Mechanisms of Leptin Resistance in Diet Induce Obesity (DIO)

**INTRODUCTION**

- Obesity results from an 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 decreases 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 mechanisms:
  1. Deficiency transport across de blood-brain barrier (BBB)
  2. Attenuation of leptin signaling in LIR receptor

**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 LIR ReCEPTOR**

- Leptin binds to its receptor LIRs, which undergoes a conformational change that activates the receptor-associated JAK3 tyrosine kinase. Activated JAK3 will autophosphorylate itself and the tyrosine residues (Tyrs) at positions 1102, 1077, and 1136 located in the LIRs tyrosine complex. Phosphorylated Tyrs serves as a docking site for other signaling proteins. Some proteins modulate in a positive or negative way this signal cascade. Furthermore leptin activates other pathways, which are also involved in energy homeostasis and body weight.

**PROTEIN**

- POMC
- NPY/Agouti
- SLC16A1
- SLC16A2
- NPY
- Agouti

**FUNCTION**

- Localized in 1102, 1077, and 1136
- Leptin receptor
- SLC16A1 and SLC16A2
- SLC16A1 and SLC16A2
- HIF-1
- HIF-1

**RESISTANCE**

- Phosphorylates in response to leptin binding
- Phosphorylates in response to leptin binding
- Phosphorylates in response to leptin binding
- Phosphorylates in response to leptin binding
- Phosphorylates in response to leptin binding
- Phosphorylates in response to leptin binding

**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 LIR.
- In vivo mice serum leptin levels >> than cerebral blood fluid + error in the transport across the BBB that confuses to leptin resistance.

**CAUSES**

- ↑ leptin levels (5–10 ng/mL) + transport saturation
- Triglycerides: ↑ triglycerides & anorectic effect of leptin
- L-reactive protein (LRP) co-met with leptin + transport across BBB + leptin resistance.
- Life leptin soluble receptor: antagonists to the leptin transport receptor LIRs.

**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.