Mónica del Águila Conde - Environmental Biology - Final Project

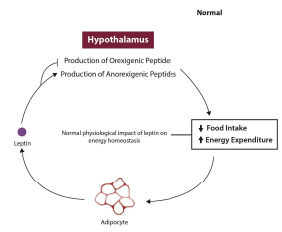
Universitat Autònoma de Barcelona

Mechanisms of Leptin Resistance in Diet Induce Obesity (DIO)

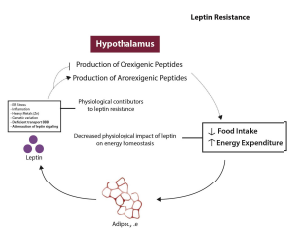
INTRODUCTION

- Obesity resulted to and imbalance between caloric provide and energy expenditure.
- The exact mechanisms of obesity are not clear at present, but the feedback control system that maintains body weight (fig. 2) seems to be very important.
- Leptin is a hormone that acts in the brain to decrees feeding and increase energy expenditure. However, diet induced obesity (DIO) is associated with high leptin levels, which suggest resistance process for this hormone.
- Nowadays the mechanisms of this resistance are unclear, but several possibilities have been proposed.
- **The aim of this review is to explain the role and advances in two of this mechanism:**
  1. **Deficient transport across de blood-brain barrier (BBB)**
  2. **Attenuation of leptin signaling in LRb receptor**

Fig.1



Leptin role in energy homeostasis under normal conditions



Leptin deficient in DIO, causes → Deficient transport across de blood-brain barrier (BBB), the attenuation of leptin signaling in LRb receptor, deficiencies and variation in leptin and LEPR receptor gens, endoplasmatic reticulum stress, inflammatory response and exposition to heavy metals.

METHODOLOGY

Literature research on PubMed and Google scholar database using the following keywords: Leptin; Leptin resistance; Blood–brain barrier; obesity; central nervous system; Leptin receptor; Attenuation leptin signaling.

RESISTANCE MECHANISMS

ATTENUATION OF LEPTIN SIGNALING IN LRb RECEPTOR

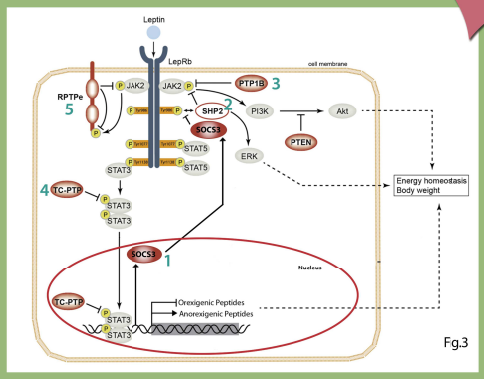


Fig.3

Fig. 3 Leptin binds to its receptor LRb, which undergoes a conformational change that activates the receptor-associated Jak2 tyrosine kinase. Activated Jak2 will autophosphorylate itself and the tyrosine residues (Tyr) at positions 985, 1077, and 1138 located in the LRb/JAK2 complex. Phosphorylated Try serves as a docking site for other singnaling proteins. Some proteins modulate in a positive or a negative way this signal cascade. Furthermore leptin activates other pathways, which are also involved in energy homeostasis and body weigh.

	PROTEIN	FUNCTION	RESISTANCE
1	Suppressor of cytokine signaling 3 (SOCS3)	➢ Activated by STAT3 ➢ Binds to Tyr985 attenuating STAT3 and leptin signaling →inhibitory feedback	➢ ↑ SOSC3 levels derived in leptin resistance. ➢ Mice with delection in SOCS3 are resistance to DIO.
2	SH2 domain-containing protein tyrosine phosphatase-2 (SHP2)	➢ Binds in Tyr985, like SOCS3. ➢ Negative and positive regulation: • + Promote ERK signal • - ↓ JAK2 phosphorylation → ↓ JAK2/STAT3 signal	➢ Mice with neuronal delection of SHP2 are obese → positive > negative regulation. Competition with SOCS3 for Tyr?
3	Non-receptor protein PTP1B	➢ Negative leptin regulator that dephosphorylates JAK2.	➢ DIO is accompanied by ↑ PTP1B expression. ➢ Mice deficient in this protein (PTP1B -/-) and mice with neuronal delection of PTP1B are resistant to DIO.
4	TC-PTP non-receptor protein	➢ Shares 72% identity and structural similarity with PTP1B. ➢ PTP1B and TC-PTP acts at sequential leves (PTP1B on Jak2 and TC-PTP in STAT3)	➢ Synergy effect: Mice without PTP1B and TC-PTP in neurons present more resistance to DIO tan mice without PTP1B or TC-PTP
5	RPTP epsilon (RPTPe)	➢ Receptor localized to the plasma membrane. ➢ Activation of leptin phosphorylate Try605 and activates RPTPe. ➢ RPTPe acts as a negative feedback dephosphorylating JAK2 and inhibiting leptin signal.	➢ Mice lacking in RPTPe are resistance to DIO.

Table 1. Proteins that regulate leptin signal in receptor LRb. The numbers on the right correspond with the blue numbers on Fig.3

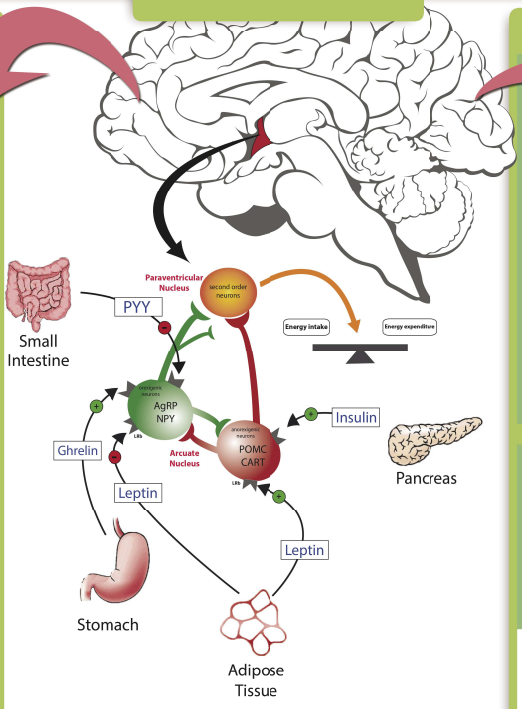
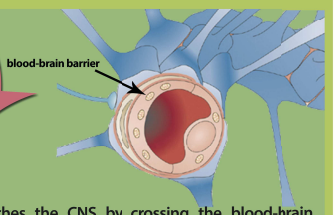


Fig 2. Hormones involved in the energy homeostasis binds to receptors on orexigenic and/or anorexigenic neurons in the arcuate nucleus. The neuropeptides resulted from these interactions travel along axons to secondary neurons in other areas of the hypothalamus and changes the sensation of hunger and satiety.
Leptin promotes anorexigenic peptide and the decreased the orexigenic neuropeptide.

DEFICIENT TRANSPORT ACROSS THE BLOOD-BRAIN BARRIER



- Leptin reaches the CNS by crossing the blood-brain barrier (BBB) through specific, saturable, and unidirectional transport system.
- The main transporting receptor for leptin at the BBB is LRa
- In DIO mice serum leptin levels >> than cerebrospinal fluid → error in the transport across the BBB that conduces to leptin resistance.

CAUSES

- ↑ leptin levels >5–10 ng/mL → transport saturation
- Triglycerides: ↑ triglycerides ↓ anorectic effect of leptin
- C-reactive protein (CRP): binds with leptin ↓ transport across BBB → leptin resistance.
- LRe leptin soluble receptor: antagonists to the leptin transport receptor LRa.

Fig.4

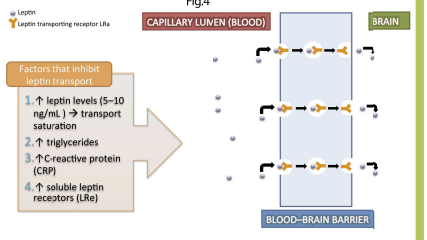


Fig. 4 Leptin transport across the blood-brain barrier through receptors-mediated endocytosis and factors that inhibit this transport

CONCLUSION

- **Mechanism of leptin resistance are still unclear and its comprehension is mandatory in order to understand the energetic disequilibrium caused by obesity and enhance the treatment research to deal with this disorder.**
- **Proteins that block leptin's signal in the hypothalamus are an interesting focus of study for the design of novel therapeutic strategies.**
- **A deeper research on this topic is needed in order to reach the comprehension of the side effects that may be caused by the inhibition of these proteins.**
- **Studies that show the equilibrium between the mechanisms that facilitate or disturb the transference of leptine through the BBB are also needed.**
- **Finally, the relationship between obesity, leptine resistance and sicknesses derived from obesity must be also carefully analysed as leptine also participates in other physiologic functions such as reproduction, bone homeostasis and immune function.**