IL-6: Inflammatory Marker with Controversial Role in Metabolism

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Introduction

The interleukin-6 (**IL-6**) is a well-known inflammatory cytokine with pleiotropic action throughout the body.
Lately, several studies have reported an **IL-6 METABOLIC ROLE** suggesting that this cytokine:

1. Can directly act on its membrane receptor (**IL-6Rα**), extensively distributed in different hypothalamus sites, regulating fat mass.
2. Mediates the expression of some neuropeptides involved in energy homeostasis in a **GENDER-DEPENDENT-MANNER**.
3. Leads to body weight decrease mainly through **ENERGY EXPENDITURE**, rather than controlling food-intake.

Since IL-6 mechanism of action in the central nervous system is currently unclear, much more research on this matter is required in order to provide **NOVEL TREATMENT TARGETS** for some diseases with a remarkable impact on population, as it is **OBESITY**.

Methodology

The discussion carried out in this review, about the IL-6 role in the energy balance, was basically based on:

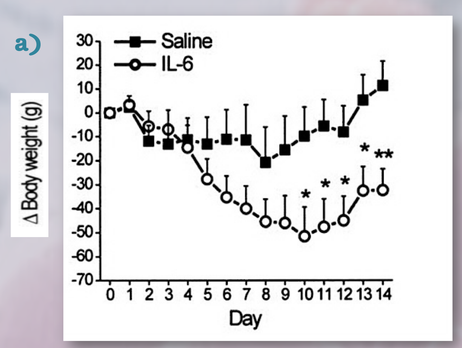
1. Bibliographic revision**: 51 original and review articles read, 22 CITED.**
2. Online databases**: mainly PUBMED.**
3. Scientific journals of high impact as: **Journal of Neuroendocrinology.**

IL-6 and obesity

The general believed of obesity as **PRO-INFLAMMATORY STATE**, involving high IL-6 levels, could seem inconsistent with results shown in **a)** and **b)**. However, these results demonstrate a metabolic role of the IL-6 in the energy balance regulation (see *Conclusions*).

a) Intra-cerebro-ventricular (i.c.v) administration decreases body weight.

b) Mice lacking the IL-6 gene (IL-6-KO) developed later-onset obesity.



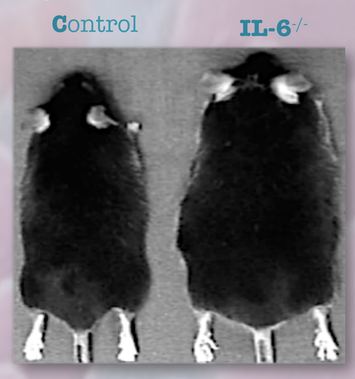
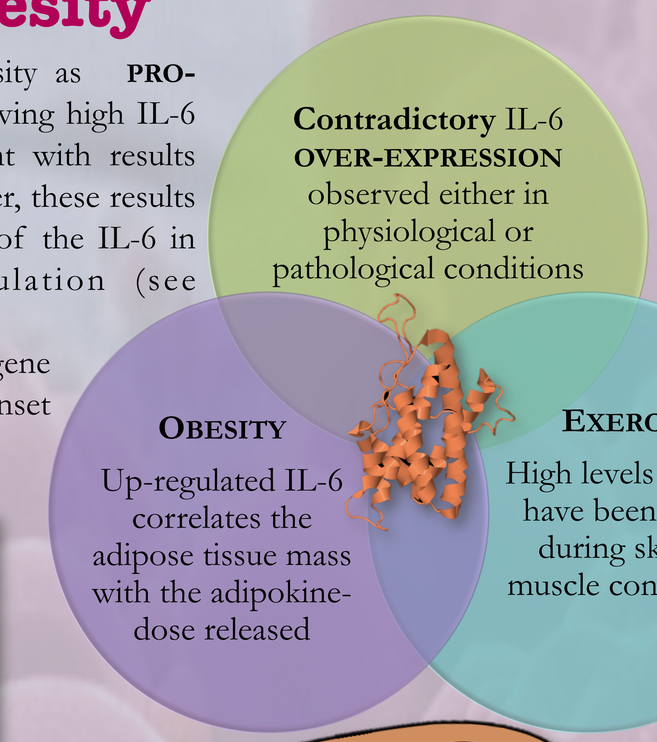
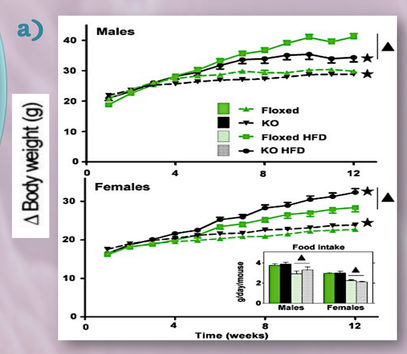


Fig. 1. **a)** Changes in body weight during two weeks of i.c.v treatment with IL-6 in comparison with saline.
b) IL-6 $^{-/-}$ *(IL-6-KO)* mice developed mature-onset obesity.
Results from *Wallenius, K. et al.*, and *Wallenius, V. et al.* see *References*[1,2].



IL-6 and exercise

Contracting muscle is considered an **IMPORTANT SOURCE** of IL-6 since this cytokine is over-expressed during exercise.
Muscle IL-6 has a role in a sex-specific fashion decreasing body weight, as shown in Fig.2. **a**.
Adittionally, neuropeptides related with fat mass regulation seemed to be mediated by muscle IL-6, as shown in Fig.2. **b** (see *Conclusions*).



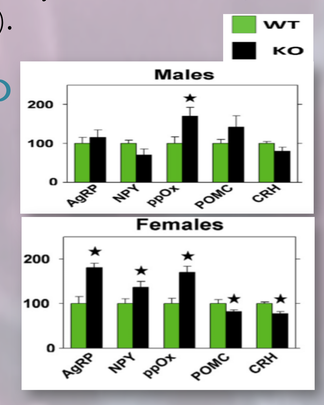


Fig. 2. **a)** Body weight gain in IL-6-KO and floxed mice fed the control diet and the HFD with sex-specific differences.
b) Gender-dependent quantification for the main neuropeptides involved in food intake and energy expenditure in specific hypothalamic nuclei: corticotrophin-releasing hormone (CRH), prepro-orexin (ppOx), agouti-related peptide (AgRP), neuropeptide Y (NPY) and pro-opiomelanocortin (POMC).
Results from *B. Ferrer et al.*, see *References*[3].

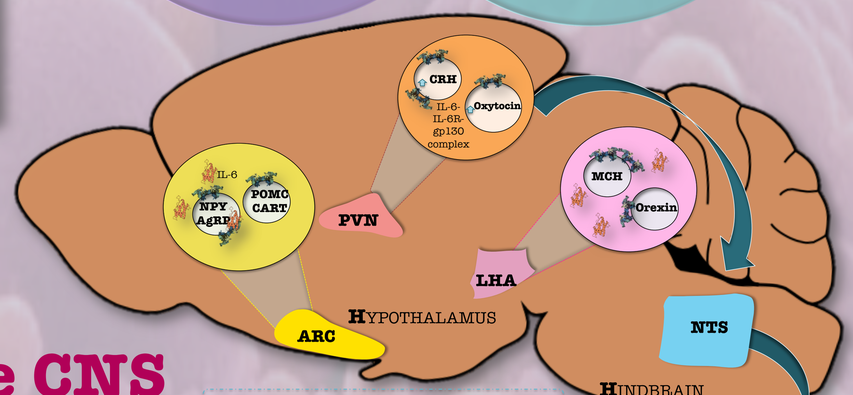


Image modified from *Schéle et al.*.

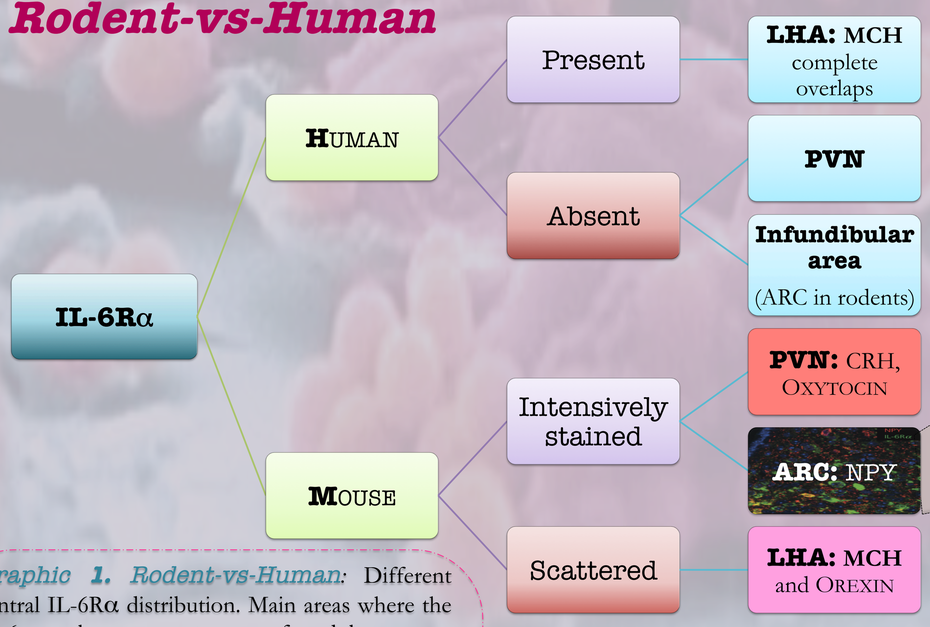
⇧ SYMPATHETIC NERVOUS STIMULATION

⇧ ENERGY EXPENDITURE

⇩ BODY FAT

IL-6 in the CNS

Rodent-vs-Human



Graphic 1. Rodent-vs-Human: Different central IL-6Rα distribution. Main areas where the IL-6 membrane receptor was found by current studies and principal neuropeptides which expression was altered by IL-6: lateral hypothalamic area (LHA), paraventricular nucleus (PVN), arcuate nucleus (ARC) and melanin-concentrating hormone (MCH).

IL-6 and IL-1

- **COOPERATIVE FUNCTION** of IL-6 with IL-1 appears to be important for obesity development.
- Influence on fat regulating neuropeptides was observed in IL-6 and IL-1R1-KO mice, as shown in *Fig. 3.* **b** and **c**.
- Both cytokines might exert anti-obesity effect acting on the GLP-1 receptor in the **HINDBRAIND**.

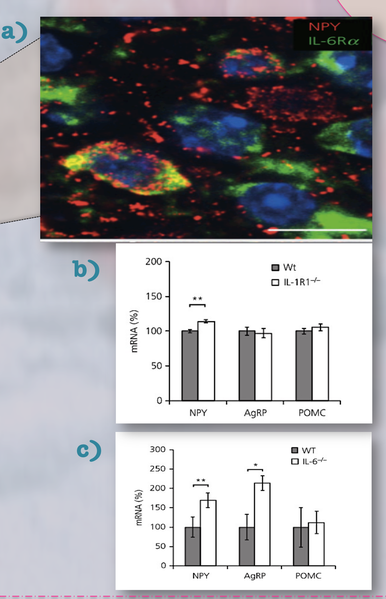


Fig. 3. **a)** Cells with co-localised IL-6Rα-and NPY in the ARC.
Hypothalamic NPY, AgRP and POMC mRNA levels in IL-1 receptor type I deficient (IL-1R1-/-) mice **(b)** and IL-6 deficient (IL-6-/-) mice **(c)** .
Results from *Schéle et al.*, see *References*[4].

Conclusions

1. Since the adipose-derived hormone leptin correlates with adipose tissue mass during obesity, the IL-6 might correlate with the pro-inflammatory state of obese patients as well as with their adipose tissue mass in a similar way as leptin. Thus, it is suggested that IL-6 could signal the CNS to regulate fat mass in analogous form as leptin does.
2. The IL-6 influence on homeostasis is exerted via some energy balance-related nuclei and neuropeptides in the hypothalamus and hindbrain, regulating body weight mainly through increased energy expenditure rather than controlling food intake.
3. Deletion of cell-specific IL-6 seems to have similar repercussions on energy balance. Development of gender-cell-specific IL-6 knockout mice is, indeed, an efficient tool suggested for future studies.

References

1. Wallenius, V. *et al.* Interleukin-6-deficient mice develop mature-onset obesity. *Nat. Med.* 75–79 (2002).
2. Wallenius, K., Wallenius, V., Sunter, D., Dickson, S. L. & Jansson, J.O. Intracerebroventricular interleukin-6 treatment decreases body fat in rats. *Biochem. Biophys. Res. Commun.* **293,** 560–5 (2002).
3. Ferrer, B. *et al.* Muscle-specific interleukin-6 deletion influences body weight and body fat in a sex-dependent manner. *Brain. Behav. Immun.* **40,** 121–30 (2014).
4. Schéle, E. *et al.* Inter-relation between Interleukin (IL)-1, IL-6 and Body Fat Regulating Circuits of the Hypothalamic Arcuate Nucleus. *J. Neuroendocrinol.* **25,** 580–589 (2013).