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Minireview

# Leptin, 20 years of searching for glucose homeostasis

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ABSTRACT

Leptin was discovered in 1994 (20 years ago). In addition to having well-characterized effects on the regulation of energy homeostasis, leptin clearly also plays a major role in metabolic homeostasis. In fact, leptin plays an important role in the regulation of glucose homeostasis independent of food intake and body weight. The mechanism underlying the modulation of glucose metabolism by leptin is not completely understood, although evidence indicates that the effect occurs at both the central and peripheral levels. In this review, we will focus on the role of leptin in glucose homeostasis at the central level and its role in insulin secretion and in counteracting hormones, such as glucagon, growth hormone, cortisol and catecholamines.



**Contents**



## 1. Introduction

Leptin is a peptide hormone containing 167 amino acids that is principally produced in the adipose tissue but is also found in the placenta, mammary gland, ovary, skeletal muscle, stomach, pituitary gland, and others [1]. Leptin marks the state of energy storage and body weight, and circulating leptin levels are proportional to body fat content [2].

The role of leptin in glucose metabolism was demonstrated in 1995 using ob/ob (leptin deficient) mice that were extremely obese and diabetic [3]. It was shown that treatment with leptin in low doses, which did not affect the body weight or food intake, normalized severe hyperglycemia [4]. This result demonstrated that leptin exerts direct effects on glucose levels independently of body weight and food intake. This finding raised a question about the mechanism behind this effect. Data gleaned over the last few years have shown that this effect is mediated through a vast array of mechanisms. Thus, in vitro studies

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have shown that leptin inhibits glucose absorption via PKC (protein kinase C), p38MAPK (P38 mitogen-activated protein kinase), PI3K (phosphatidylinositide 3-kinase) and MEK/ERK [5]. In vivo studies performed in mice with a genetic deletion of the leptin receptor in intestinal epithelial cells showed a decrease in the activities of GLUT5-mediated fructose transport and PepT1 (peptide transporter 1)-mediated peptide transport, whereas the $Na^+$/glucose cotransporter SGLT-1 (sodium-glucose linked transporter-1) and GLUT2 were unaffected [6]. Taken together, these data indicate a regulatory role of leptin in glucose absorption. Nevertheless, it remains to be determined to which point this effect could be under central control from the autonomic nervous system. In addition clear evidences show that leptin influences glucose homeostasis: by regulating insulin-sensitive peripheral tissues, by pancreatic endocrine function or by directly affecting the central nervous system (Fig. 1).

## 2. Leptin and glucose homeostasis

Leptin was originally recognized for its role as a satiety factor in the regulation of energy homeostasis; however, leptin has been shown to have important effects in the regulation of glucose homeostasis. This evidence resulted from studies of ob/ob mice (genetic leptin-deficient mice) and *db*/*db* mice (leptin receptor-deficient mice), which both had a phenotype of hyperglycemia, hyperinsulinemia and insulin resistance (similar to human type 2 diabetes) [3,7]. First, it was thought that the effect of glucose alterations is secondary to obesity and hyperphagy, but some evidence suggests that leptin regulates glucose metabolism independently of this effect on energy balance. Experiments using ob/ob mice and a control pair-feeding group supported this independence by showing a marked improvement in hyperglycemia and hyperinsulinemia independent of food intake [7,8]. Consistent with other experiments, the Kieffer group demonstrated that the leptin action in glucose homeostasis precedes changes in body weight and obesity. Following the disruption of endogenous leptin tone with a leptin antagonist in wild-type mice and during fasting, the mice exhibited glucose-stimulated hyperinsulinemia and insulin resistance within 3 days without changes in body weight [9].

Conversely, data from humans with a disease similar to that of ob/ob mice revealed the importance of leptin in glucose homeostasis; these humans had congenital leptin deficiency, due to mutations in the leptin gene, hyperinsulinemia and/or diabetes mellitus, which it is a common feature of this deficiency. Following replacement therapy with leptin, these patients exhibited a marked increase in insulin sensitivity with a decrease in circulating insulin levels and hepatic insulin extraction. On the contrary, patients with mutations of the leptin receptor exhibited normal glucose levels both at fasting or following an oral glucose load in most instances despite the extreme obesity of these patients [10].

More interesting data resulted from humans with severe insulin resistance and diabetes due to "lipodystrophy" (characterized by reduced leptin levels due to disorders in adipose tissue development). These patients develop lipodystrophy in the presence of several mutations that impair adipogenesis and limit the capacity to store triglycerides. In humans, the two most common genetic lipodystrophies are CGL (congenital generalized lipodystrophy) and FLP (familial partial lipodystrophy). In CGL, there is an absence of body fat from birth; meanwhile, in FLP, fat loss is progressive and variable during childhood and puberty [11]. One of the consequences of these disorders is that the patients lose the lipid storage capacity of adipocytes, leading to the accumulation of nutrients in different organs, such as the liver, muscle and other tissues. This accumulation translates to a state of insulin resistance and diabetes [10–14]. The relevance of leptin in the development of

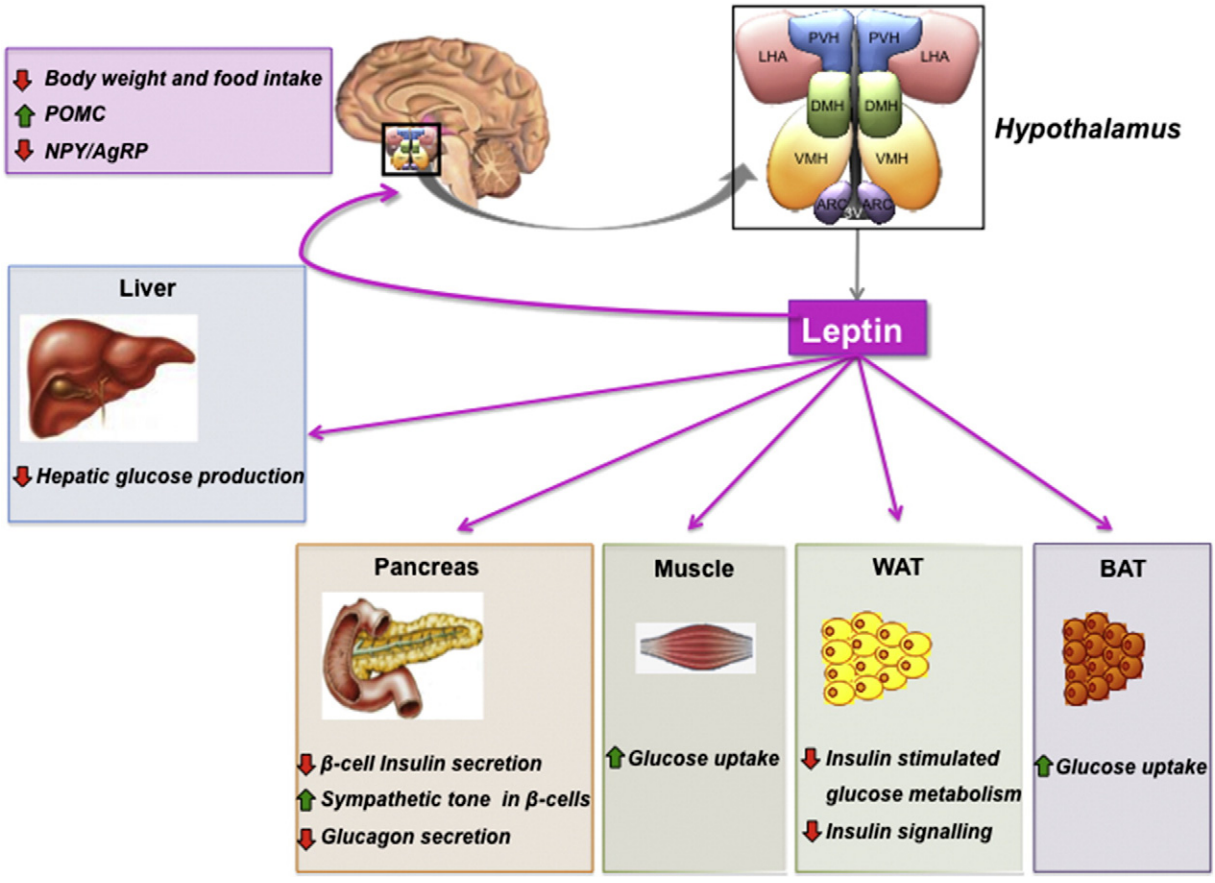


**Fig. 1.** Effects of leptin on the glucose homeostasis in different organs. Main actions performed by central leptin in different tissues.