

Pharmacological Management of Obesity: New Approaches



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Abstract

Obesity affects about 300 million people in the world. More alarming is the fact that there is a strong correlation between the development of childhood obesity and its prevalence in adulthood. The Food and drug administration (FDA), has approved four long-term anti-obesity drugs in adults: Belviq, Contrave, Qsymia and liraglutide in the past two years. Therefore, new pharmacological alternatives are investigated. It is very important to know the intestine-brain axis and hence leptin, which regulates food intake and energy balance, in subjects of normal weight and is a key hormone in the food and body regulation in children and adults.

Keywords : Diet; leptin; Obesity induced by diet; Pediatric obesity; Gastro-intestinal system; Pharmacological synergism

Introduction

Obesity is one of the most serious problems of the 21st century and currently about 2.1 billion people. Almost 30% of the world's population are obese or overweight [1]. An important cause in the development of this disease is the increasing availability of high-calorie foods and flagrant consumption supported by the lack of physical activity to increase energy expenditure. It is estimated that 90% of cases of type 2 diabetes mellitus are attributed to overweight and obesity. It

is considered that a child is obese when it exceeds 20% of its ideal weight; this problem not only triggers physical but also psychological complications. More alarming is the fact that there is a strong correlation between the development of childhood obesity and its prevalence in adulthood. Also, children who do not have this disease are likely to stay within normal weight in adulthood [2]. The FDA has approved four new drugs so far: Lorcaserin, phentermine/topiramate, naltrexone / bupropion and liraglutide (Table 1).

Table 1 : New Weight Loss Drugs approved by the FDA [9].

Generic Name	US Generic Name	Approval Date	Use in Latin America to 2017
Lorcaserin	Belviq Arena pharmaceuticals inc. USA	June 2012	Brasil
Phentermine and Topiramate	Qsymia. Vivus Inc	July 2012	--
Naltrexona y Bupropion	Contrave XR Takeda Pharmaceuticals America Inc	September 2014	--
Liraglutide	Saxenda Novo Nordisk A/S	December 2014	--

The mechanisms of action of each have been recently reported for adult obese population [3]. Therefore, new pharmacological alternatives are investigated. An interesting pharmacological alternative to study is leptin which is the product of the OB gene (Figure 1), was identified as a hormone secreted by adipose tissue, and regulates both food intake and energy balance, in normal weight subjects. It has been received with great expectation as a potential anti-obesity therapy, due to its ability to revert excess adiposity in animal models characterized

by a deficiency of the hormone; leptin dramatically reduces body fat, suppresses appetitive behaviors and improves other abnormalities in children and adults with congenital hormone deficiency (Figure 2). The adipostatic signal occurs when there is food intake, which stimulates the production of leptin and in turn activates neurons that express hormones that inhibit food intake (pro-opiomelanocortin (POMC), a precursor of the neuropeptide α -MSH (melanocyte-stimulating hormone) AND CART (Cocaine-amphetamine-related transcriptase) (Figure 3).

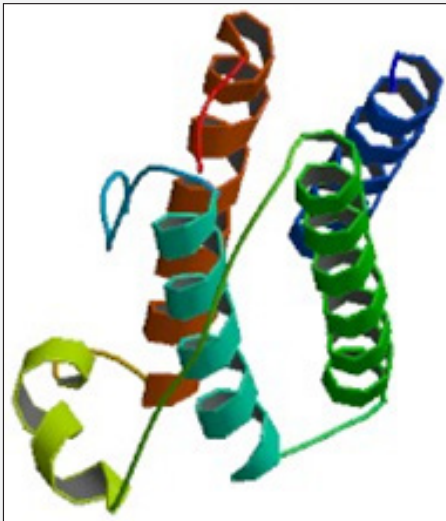


Figure 1: Structure of leptin [7].



Figure 2: Monogenetic model of obesity [6] Weight = 40 kg, 3 years old BEFORE LEPTIN Weight = 29 kg, 6 years old AFTER LEPTIN.

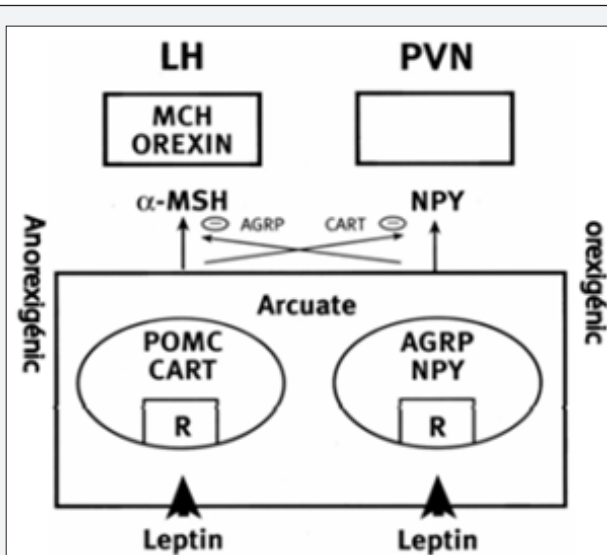


Figure 3: Main populations of neurons in Functional and nonfunctional leptin the arcuatenucleus of the signaling [8]. Hypothalamus [3].

Leptin acts through its receptors, which are generally called (OB-R). This receptor is expressed in the CNS and in peripheral tissues such as adipose, skeletal muscle, pancreatic β cells and liver. This receptor is produced in several spliced forms OBRA, OB-Rb, OB-Rc, OB-Rd, OB-Re and OB-Rf that have in common an extracellular domain of 800 AA, a transmembrane domain of 34 AA and a variable intracellular domain, characteristic of each isoform. Thus they can be classified into three classes: short, long and soluble [4] (Table2).

Table 2: Functional description of leptin receptor isoforms (OB-R) [4].

Isoform	Location	Funcions
Large OB-Rb	Arcuate nucleus (ARC), medial and ventromedial dorsal hypothalamus (VMH). Thalamus and the cellular and Purkinje layers of the cerebellum and pancreatic β cells.	1. Regulation of the alimentary behavior of regulation and energy balance. 2. Inhibition of insulin secretion. 3. Activation of the Jak-Stat \rightarrow transduction of the signal to the interior of the cell.
Short (OB-Rc, OB-Rd y OB-Rf)	Peripheral tissues (intestine, lung and kidney)	Transport and clarification of leptin and regulation of the immune system.
Soluble OB-Re		Transport of leptin in plasma and through the blood-brain barrier. Modulates the biological activity

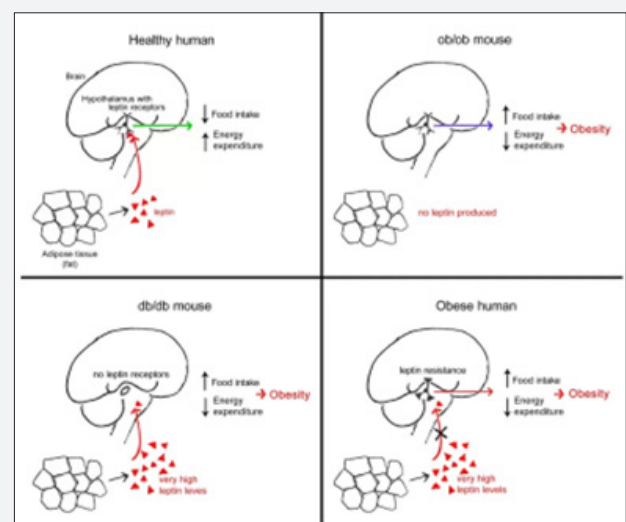


Figure 4: Signs of functional and non-functional leptin [8].

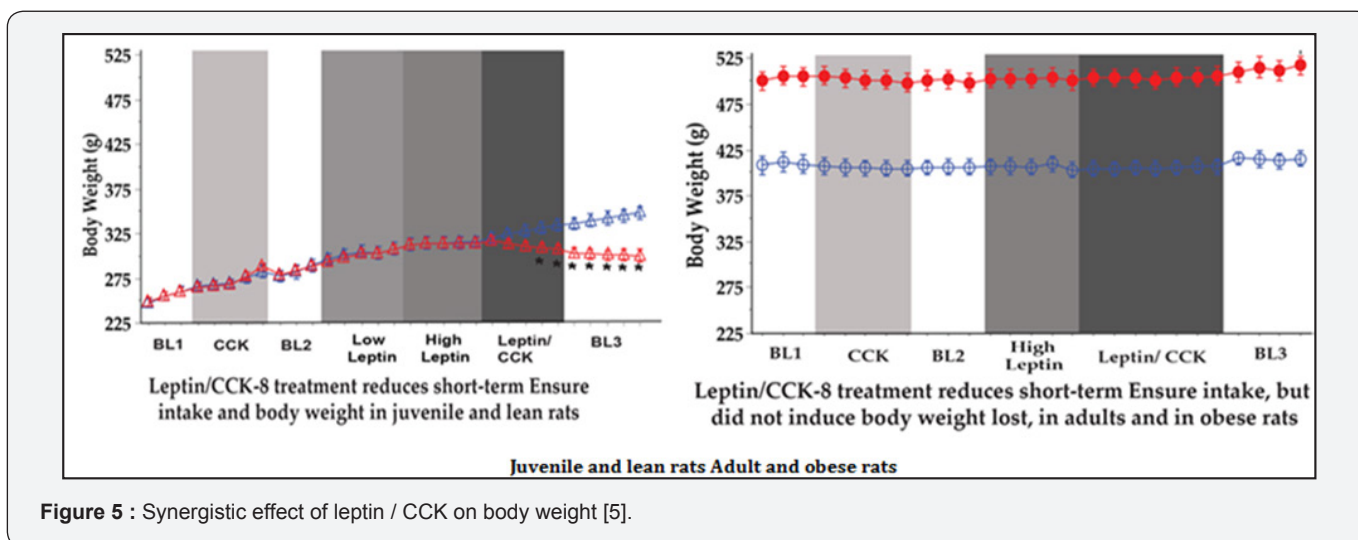
It has been observed that serum concentrations of this hormone correlate positively with adipose tissue mass. Although leptin is a circulating signal that reduces appetite mainly by central action, in general, obese subjects have unusually high

concentrations of circulating leptin and thus, resistance to this hormone develops (Figure 4). Therefore, the application of additional exogenous leptin (Metreleptin) does nothing to help these patients; instead, what we should do is make them more sensitive to leptin. It is a problem that is not easy to solve, and researchers have not been very successful so far. Therefore the research question would be: So the research question that has been sought answer is: What treatment will be useful to sensitize dysfunctional leptin and thus combat obesity?

Results and Discussion

Pharmacological treatment

We Recent demonstrated a pharmacological combination between leptin and cholecystokinin-8 (CCK-8), a hormone that acts as a signal of satiety in the short term. The study was done in a model of diet-induced obesity (OID) and the main conclusion is that the synergistic effect between leptin and CCK depends on the age of the animal but not on the diet they consume (Figure 5) [5].



Implementation of a leptin-sensitive diet

If you have a large amount of body fat, especially in the abdominal area, then it is almost certainly a leptin-resistant. Therefore, a key to reversing resistance to leptin is the induction of a pro-leptin diet. There are several things that should be done:



- A. Avoid processed foods: Highly processed foods endanger the integrity of the intestine and lead to intestinal inflammation Ghanim et al.
- B. Eat soluble fiber: Soluble fiber helps improve intestinal health and protects against obesity Salas-Salvado et al.

C. Lower your triglyceride levels: Having high triglycerides in the blood prevents the transport of leptin from the blood to the brain Banks WA. The best way to reduce triglycerides is to reduce the intake of carbohydrates Samaha FF.

D. Eat protein: Eating lots of protein causes automatic weight loss. There are many reasons for this; one of them is the improvement in the sensitivity to leptin Weigle et al. See Figure 6.

Other considerations

- A. Graphics (Figure 1-7)
- B. Tables (Table1 & 2)

Discussion

To reverse the resistance to the production of endogenous leptin and this hormone can pass to the blood and then to the hypothalamus where it generates an anorexigenic effect or induction of satiety in the obese subjects, strategies that mitigate the OID, induced by the consumption of foods rich in fats and carbohydrates, as well as avoiding the consumption of foods rich in fructose. This strategy is based on using foods that induce an increase in metabolism through thermogenesis or increased energy expenditure, which is known as an anorexigenic effect in the hypothalamus (Figure 6) [9]. In addition to the implementation of a pro-leptin diet, the following strategies will serve as a coadjuvant in said non-pharmacological treatment:

a. Exercise: Physical activity can help reverse leptin resistance [11] (Figure 7).

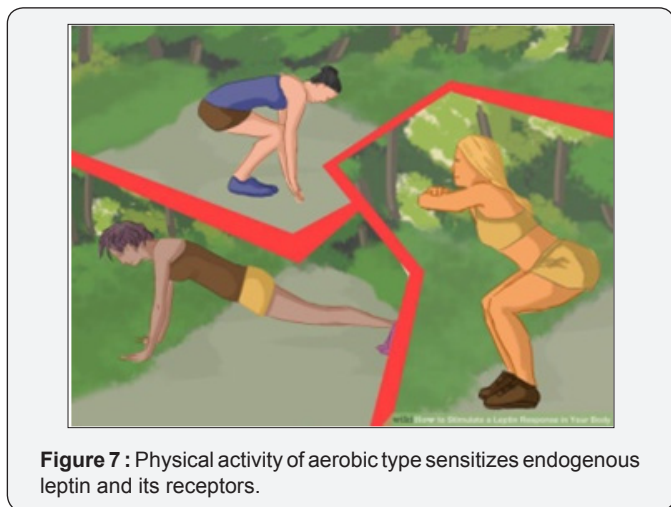


Figure 7 : Physical activity of aerobic type sensitizes endogenous leptin and its receptors.

b. Sleep: Lack of sleep has been implicated in problems with leptin [12].

On the other hand, we recently synthesized and characterized coordination compounds derived from a precursor to serotonin called L-5-Hydroxytryptophan (L-5-HTP). Like leptin, the anorectic serotonergic drugs activate the hypothalamic neurons of the arcuate nucleus (ARC) that express the pro-opiomelanocortin peptide (POMC), so inducing the production of endogenous serotonin would induce to increase the bioavailability of endogenous leptin and thus reversing its endogenous resistance in adipose tissue in obese subjects [13]. As is the case with the Belviq, which recently reported the role of leptin in this serotonergic drug [14].

Conclusion

There are currently four antiobesity drugs approved for the treatment of long-term obesity in the United States, while in Colombia they have not been approved for use. On the other hand the new pharmacological alternatives for the treatment of this disease that derives from the bowel-brain axis approach and more specifically from the in-depth study of the hormone leptin that induces adipostatic signals that regulate body weight and increases the caloric expenditure in the arcuate nucleus of the lateral hypothalamus. A research project is currently being carried out at the UMB called: Regulation of Leptin in the school population exposed to childhood obesity in Colombia-District Colleges of Bogotá. That seeks to carry out this study in a period of two to three years in obese children of public school schools in Bogota to precisely determine the effect that the implementation of a diet that stimulates the production of leptin before and after the entry into force of the unique student day, according to the law 1753 of 2015 whose report appears on the page of the Colombian National Ministry of Education.

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