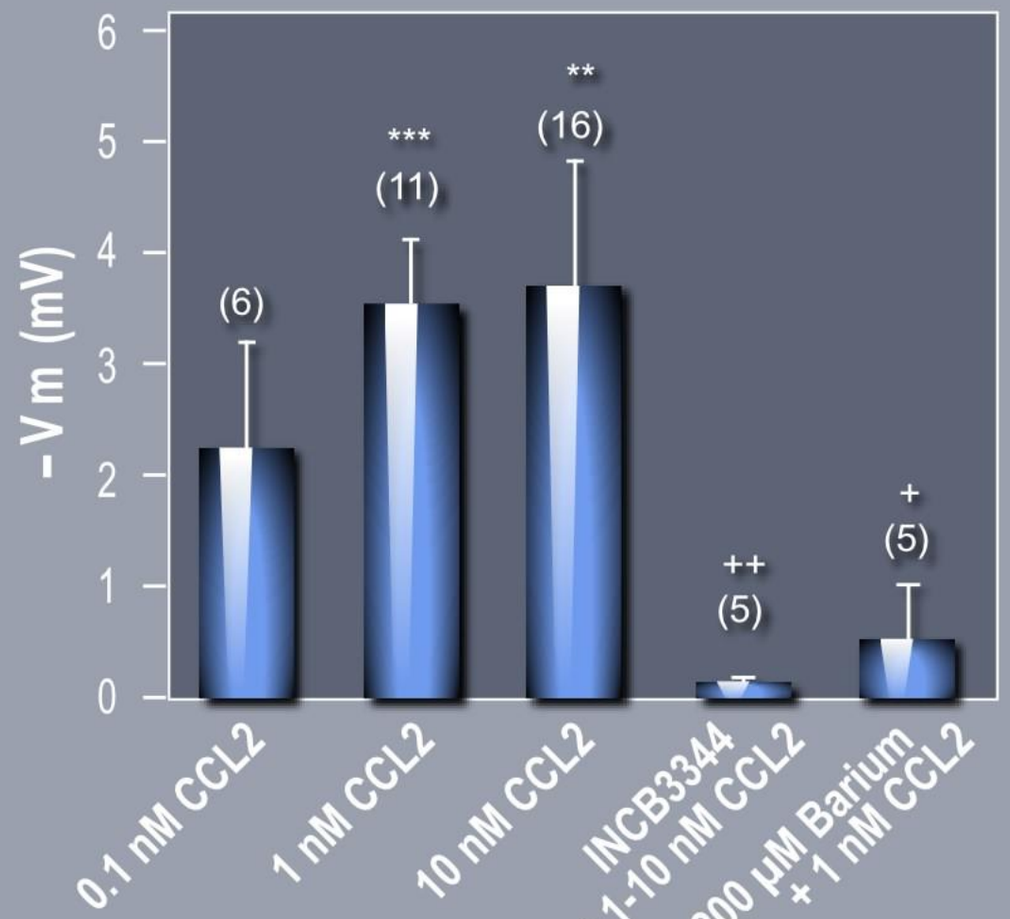


MCH neurons express CCR2

Le Thuc et al., EMBO Reports, 2016

CCL2 can directly modulate the activity of MCH neurons





CCL2 hyperpolarizes MCH neurons

Le Thuc et al., EMBO Reports, 2016

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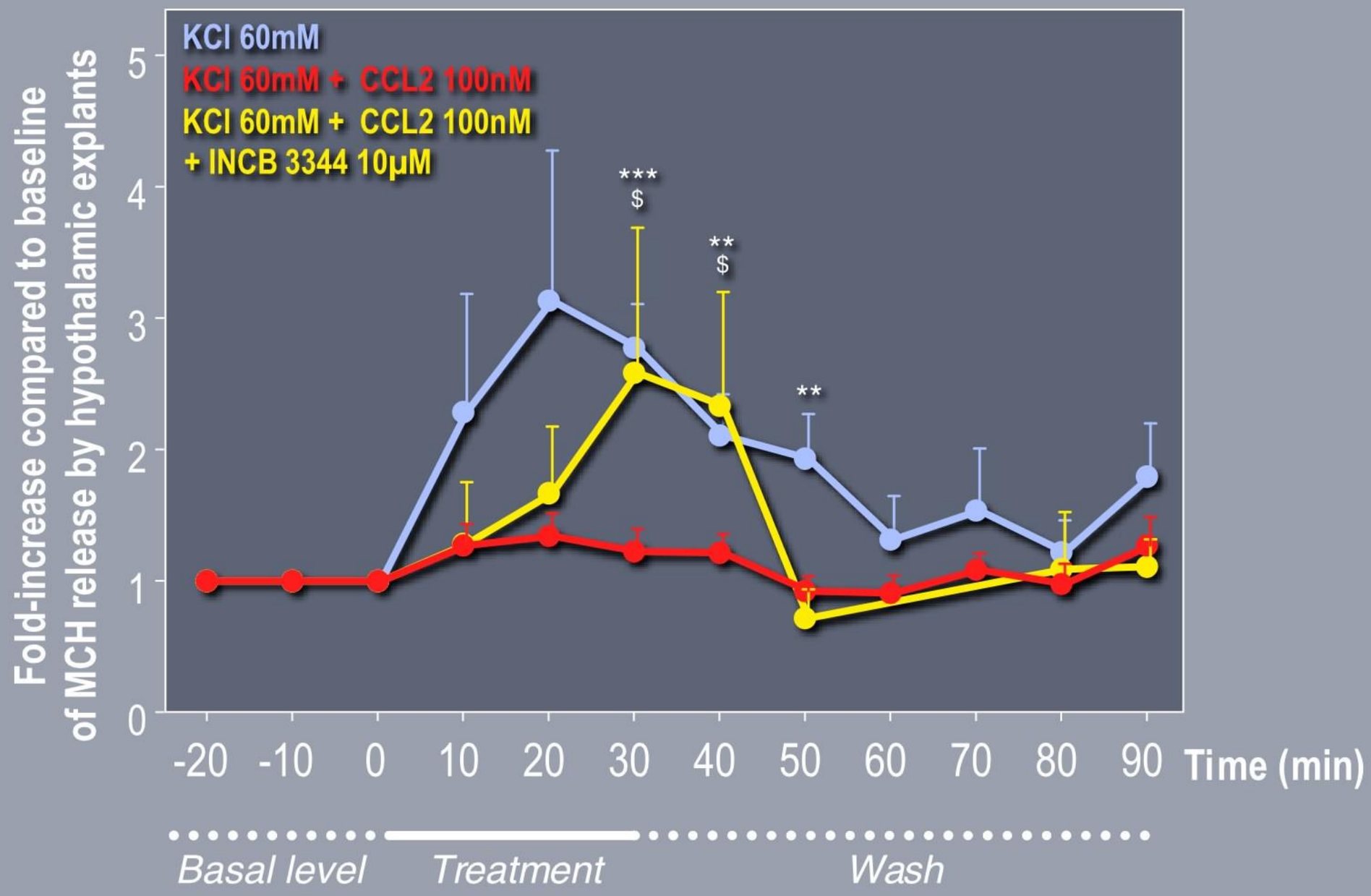
CCL2 prevents MCH secretion



CCL2 blunts the release of MCH elicited by KCl and INCB3344 rescues provoked MCH secretion

Le Thuc et al., EMBO Reports, 2016

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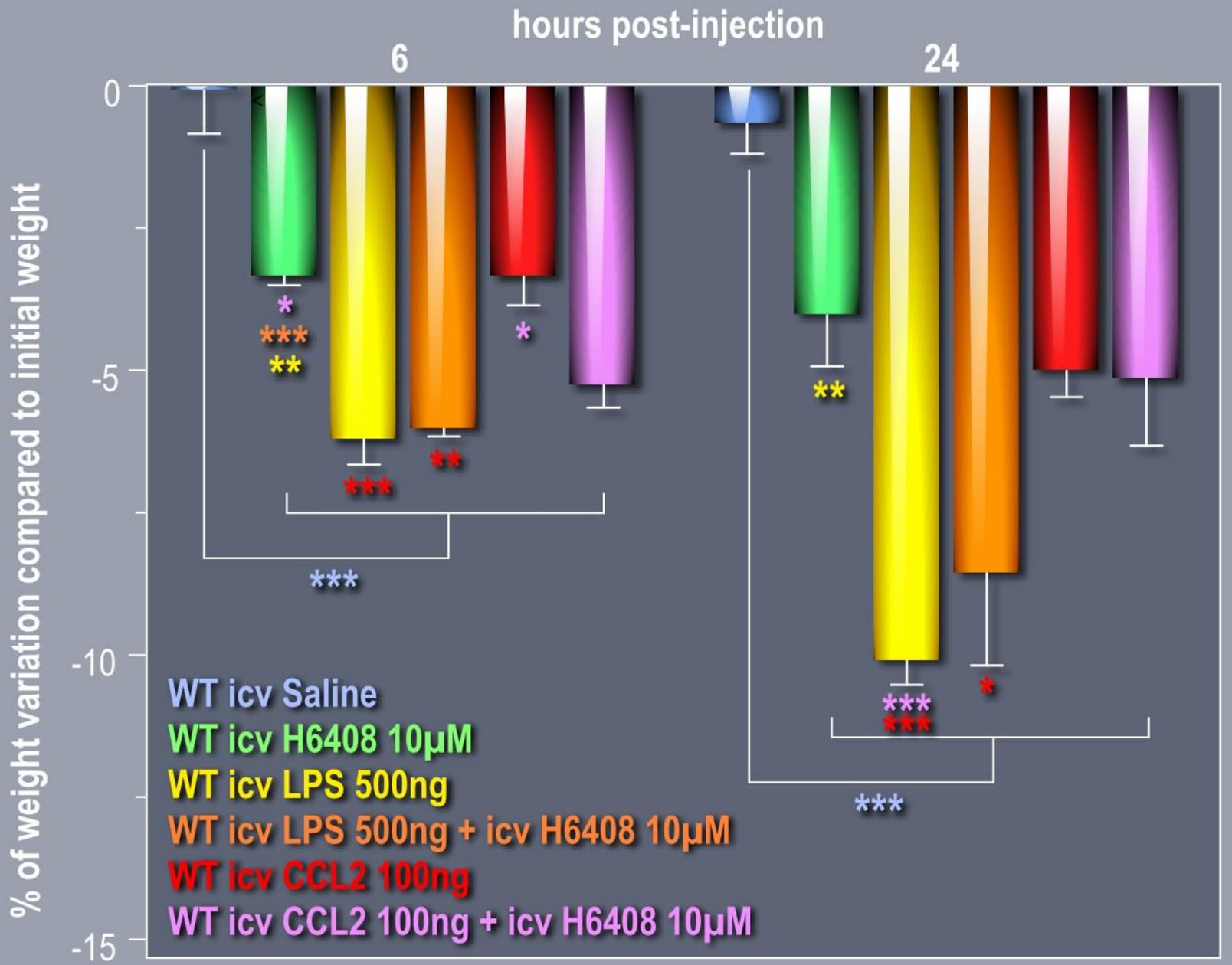
Inflammation-induced weight loss may be driven by MCHR1 signalling



Antagonizing MCHR1 induces weight loss.
Co-injection of LPS and H6408 does not induce further weight loss whereas co-injection of CCL2 and H6408 shows early additive weight-loss.
Importance of the MCHR1 pathway in early times in the inflammation-induced weight loss.

Le Thuc et al., EMBO Reports, 2016

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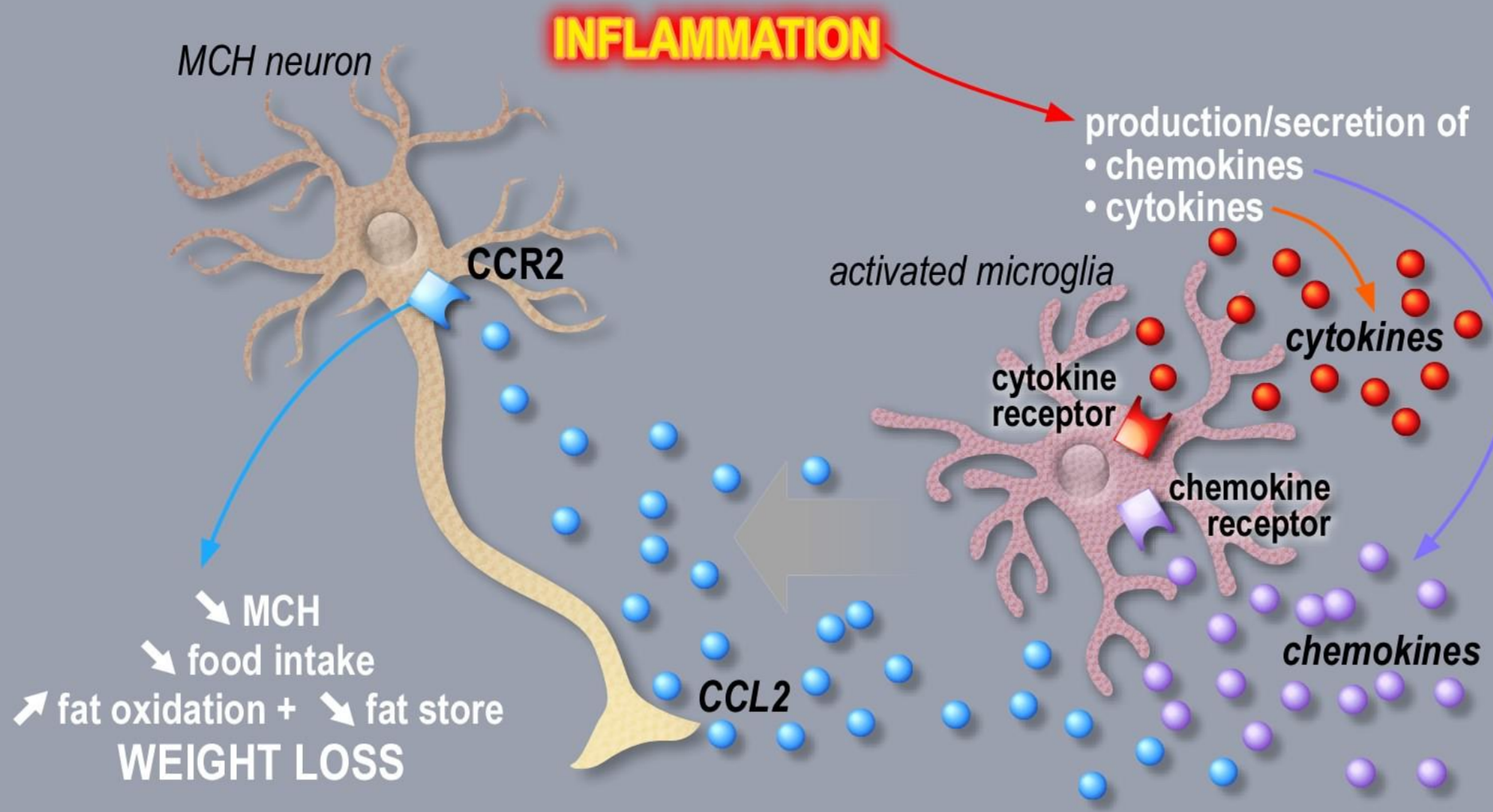
Conclusion

Systemic high-intensity inflammation induces behavioral changes (sickness behavior) and inflammation in the hypothalamus, major brain structure for the control of feeding behavior.

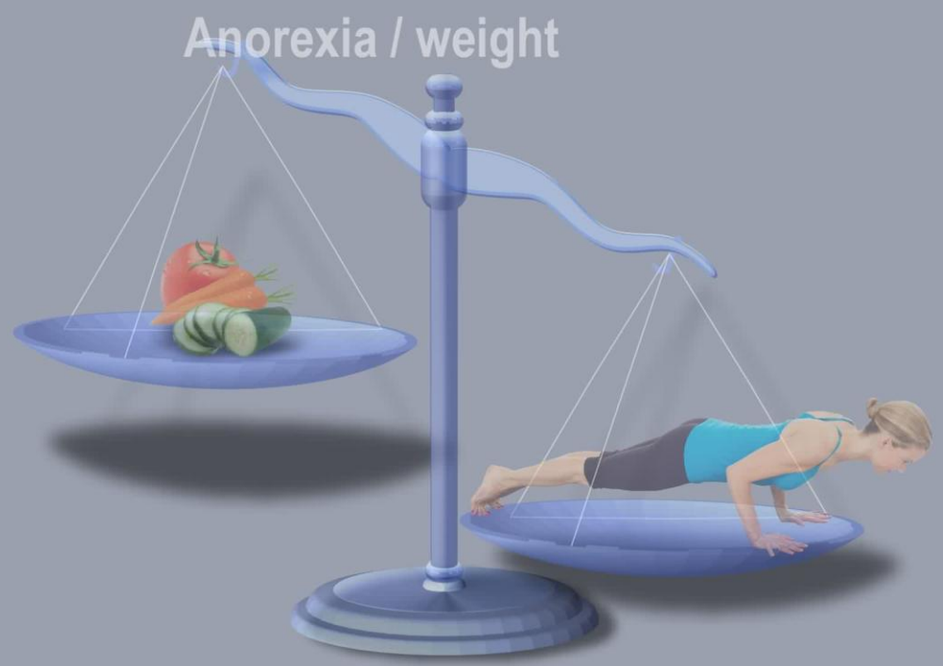
LPS-induced sickness behavior is associated with weight-loss.

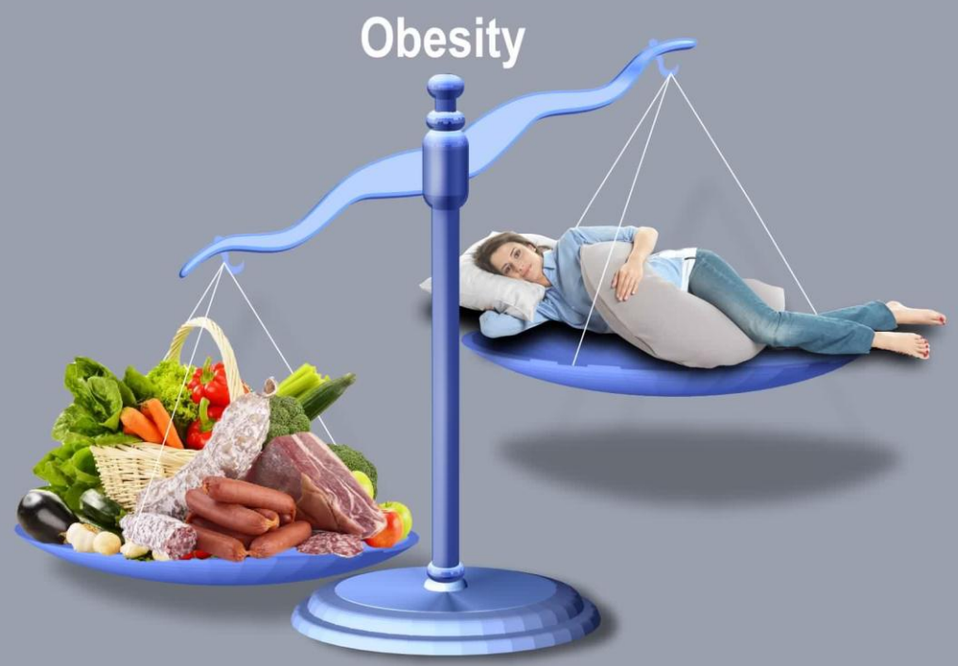


Chemokines can directly affect hypothalamic circuits regulating energy balance.
What about other energy balance deregulations?

Le Thuc et al., EMBO Reports, 2016

For each pathology, an inflammation state





High-grade inflammation intensity with high levels of pro-inflammatory mediators

Low-grade inflammation intensity with low levels of pro-inflammatory mediators

Acute, often limited in time

Chronic

Inflammation by systemic infection, lesion, cancer ...

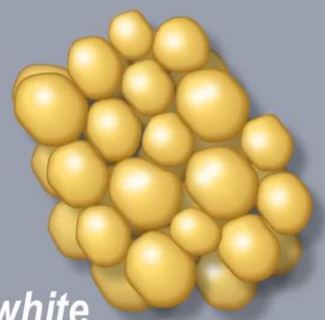
Aseptic inflammation, metabolic inflammation

Obesity and inflammation

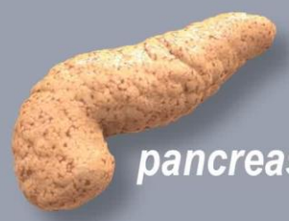
central inflammation

peripheral inflammation

brain
hypothalamus



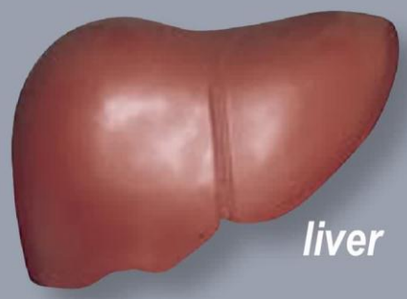
white adipose tissue



pancreas

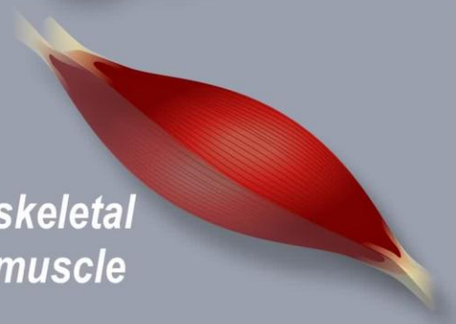
+ insulin resistance
(with hyperinsulinemia)

+ leptin resistance
(with hyperleptinemia)



liver

gastrointestinal tract



skeletal muscle

MyD88 Signaling in the CNS Is Required for Development of Fatty Acid-Induced Leptin Resistance and Diet-Induced Obesity

André Kleinridders,[1,2,3,5] Dominik Schenten,[4,5] A. Christine Könner,[1,2,3,5] Bengt F. Belgardt,[1,2,3,5] Jan Mauer,[1,2,3] Tomoo Okamura,[1,2,3] F. Thomas Wunderlich,[1,2,3] Ruslan Medzhitov,[4] and Jens C. Brüning[1,2,3,*]

Cell Metabolism, October 2009

Does Hypothalamic Inflammation Cause Obesity?

Brent E. Wisse[1] and Michael W. Schwartz[1,*]

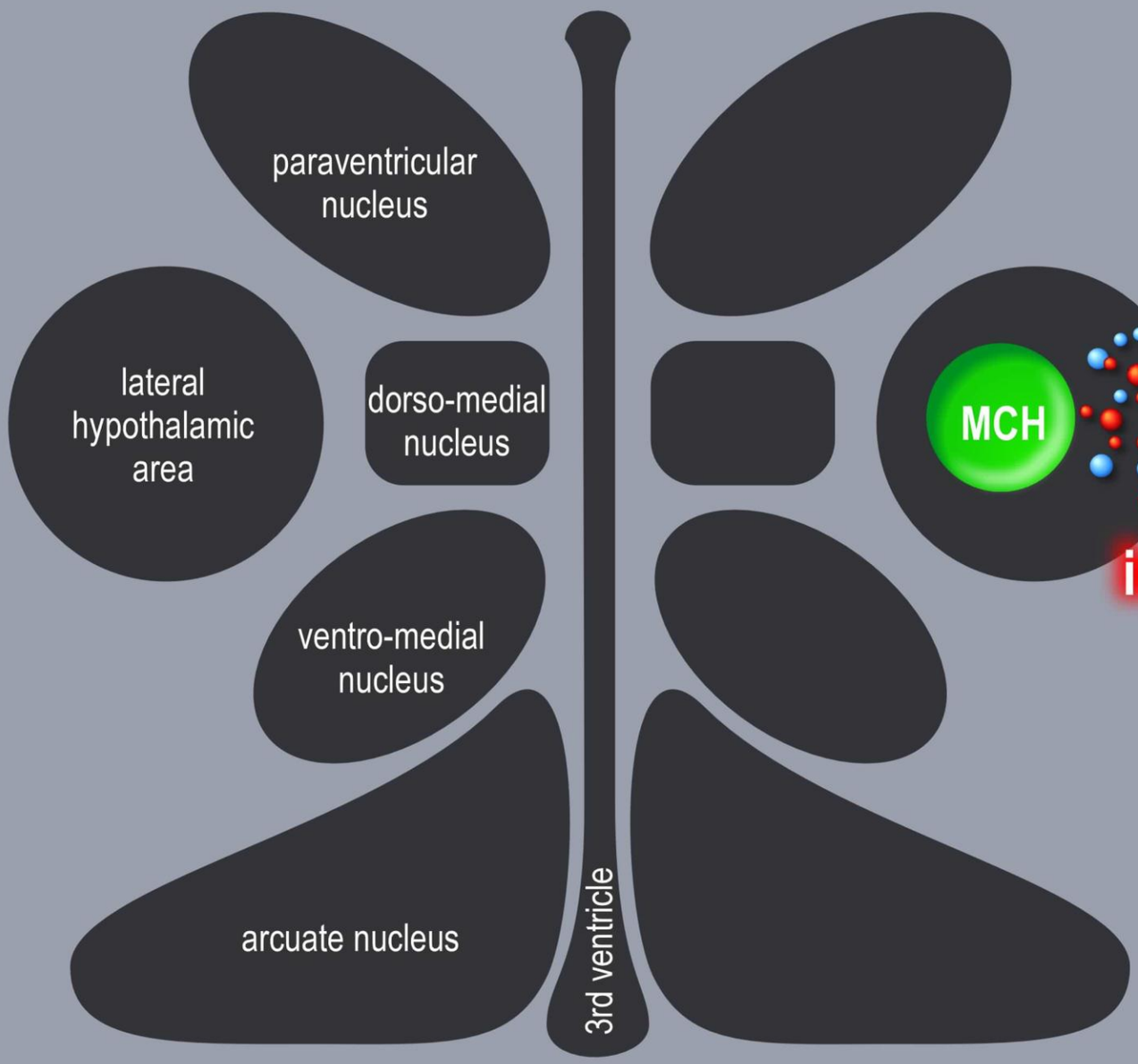
Cell Metabolism, Previews, October 2009

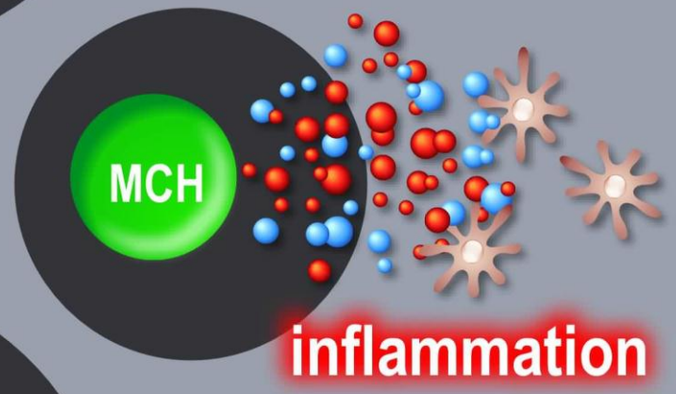
... diminished hypothalamic inflammation and leptin resistance protects against obesity...

ijpmc

Hypothesis

low-grade inflammation in the hypothalamus





↗ of production and secretion of orexigenic peptides (MCH)

→ ↗ obesity + body weight

Development of a murine Diet-Induced Obesity model

4 week-old male
C57Bl/6J mice

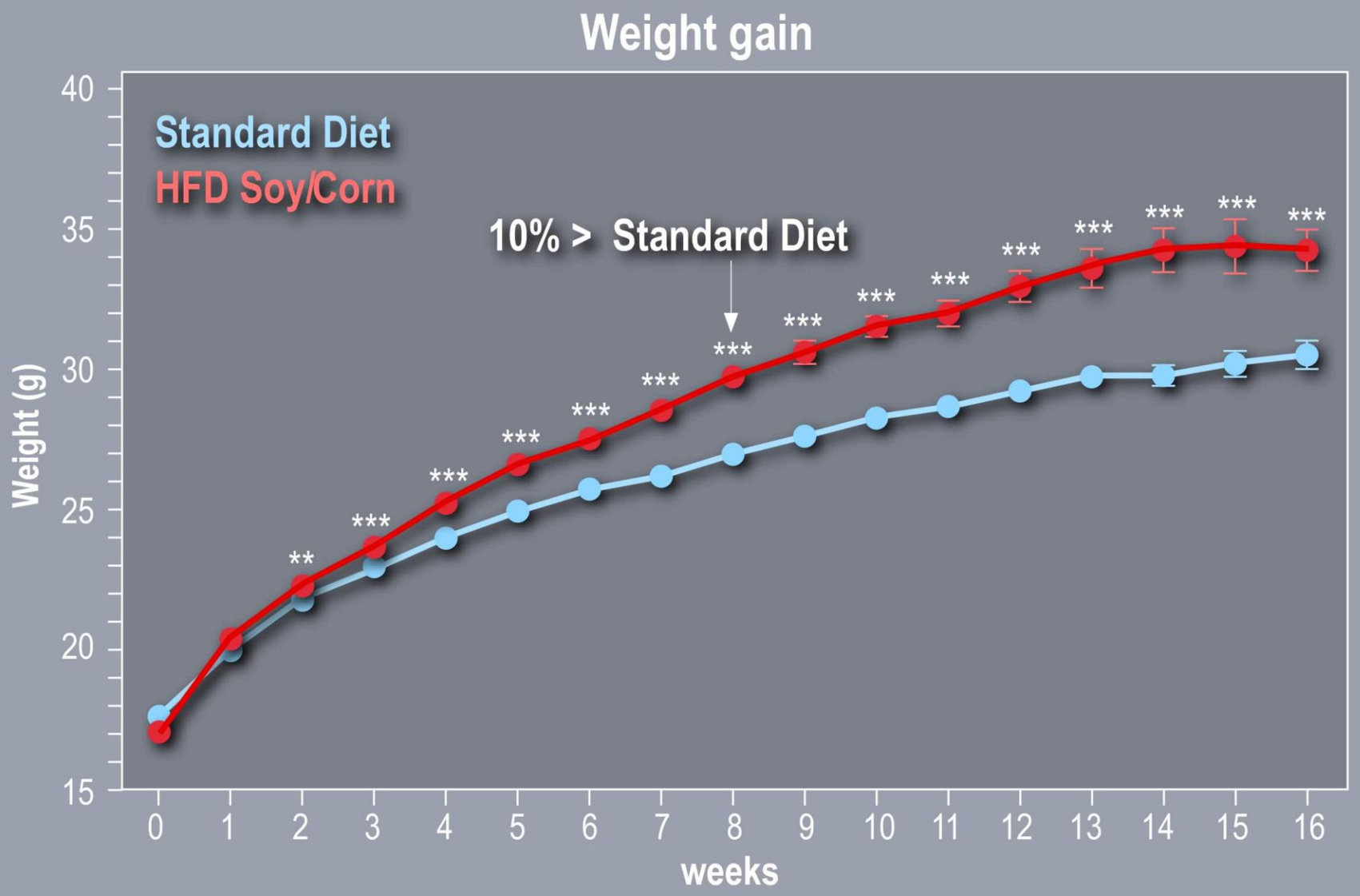
STANDARD DIET (5% lipids ⟷ 14% of total energy)

HIGH FAT DIET (HFD) SOY/CORN (20% lipids ⟷ 40% of total energy)

0 — 8 — 16 weeks

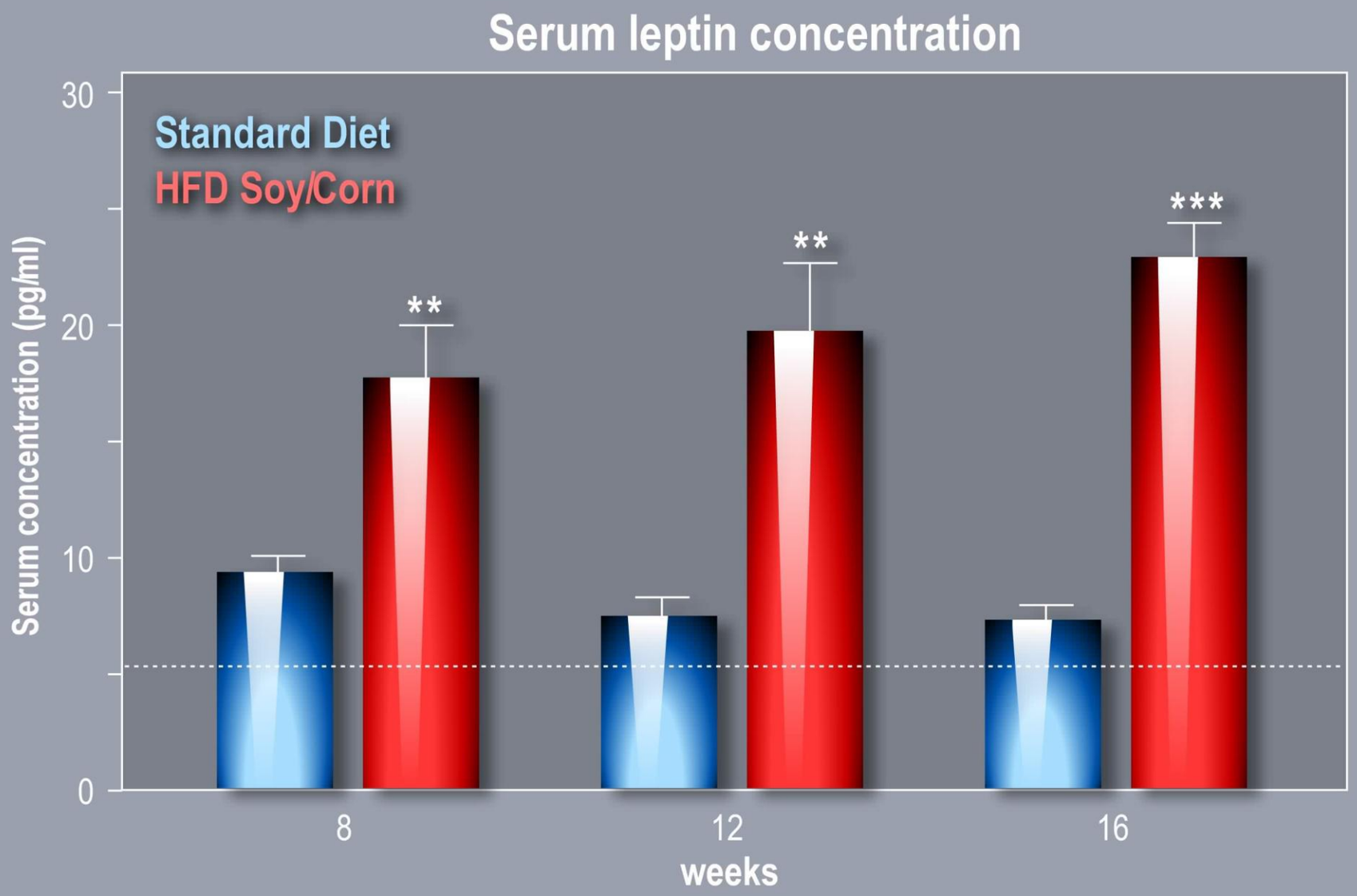
- Metabolic parameters (weight, food and water intake, leptinemia, ...)
- Inflammatory profile in the hypothalamus and serum
- Expression of hypothalamic neuropeptides involved in food intake regulation

Effects of Soy / Corn HFD consumption on weight gain ?



- HFD-fed mice have a weight of 10% higher compared to control animals from 8 weeks of diet

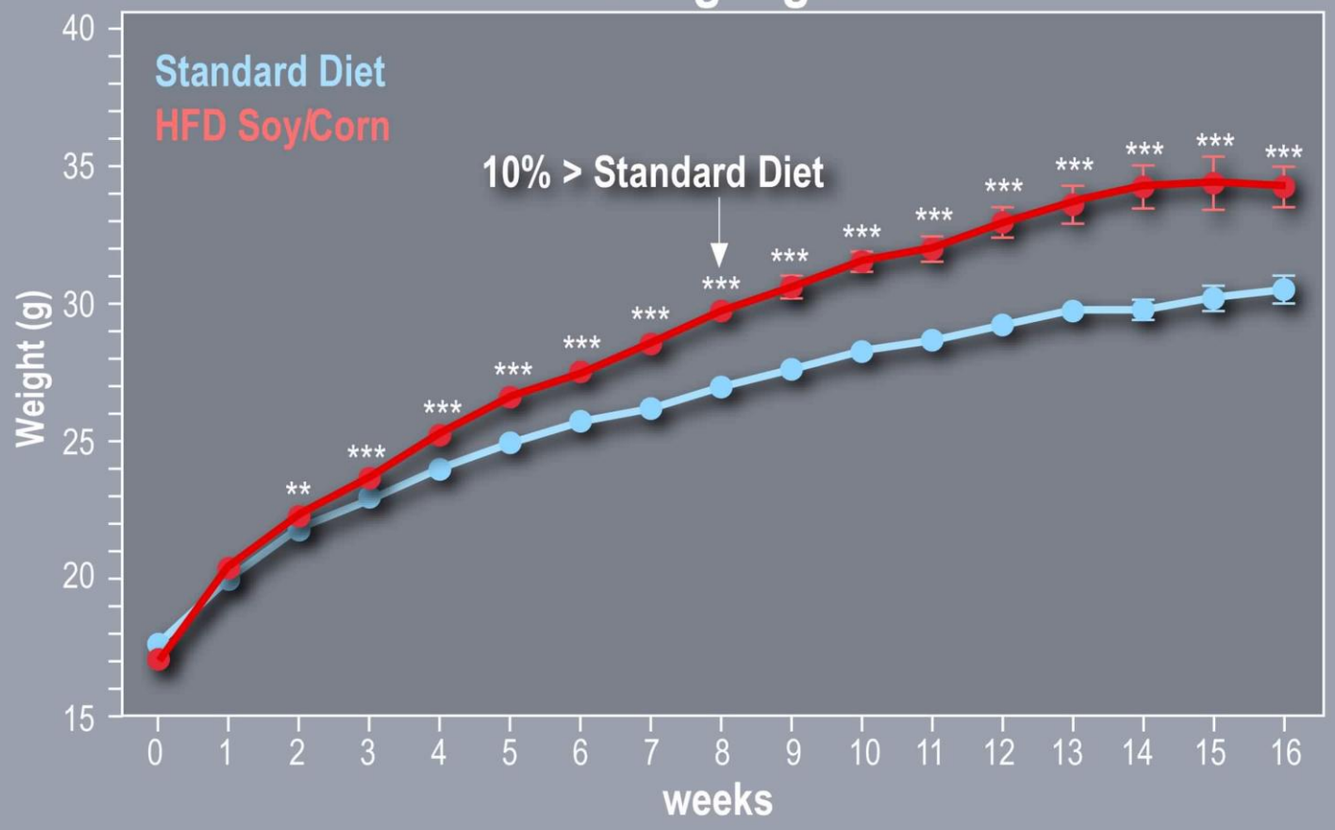
Effects of Soy / Corn HFD consumption on leptinemia ?



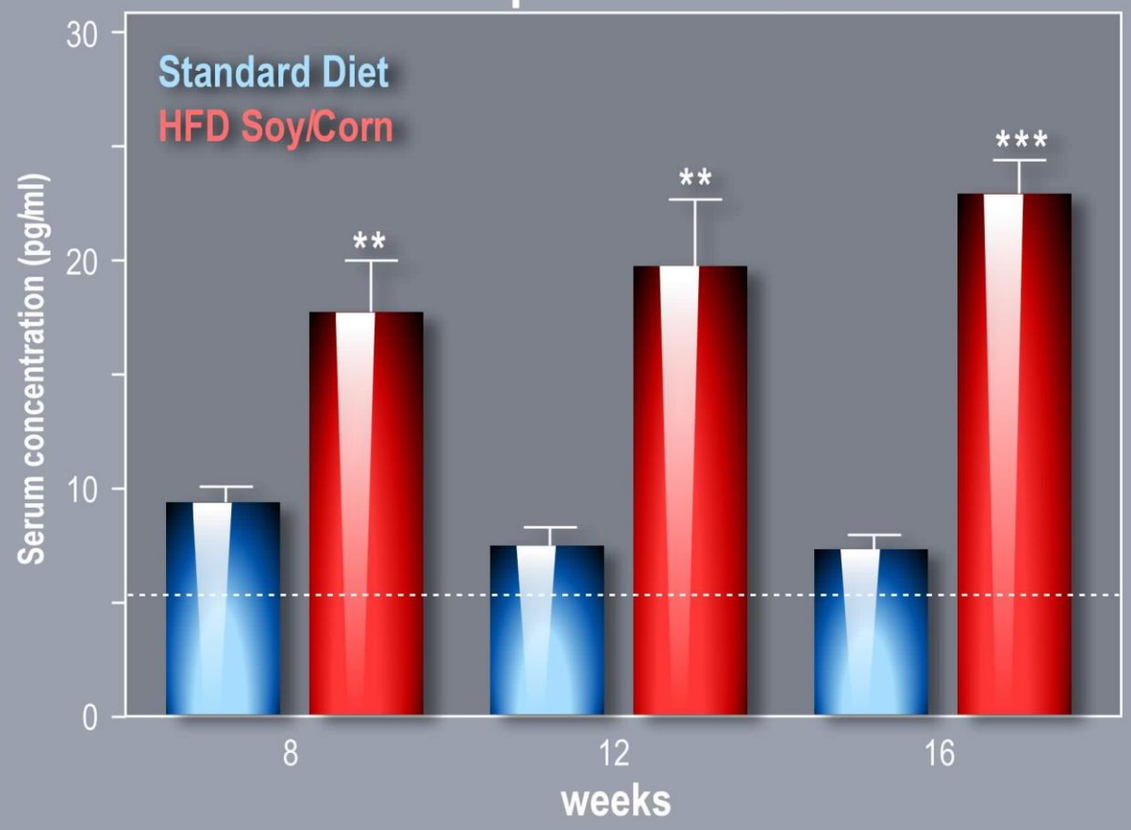
- HFD-fed mice show significant hyperleptinemia from 8 weeks of diet

Effects of Soy / Corn HFD consumption on metabolic parameters ?

Weight gain



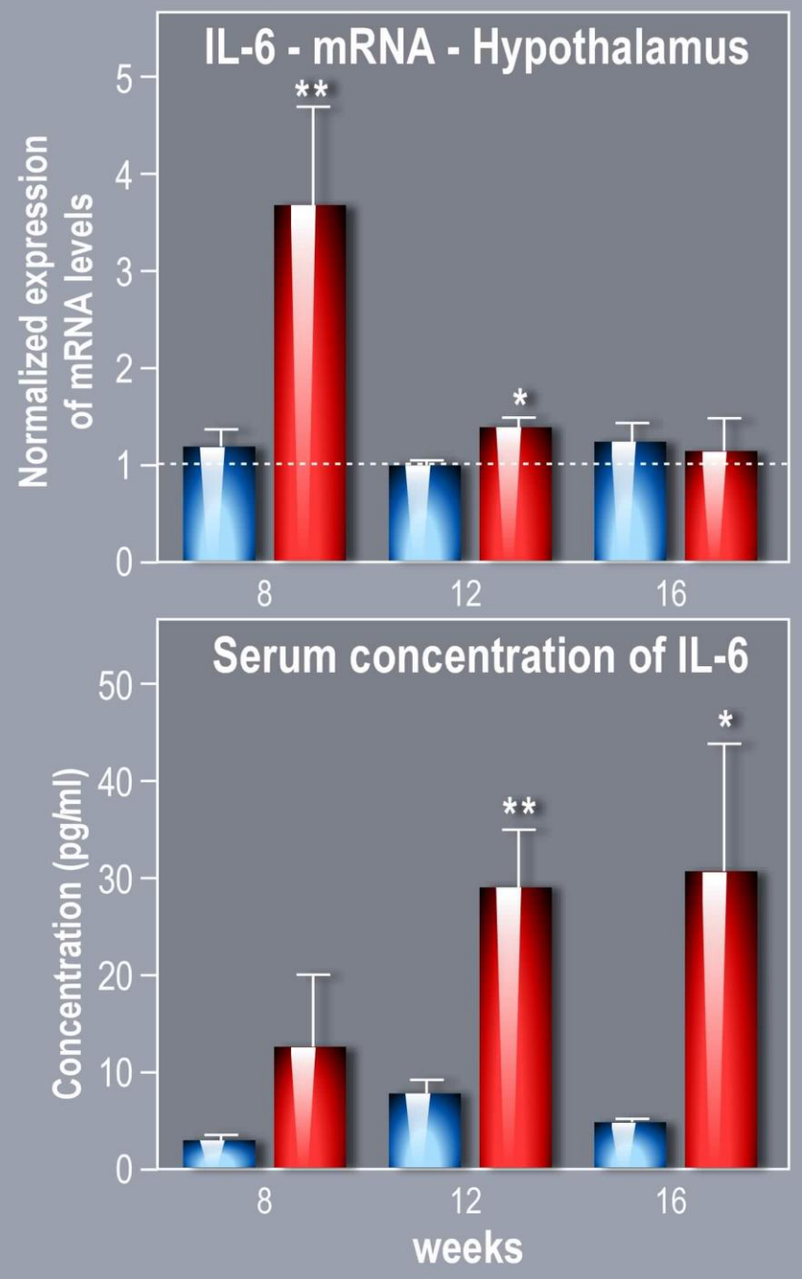
Serum leptin concentration

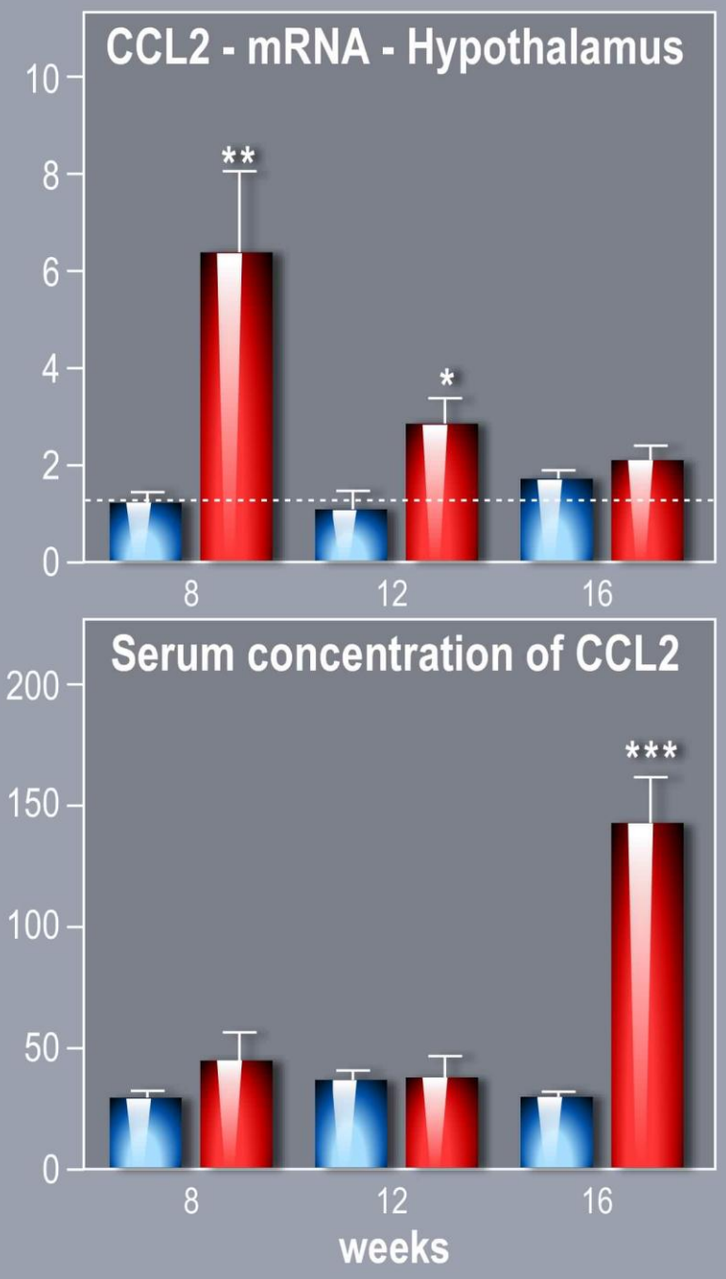


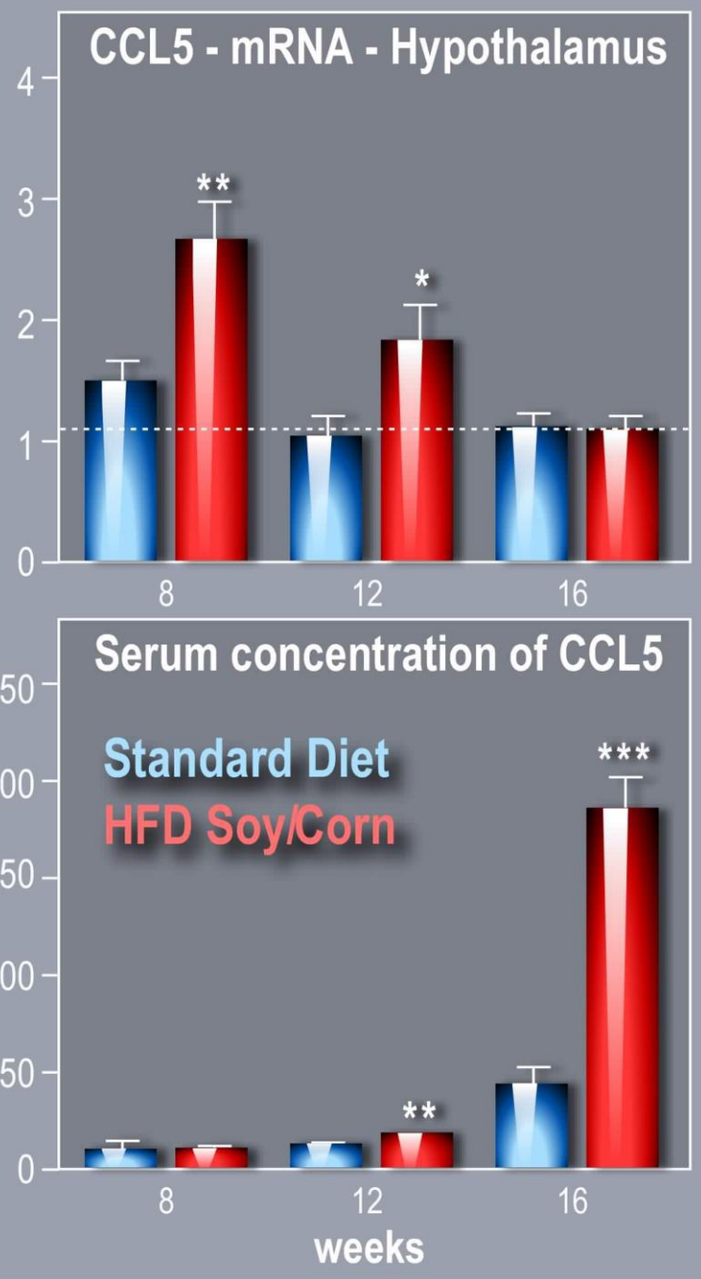
- HFD-fed mice have a weight of 10% higher compared to control animals from 8 weeks of diet
- HDF-fed mice show significant hyperleptinemia from 8 weeks of diet
- **The first signs of obesity are observed after 8 weeks of Soy/Corn High-Fat Diet**

Effects of Soy / Corn HFD consumption on inflammatory profile ?

HYPOTHALAMUS





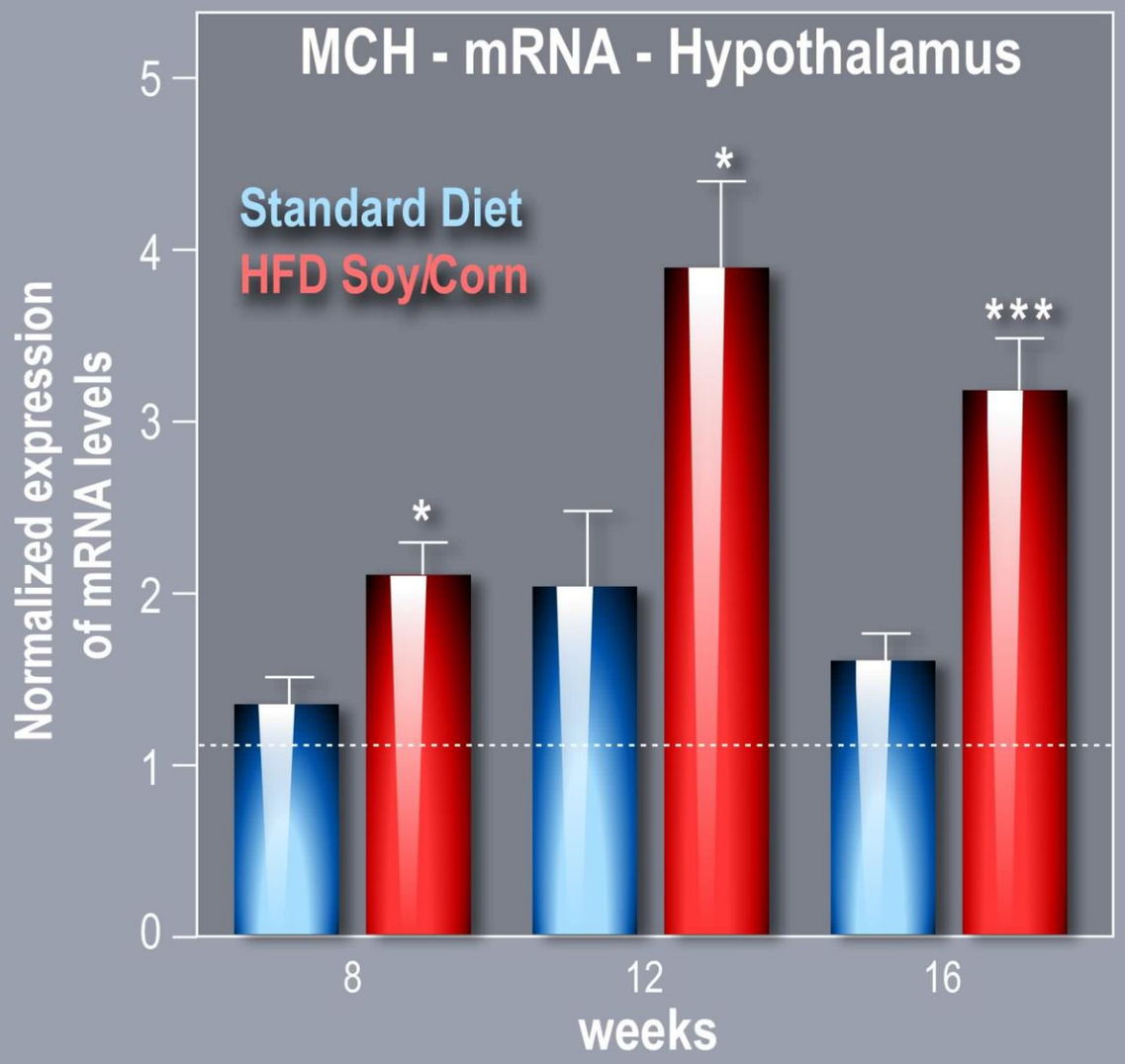


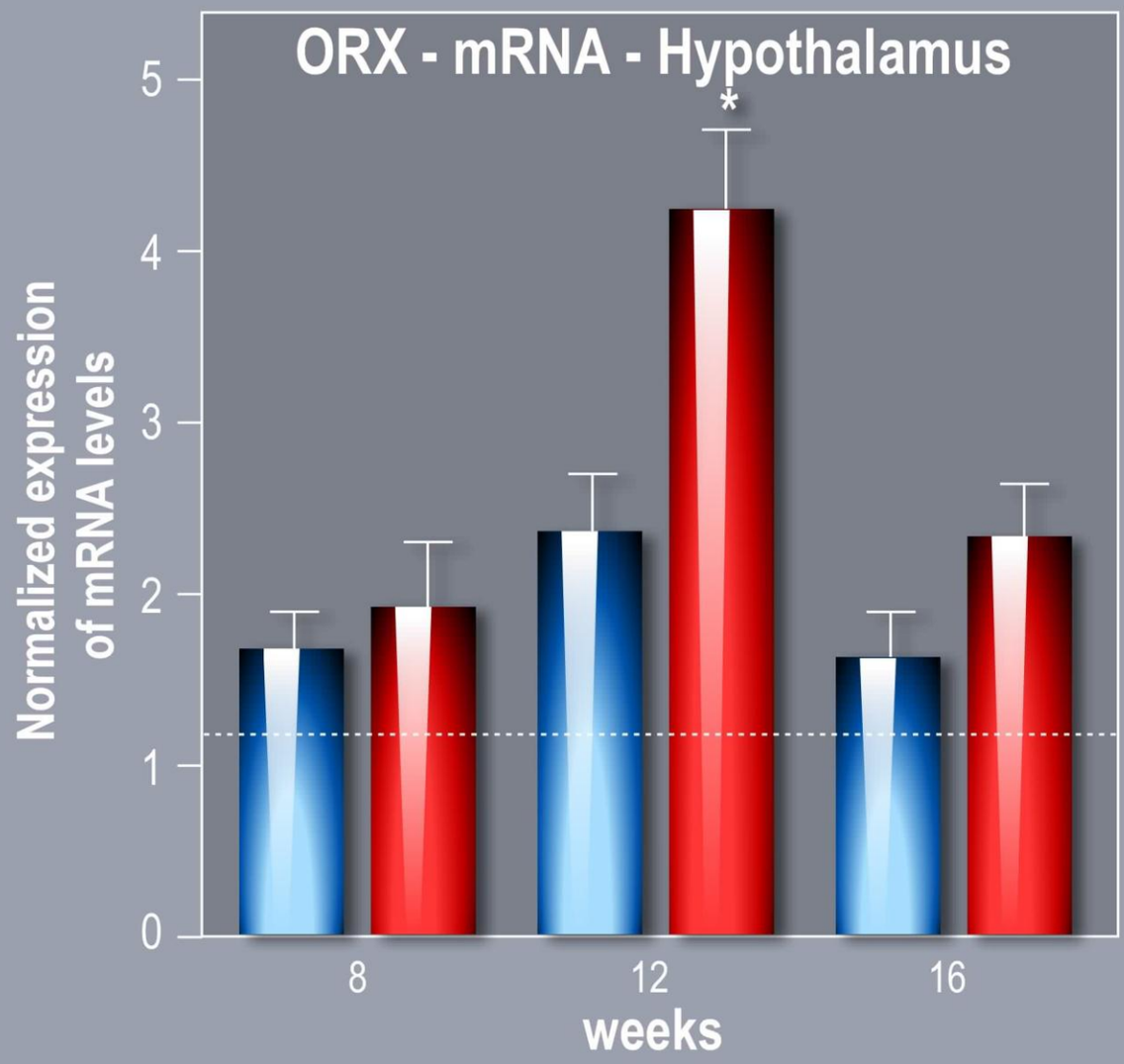
SERUM

- HFD consumption induces both peripheral and hypothalamic inflammation
- Hypothalamic inflammation occurs before the peripheral inflammation

ijpuc

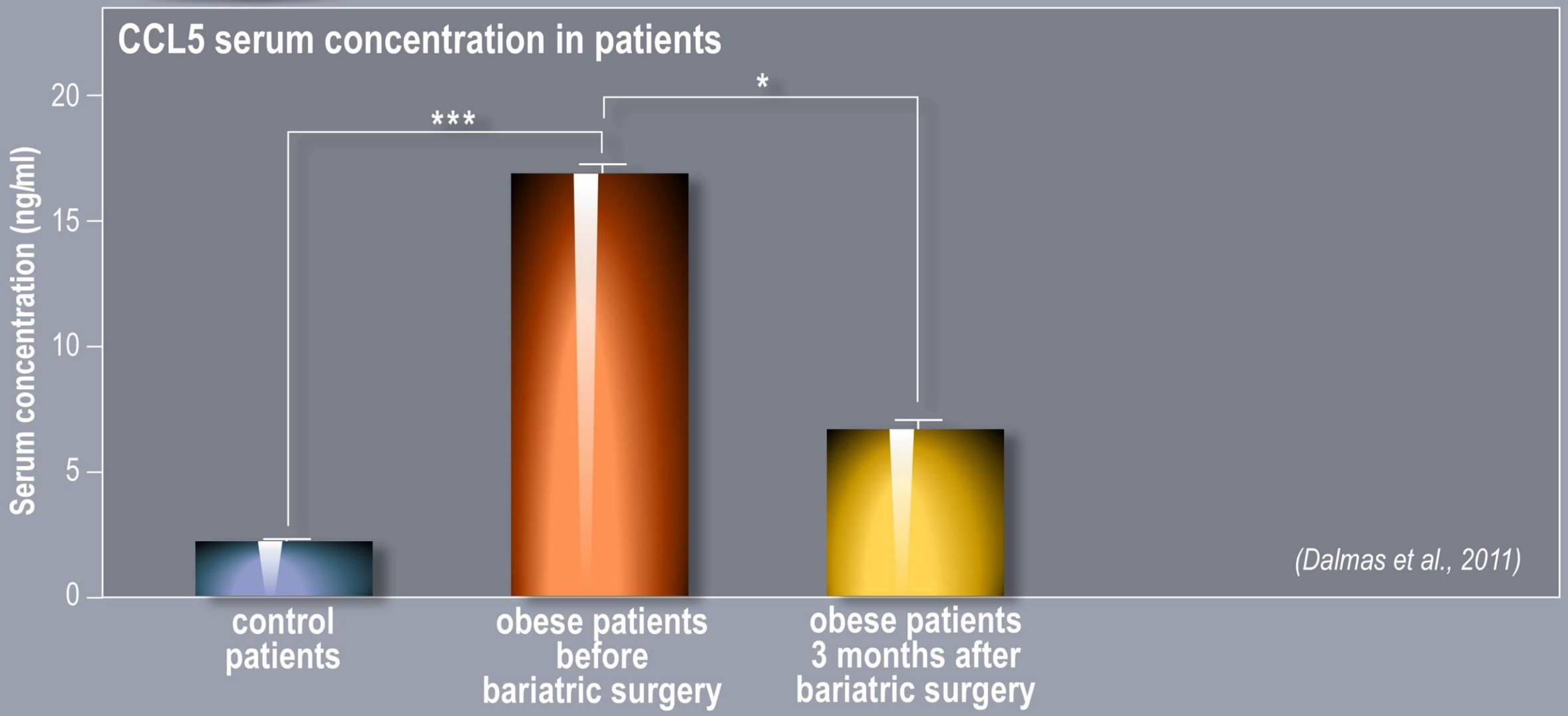
Effects of Soy / Corn HFD consumption on hypothalamic neuropeptides expression?



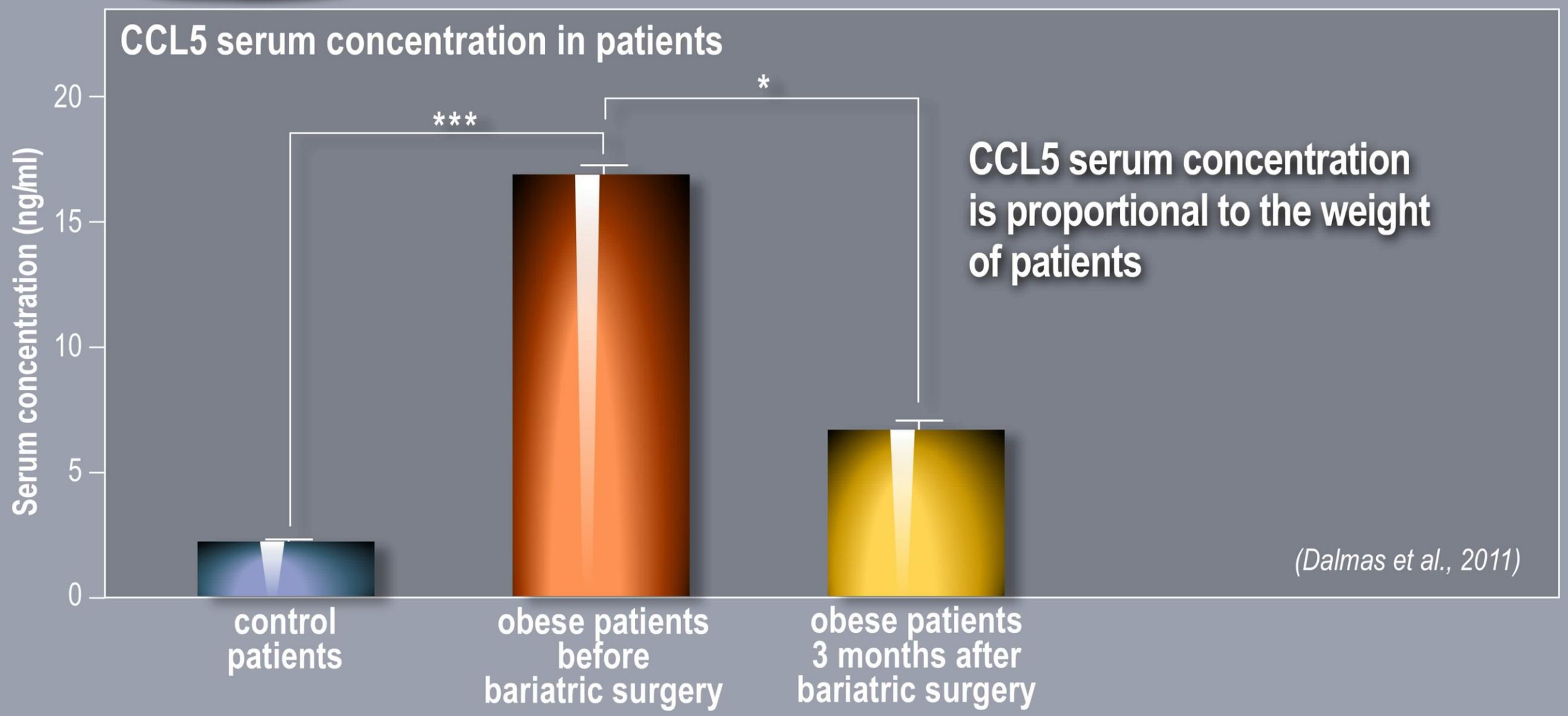


- HFD consumption induces an early and stable increase of the orexigenic peptide MCH expression
- **Does this overexpression of MCH contribute to the development of obesity?**
  Does inflammation contribute to this overexpression of MCH?

Link between CCL5 and weight ?



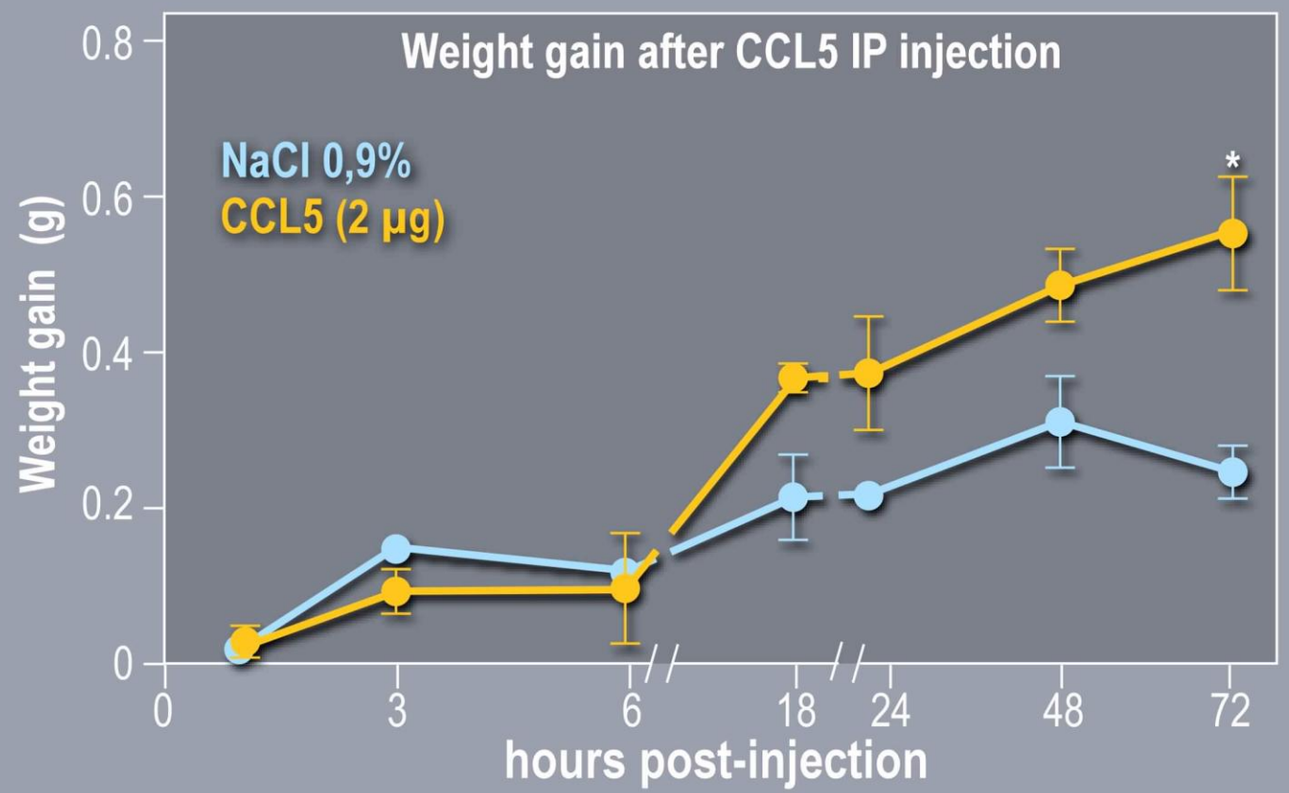
Link between CCL5 and weight ?



Effects of CCL5 injections in mice?

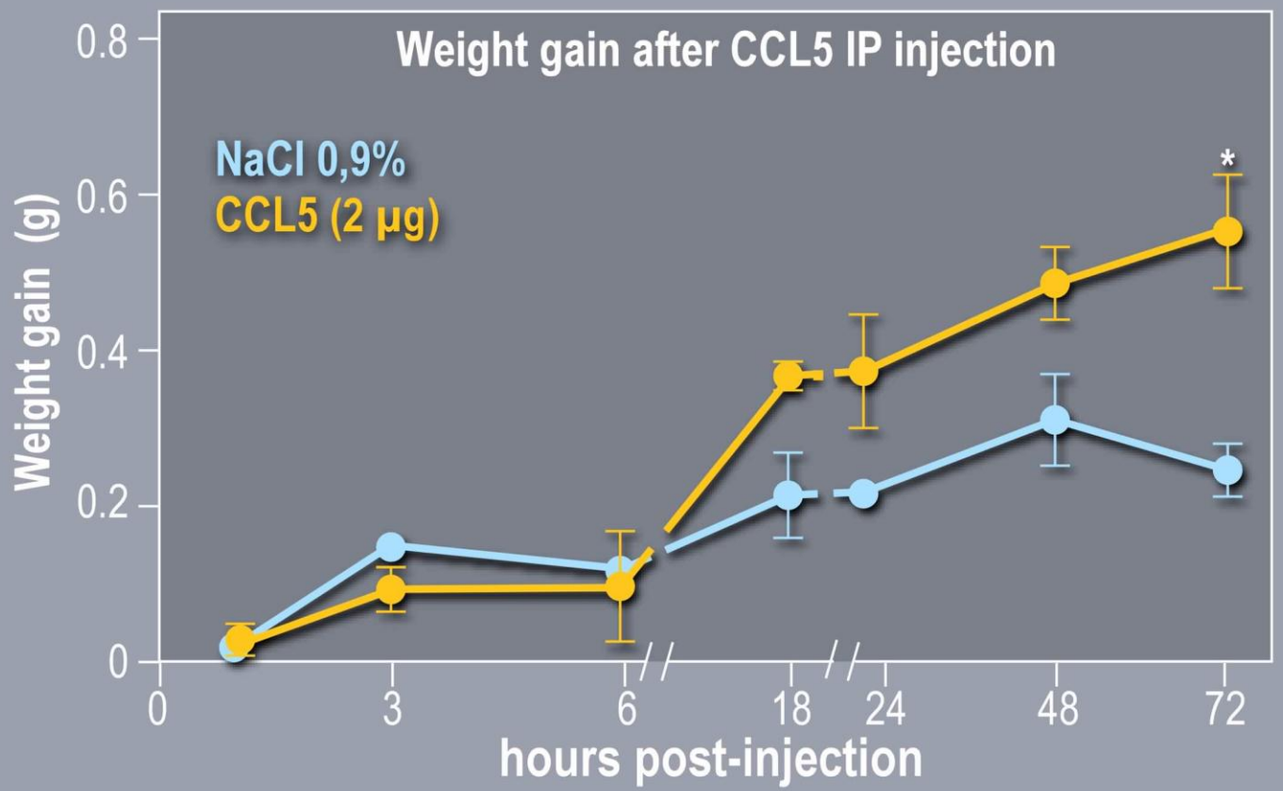
- on the weight?
- on the hypothalamic neuropeptides expression?

Effects of CCL5 central injection on weight?

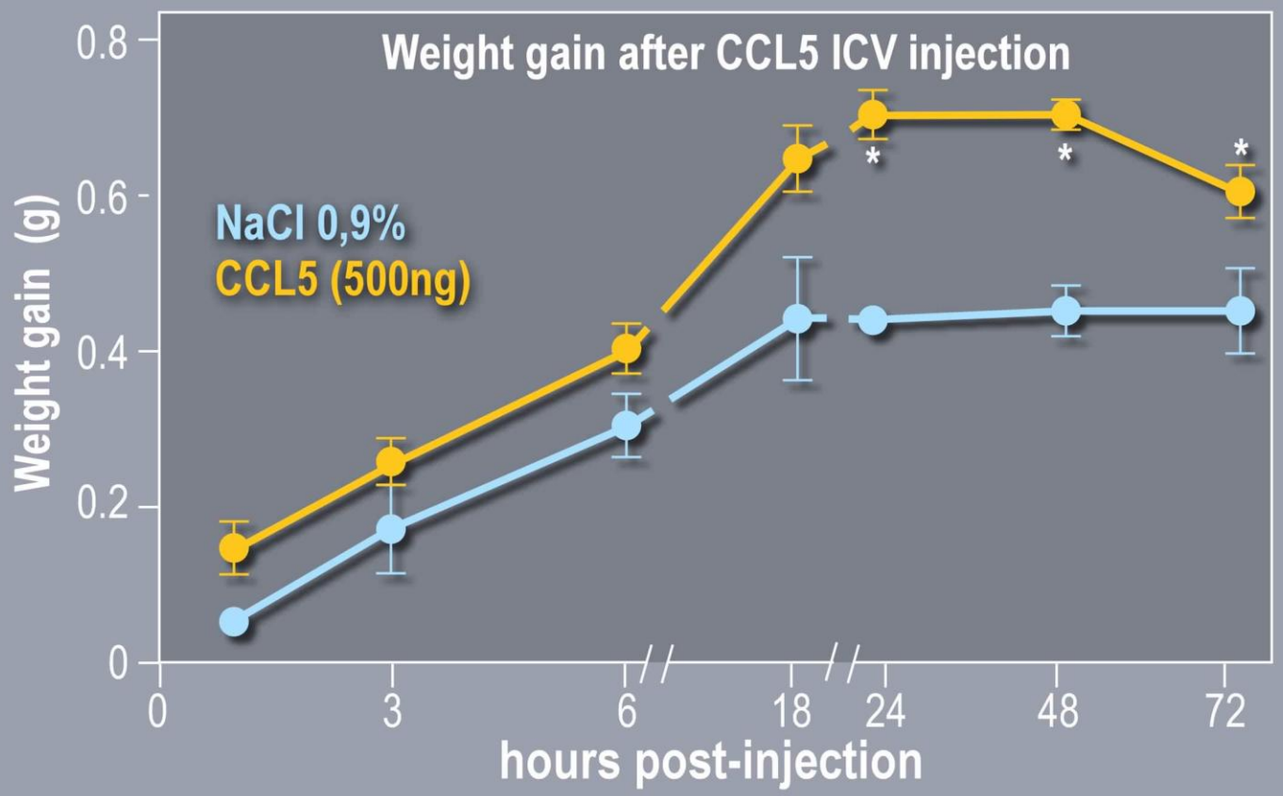


IP injection induces a weight gain in mice after 72h post-injection

Effects of CCL5 central injection on weight?

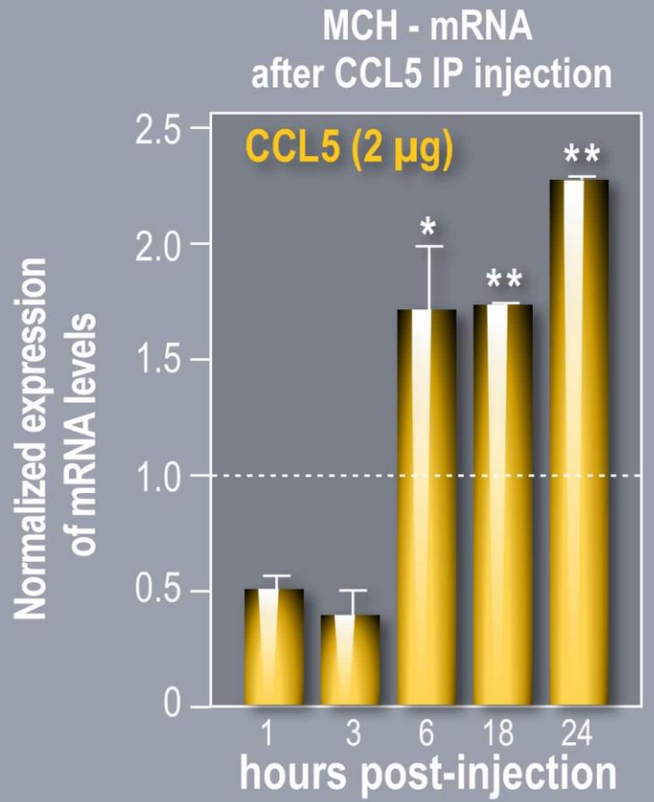


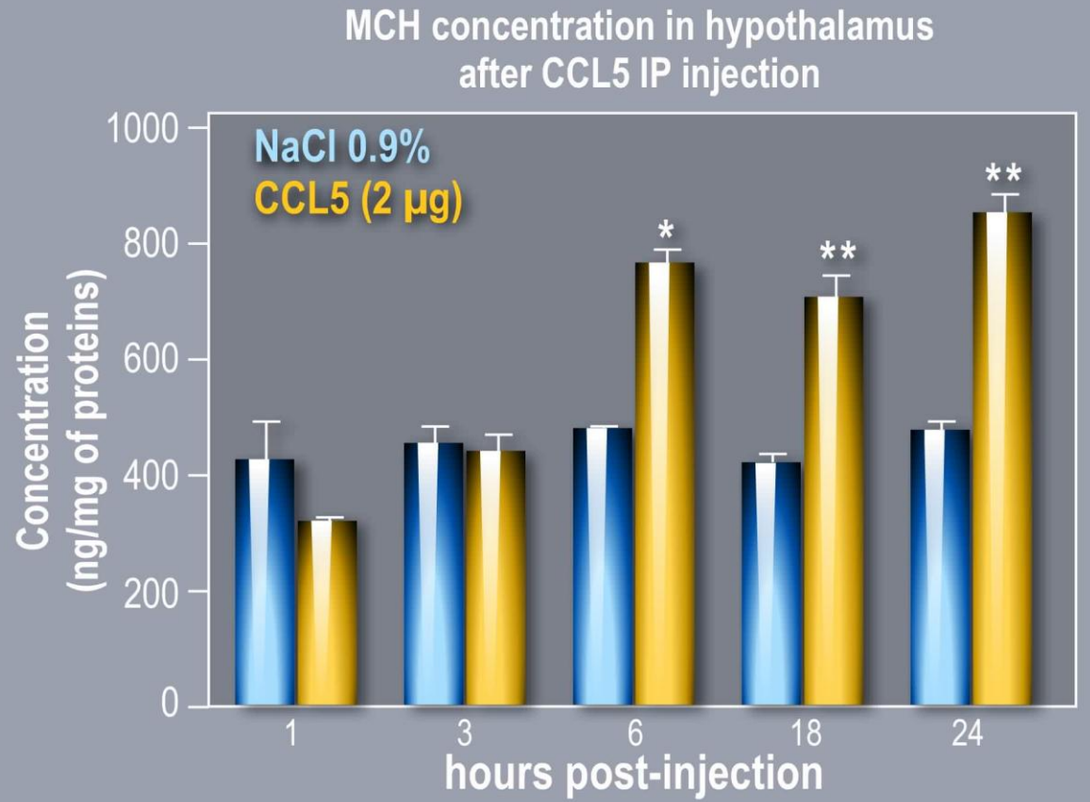
IP injection induces a weight gain in mice after 72h post-injection

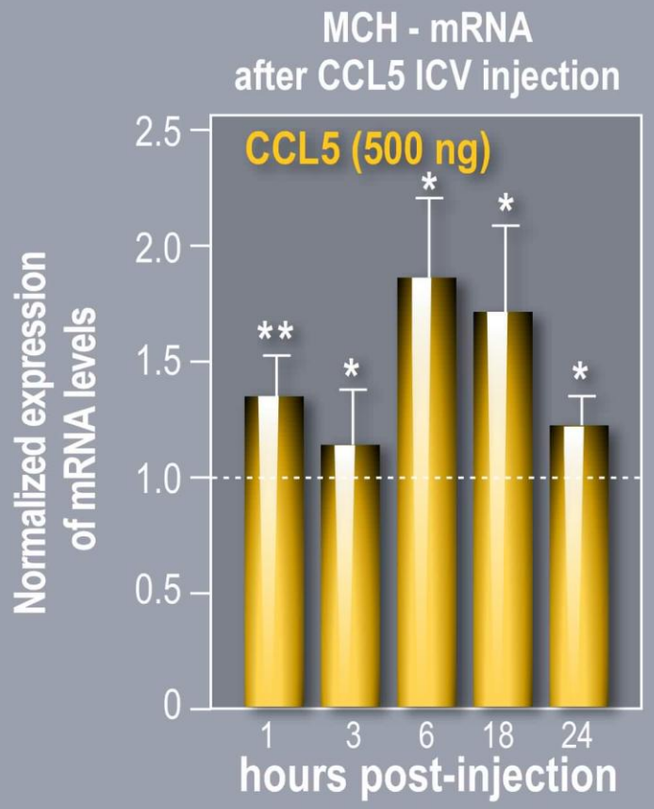


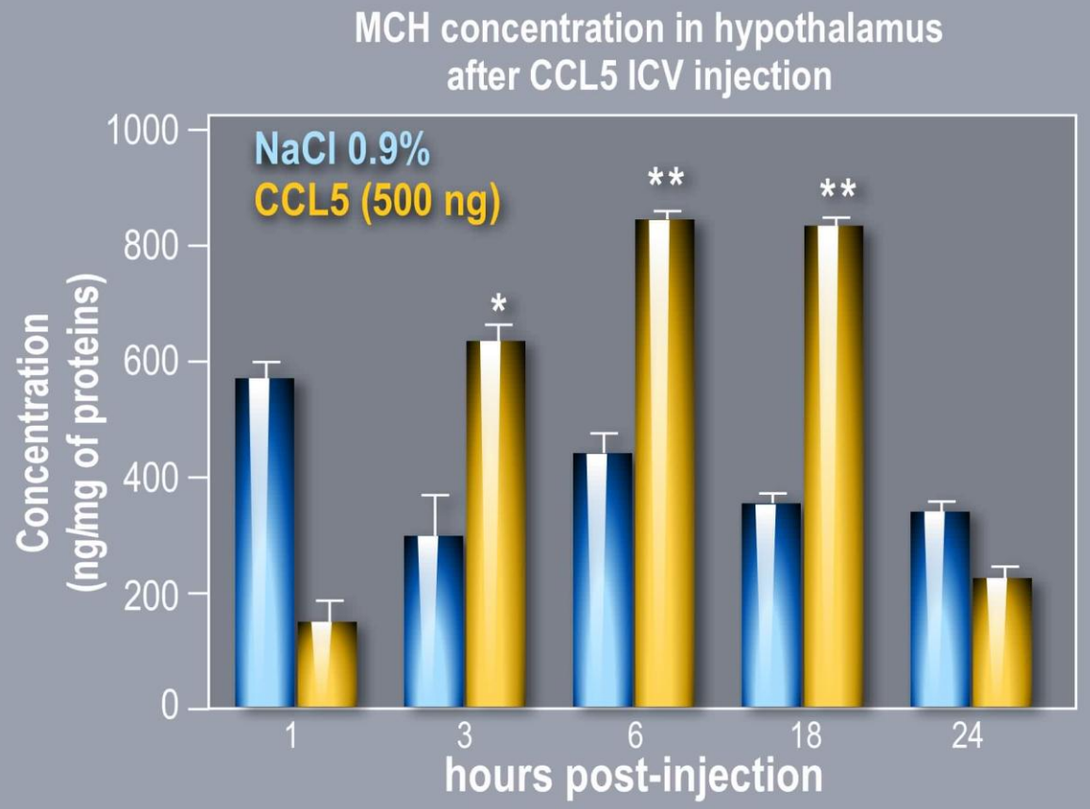
ICV injection induces a weight gain in mice after 24h post-injection

Effects of CCL5 injections on hypothalamic MCH expression?

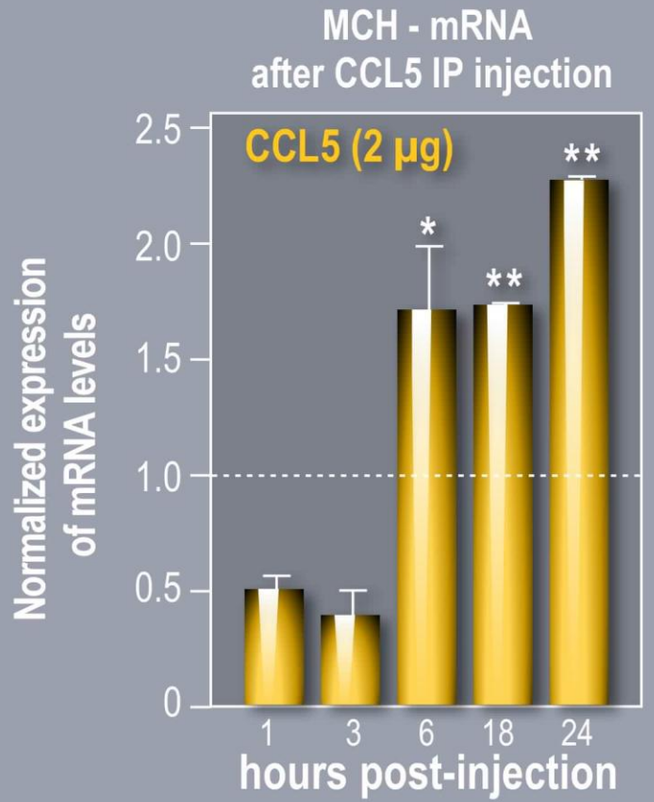


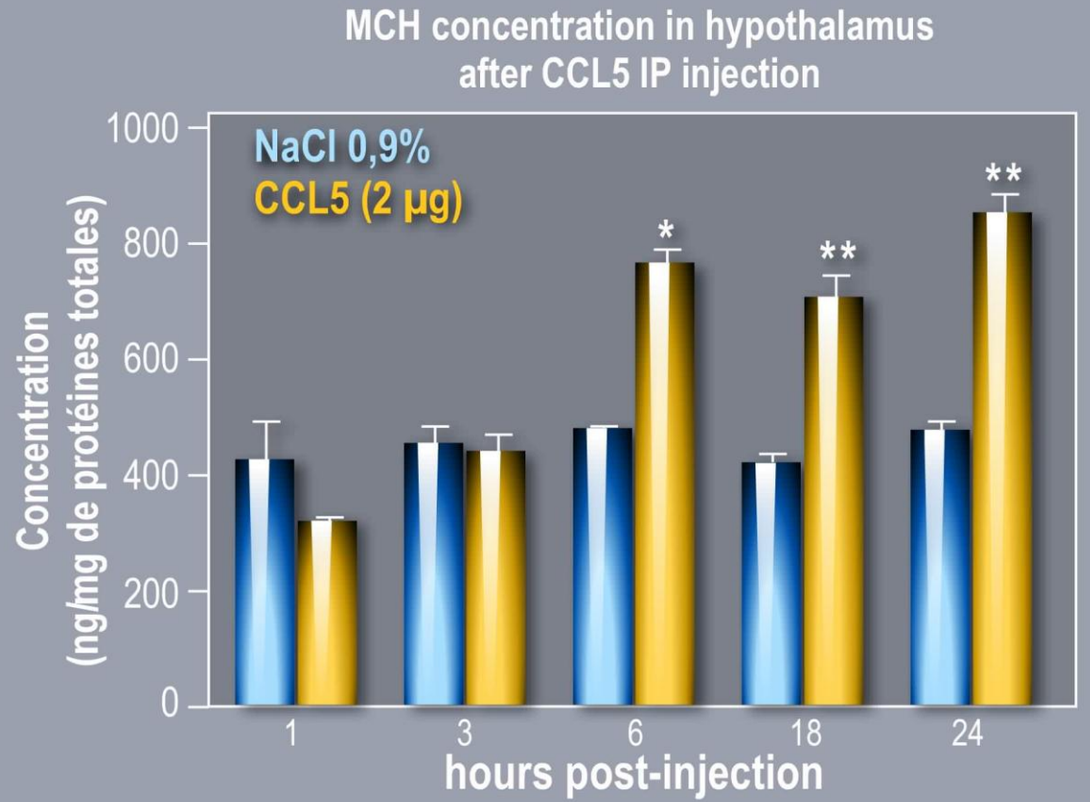




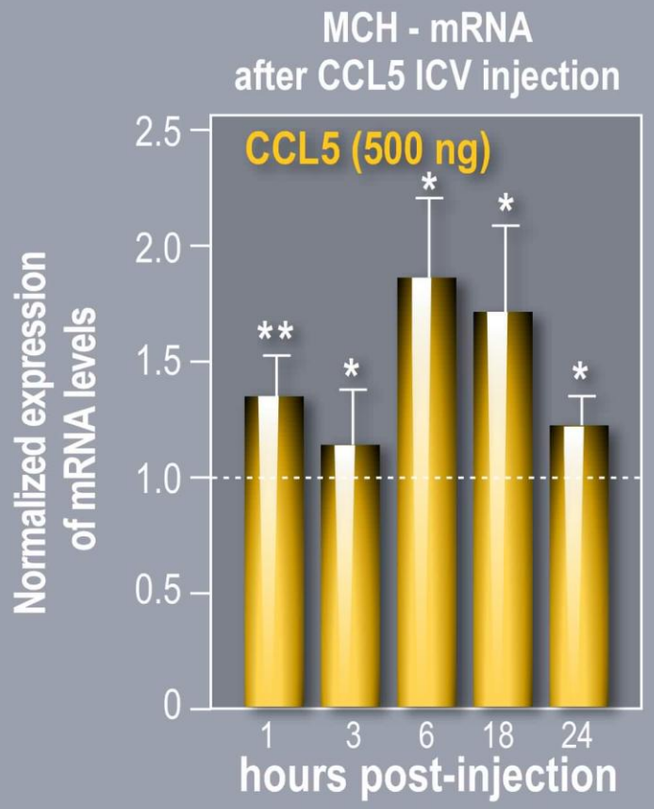


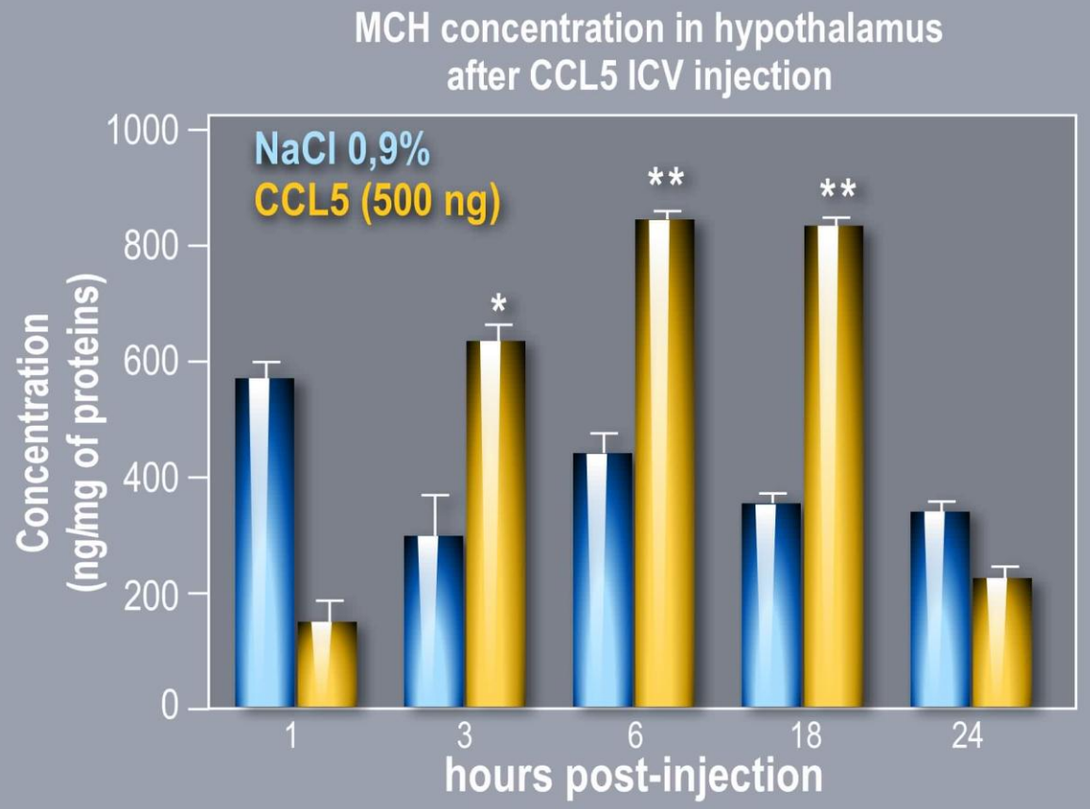
Effects of CCL5 central injection on hypothalamic MCH expression?



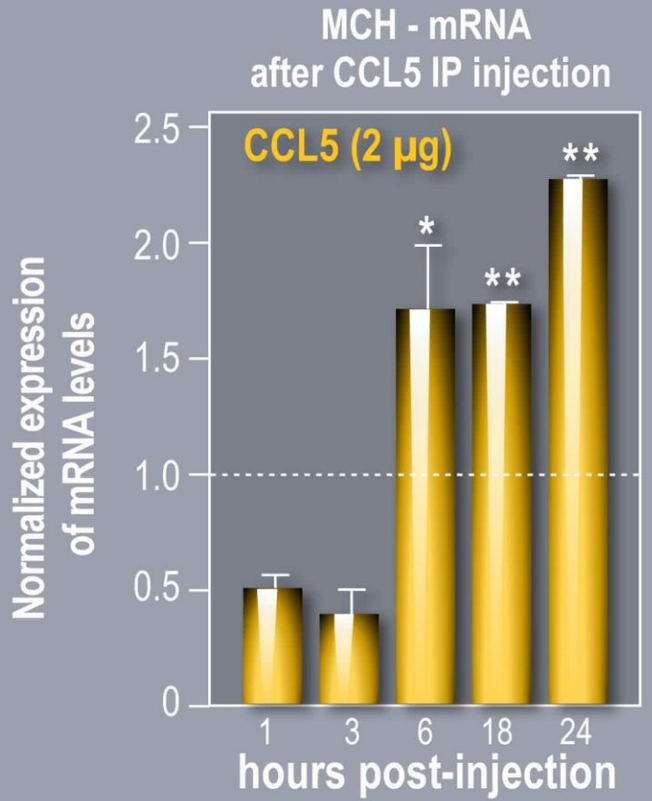


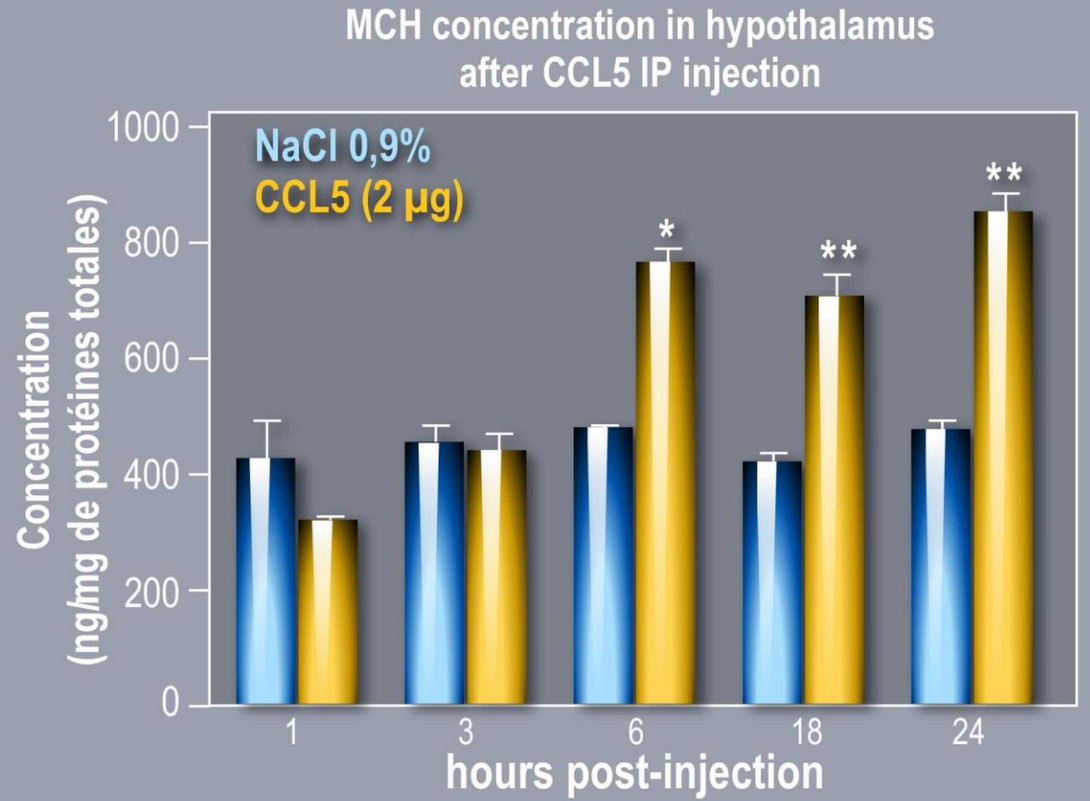
MCH expression is increased by IP CCL5 injection



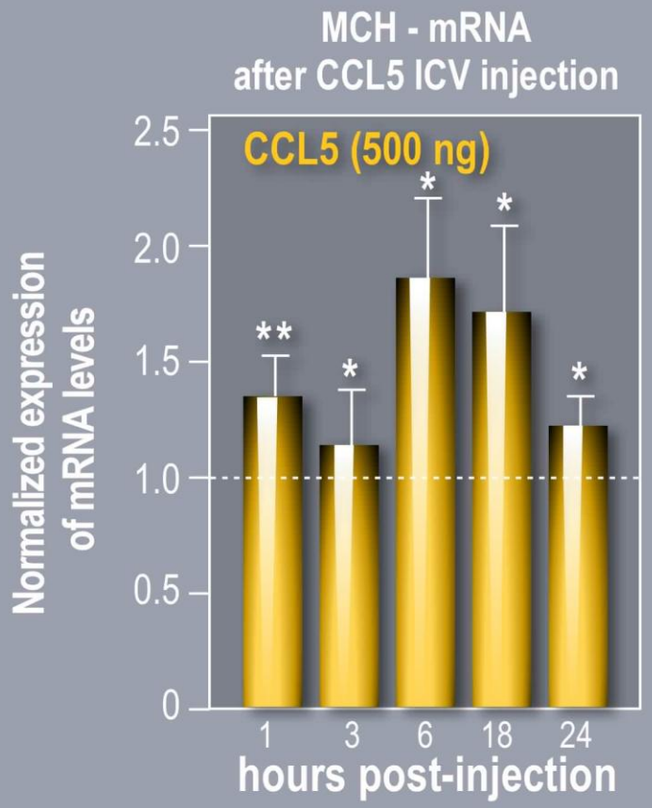


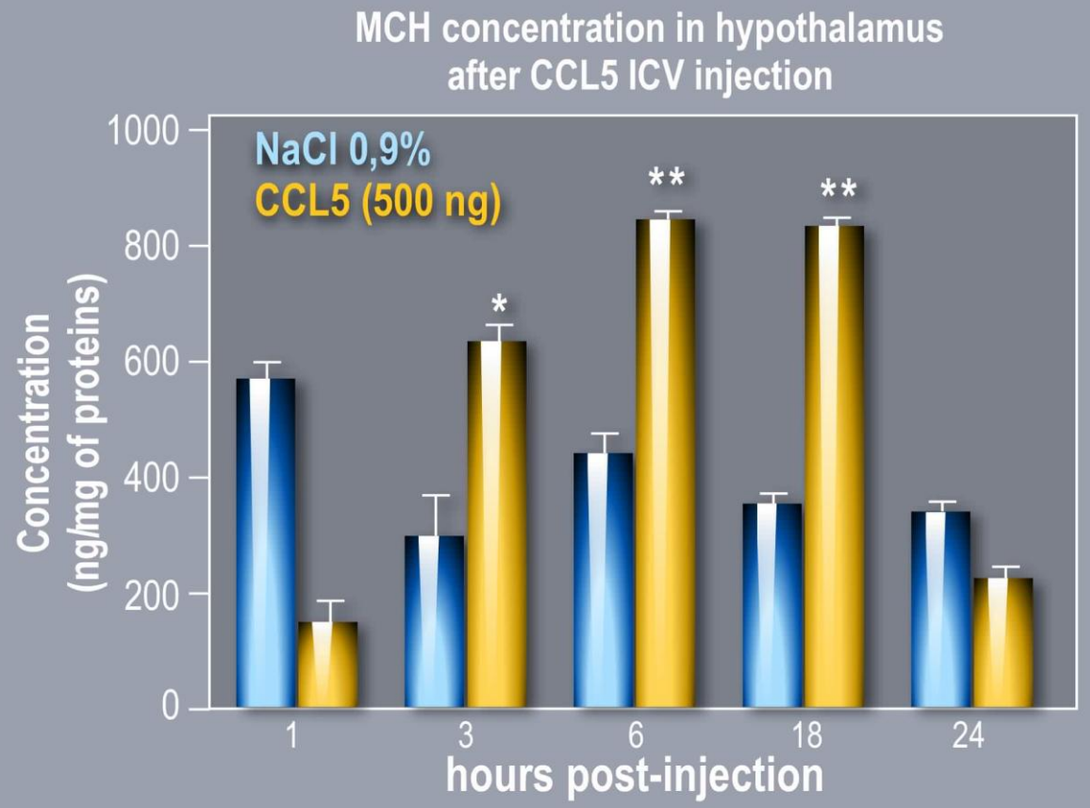
Effects of CCL5 central injection on hypothalamic MCH expression?





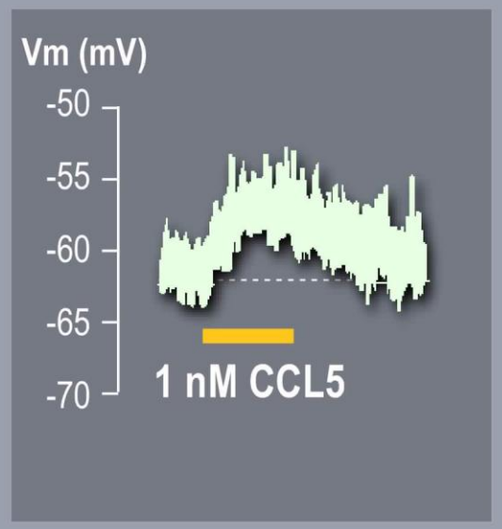
MCH expression is increased by IP CCL5 injection

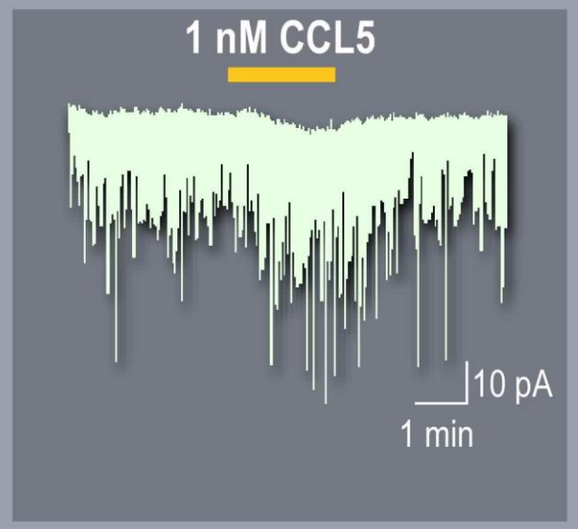


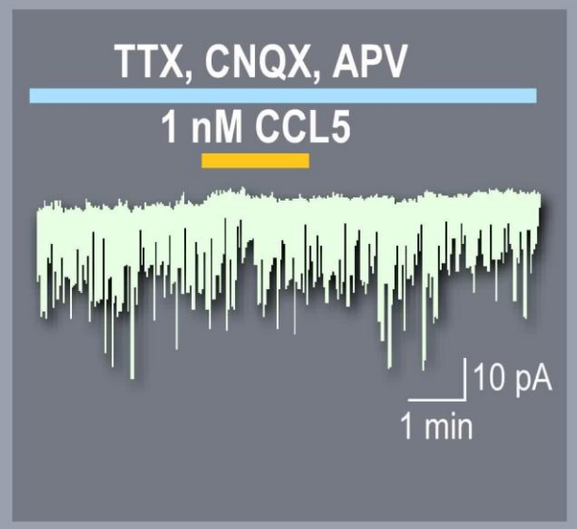


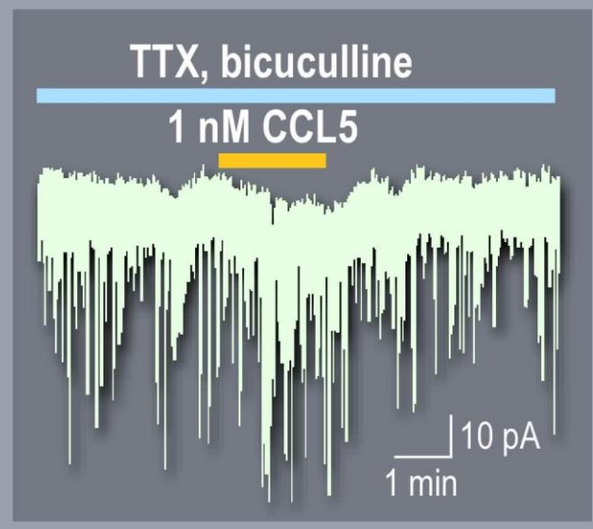
MCH expression is increased by ICV CCL5 injection

Effect of CCL5 on MCH neurons activity ?

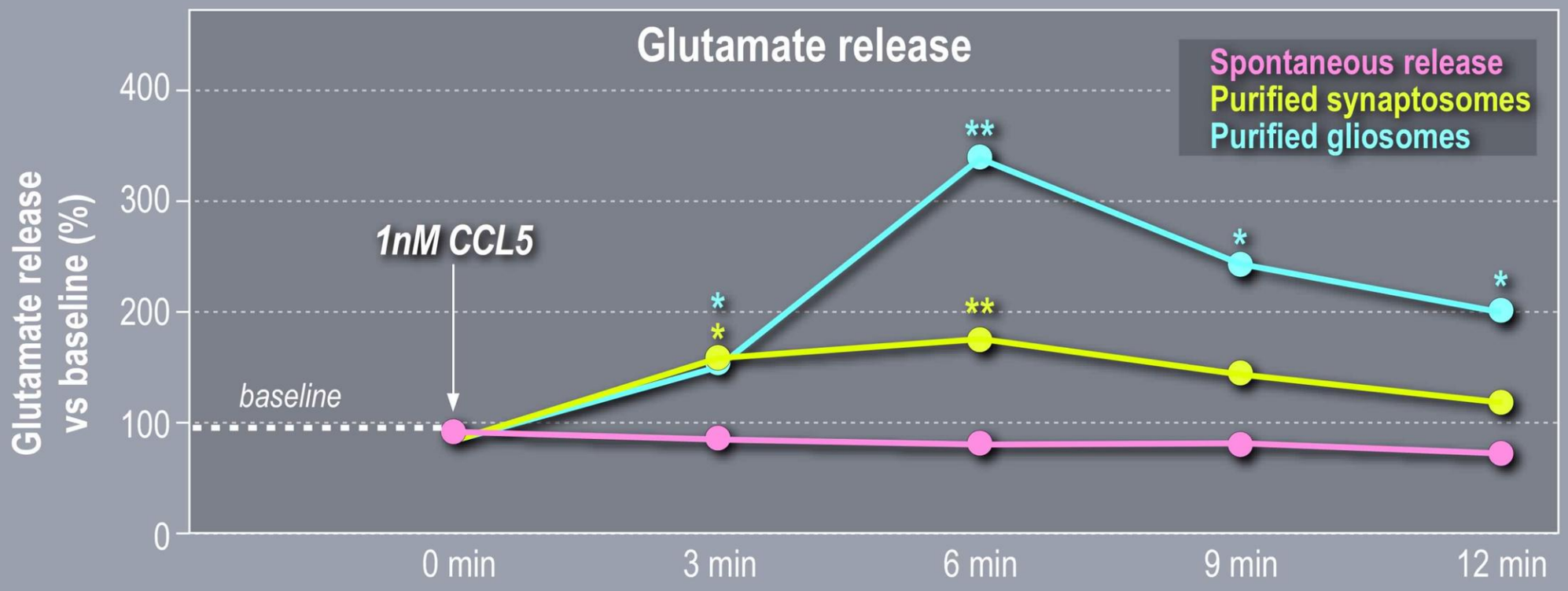








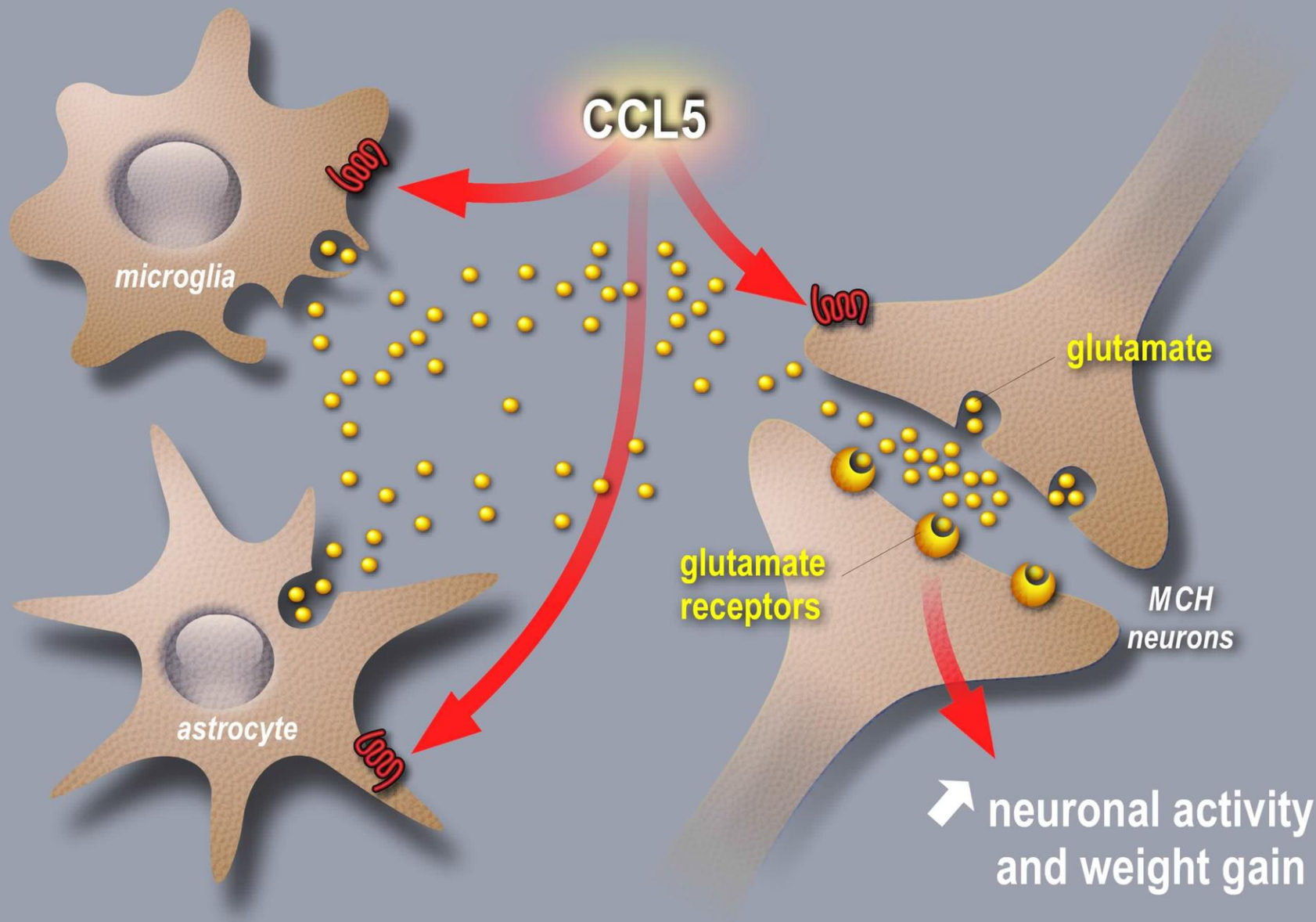
CCL5 induces a depolarization in 88% of MCH neurons, via a presynaptic release of glutamate



CCL5 induces a release of glutamate by both hypothalamic gliosomes and synaptosomes

Conclusion

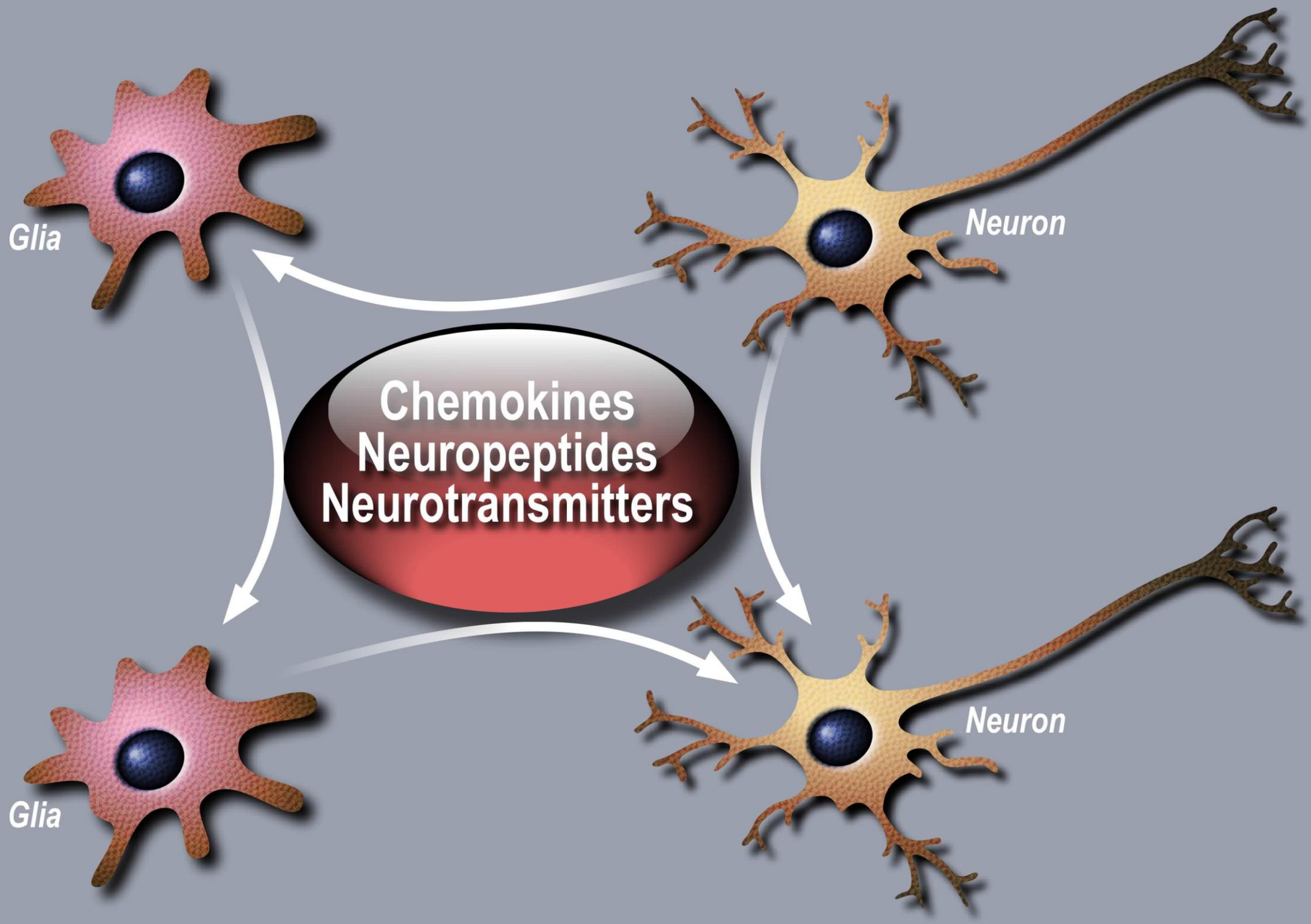
The hypothalamic inflammation seems to play a primary role in the initiation of diet-induced obesity



CCL5, a major central actor in the initiation of obesity ?

A new role for chemokines

Chemokines could be a new class of neurotransmitter, neuromodulator or neuropeptide/neurohormone in the mature brain



Acknowledgements

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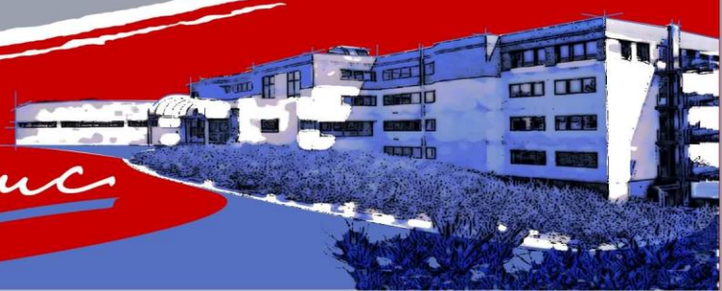

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