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Minireview

20 years of leptin: Role of leptin in cardiomyocyte physiology and physiopathology

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ABSTRACT

Since the discovery of leptin in 1994 by Zhang et al., there have been a number of reports showing its implication in the development of a wide range of cardiovascular diseases. However, there exists some controversy about how leptin can induce or preserve cardiovascular function, as different authors have found contradictory results about leptin beneficial or detrimental effects in leptin deficient/resistant murine models and in wild type tissue and cardiomyocytes. Here, we will focus on the main discoveries about the leptin functions at cardiac level within the last two decades, focusing on its role in cardiac metabolism, remodeling and contractile function.

Contents

1. Introduction

For many years the human being has adapted its body physiology to the lack of nourishment in order to survive [10]. Nowadays, overeating and sedentary lifestyle are increasing the prevalence of obesity worldwide reaching pandemic proportions and becoming an important public health problem [10]. As the prevalence of obesity increases so does the burden of its associated co-morbidities (Fig. 1), which includes type II diabetes, metabolic syndrome, or cardiovascular diseases such as myocardial infarction, angina pectoris, congestive heart failure, stroke, hypertension, and atrial fibrillation [76].

Many scientists have studied the mechanisms of the energy balance at cellular, tissue, organ and whole body levels in order to achieve a better knowledge about how to treat or prevent the incidence of obesity and its co-morbidities. One of the most important and widely studied players in the control of energy balance is the hormone leptin [30,71], discovered 20 years ago by Zang et al. [111]. Leptin is a 16 kDa protein mostly secreted from

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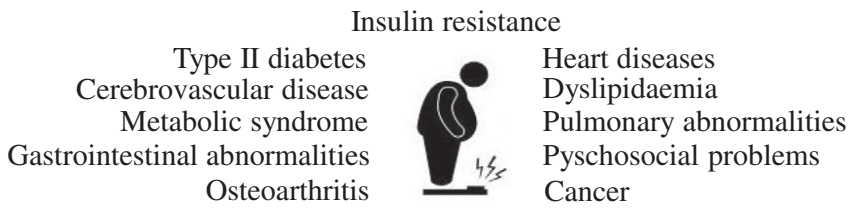

Fig. 1. Morbidities related to obesity [89].

adipose tissue which has a critical role regulating body weight and energy homeostasis [73,87]. Leptin mediates its effects by binding to specific leptin receptors (LepRs) expressed in the brain and in peripheral tissues [45]. In the hypothalamus leptin acts as an anorexigenic hormone regulating the melanocortine/neuropeptide Y system to reduce food intake, increase energy expenditure, and decrease body weight [7,71]. However, circulating leptin levels are increased in obese humans [42], suggesting that obesity may be either a result or a cause of leptin resistance [19,29,83]. In fact, local effects of leptin can be governed by deregulation of its receptor expression or downstream signaling components, in particular proteins known to suppress cytokine, and leptin signaling [38].

In an effort to better understand the pathophysiology of human obesity and its co-morbidities, several rodent models of obesity have been developed and implemented including high fat diet feeding and spontaneous mutants of leptin or its receptor such as *ob*/*ob* (mutant for leptin gene, leptin deficient) and *db*/*db* (loss-of function mutation in the leptin receptor, leptin resistant) mice or Zucker *fa*/*fa* rats (loss-of function mutation in the leptin receptor, leptin resistant) [57]. These animals have the common feature of compromised cardiac contractile function [85] and in humans circulating leptin levels are elevated in vascular and coronary heart diseases [84], favoring a contemporary perception of hyperleptinemia as an independent risk factor for the development of cardiovascular diseases.

Although the adipose tissue is the main source of leptin, it is also produced by other peripheral tissues, such as the liver, the skeletal muscle or the kidneys [53,100,102]. Within the heart, leptin and its receptor are abundantly expressed in cardiomyocytes [62,75] where it can regulate the baseline physiology of the heart, including cardiomyocyte contractility, hypertrophy, apoptosis, and metabolism [63]. In this review we will summarize the main discoveries about the leptin functions at cardiac level within the last two decades, focusing on its actions on cardiac tissue and cultured cardiomyocytes.

2. Leptin signaling and cardiomyocyte metabolism

2.1. Leptin and glucose and fatty acid metabolism

The constant pumping activity of the heart requires a permanent supply of energy [55]. It is widely accepted that fatty acids are the predominant energy substrates used in the normal adult myocardium, providing ~70% of adenosine triphosphate (ATP) necessary for the heart to maintain contractile function [55]. However, the cardiac metabolic network is highly flexible in using other substrates when they become abundantly available [47]. Thus, depending on the energetic context, the heart is capable of using different substrates (including carbohydrates, lipids, amino acids, and ketone bodies) for ATP production in the mitochondria (Fig. 2.A), a concept known as metabolic flexibility of the heart [47]. In a normal heart, mitochondria are largely fuelled by acyl-coenzyme A (CoA) and pyruvate, which are the primary metabolites of fatty acids and carbohydrates, respectively [47]. Energy production from fatty acids requires oxygen consumption, whereas carbohydrate-derived ATP is produced by both glycolysis (oxygen independent) and glucose oxidation [69]. So that, although glucose represents a small component of total myocardial energy source, it is the most efficient means of energy production, particularly in conditions of ischemia/hypoxia [69]. During exercise lactate becomes the predominant energy substrate [33], and prolonged fasting or a ketogenic diet increases circulating levels of ketone bodies resulting in an enhanced use by the heart [104]. The ability of the myocardium to switch from one energy substrate to another (or to use multiple substrates simultaneously) is lost in obesity and diabetes, a state of metabolic inflexibility in which glucose transport, glycolysis, and glucose oxidation in cardiomyocytes decrease, while fatty acid uptake and oxidation increase [20,35,47].

Despite the fact that there exist a number of studies regarding leptin function in modulating systemic and skeletal muscle metabolism, little is known about its implication in regulating cardiomyocyte metabolism. Some groups have shown that *ob*/*ob* and *db*/*db* mice, and *fa*/*fa* rats show a metabolic profile in which carbohydrate uptake and utilization are reduced both in cardiac tissue [6,17,27,32,61,92,99] and in cultured cardiomyocyte [27,61] by diminishing glucose transporters GLUT4 translocation to plasma membrane or its protein and mRNA levels, and by reducing pyruvate dehydrogenase and oxoglutarate dehydrogenase activity. In contrast, fatty acid uptake rates are increased in these leptin deficient or resistant animal models through a mechanism that involves the increase in the expression and membrane localization of the fatty acid translocase (FAT)/CD36 and the stimulation of peroxisome proliferator-activated receptor α (PPARα) signaling (Fig. 2.B) [1,12–14,61,69]. While in leptin deficient/resistant mice the increase in fatty acid uptake is accompanied by an increase in fatty acid oxidation, in *fa*/*fa* rats the increase on fatty acid uptake is uncoupled with the oxidation and yields to lipotoxicity [113]. These findings suggest a role for the disruption of leptin signaling in the development of the metabolic inflexibility observed in cardiac metabolism under pathological conditions, favoring fatty acid utilization and diminishing cardiac efficiency.

In vitro experiments with cardiac cells have shown that short-term (1 h) leptin treatment has no effect on glucose uptake and oxidation in HL-1 cardiomyocytes and in perfused rat hearts, while fatty acid uptake and oxidation are increased [1,69]. Long term leptin treatment (24 h) also has no effect on glucose uptake and oxidation in HL-1 cardiomyocytes and increases fatty acid uptake, however long term treatment induces a decrease in fatty acid oxidation leading to intracellular lipid accumulation [69], confirming the results obtained by Zhou et al. in *fa*/*fa* rats [113].

2.2. Leptin and cardiomyocyte autophagy

Autophagy is an evolutionarily conserved lysosome-mediated catabolic pathway that maintains cellular homeostasis through the renewal/recycling of cytoplasmic materials and organelles (such as