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Leptin in Health and Disease: Facts and Expectations at its Twentieth Anniversary

1. Introduction

This year marks the twentieth anniversary of the discovery of leptin [1], the prototypical adipocyte-secreted hormone or adipokine, which was named after the Greek word "*leptos*" meaning thin [2]. The first notion for a circulating factor affecting body fat had been published long ago (1959) on the basis of a parabiosis study [3], the findings of which were replicated and further expanded fifteen years later [4], i.e. after the characterization of *ob/ob* and *db/db* mice.

Leptin's discovery radically changed our understanding of adipose tissue. Twenty years ago, adipose tissue was regarded as an inert energy-storage organ and even classic textbooks of physiology presented its existence within a couple of paragraphs. Nowadays, adipose tissue is considered to be a major, and in most cases, the largest endocrine organ, secreting multiple adipokines with multi-potent effects on health and disease. Consequently, adipose tissue is the focus of intense research efforts: more than 700 different proteins have been described to date as being potentially secreted by adipose tissue. These proteins need further study and validation regarding their expression, secretion and function, before full characterization as putative novel adipokines [5]. Furthermore, publications are accumulating on the endocrine function of adipose tissue, and the new editions of physiology textbooks need to devote many pages to adipose tissue in order to present adipokines and their functions.

This issue of "*Metabolism, Clinical and Experimental*" is published to celebrate the twentieth anniversary of leptin, or in other words, the maturity of the concept of adipose tissue as an endocrine organ. We are delighted that many distinguished experts in the field have accepted our invitations to contribute important pieces of scientific work to this issue, adding their personal and invaluable insights.

In this issue, the structure, production and signaling of leptin and its physiologic role are initially presented. Subsequently, the roles of leptin in obesity and other metabolic and non-metabolic diseases are detailed. Finally, therapeutic perspectives, current and emerging, are summarized. The review articles to be published in this issue emphasize the importance of leptin as a key adipokine associated with several physiologic processes, but also its potential implications in the pathogenesis of several and diverse diseases. Given that many pieces of the pathogenetic puzzle linking leptin with pathophysiology and morbidity are missing, this issue desires to accurately present the current state of research in the field, but also to trigger future in-depth research, which may lead to a better understanding of leptin's physiology, to establish its clinical role and to unfold its therapeutic potential in the years to come.

Let us start by presenting some pieces of the knowledge and expectations that could possibly set the stage as we celebrate the twentieth anniversary of the discovery of leptin.

2. Current Knowledge of Leptin

Leptin is secreted mainly by white adipocyte tissue, and it circulates at levels positively correlated with fat mass [6], thus reflecting primarily the amount of energy stored in adipose tissue [2]. Leptin levels also change with acute changes in energy intake and thus, secondarily reflect acute energy availability [7]. Leptin has endogenous circadian rhythm, which peaks around the time of awakening [8]. The identification of the leptin receptor (LepR) came soon after the discovery of leptin [9], expanding our knowledge on its intracellular signaling. Indeed, we learned that leptin acts on multiple central (brain) and peripheral tissues. The arcuate nucleus of the hypothalamus is regarded as the primary central site of leptin's activity, where leptin activates proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons, while it inhibits neuropeptide Y (NPY)/agouti-related peptide (AGRP) neurons [10]. Leptin signaling, under normal circumstances, alters the function of the brain and other tissues to implement appropriate changes in food intake and energy expenditure [11]. This system is especially sensitive to energy deprivation [12]. On the other end of the spectrum, this system is non-responsive in garden-variety obesity, due to leptin tolerance/resistance [13]. Apart from this classic role of leptin in obesity and obesity-related diseases, including type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD) and

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cardiovascular disease (CVD), leptin seems to mediate changes in adiposity or food intake and adaptive responses in other systems, including, but not restricted to, autoimmune, gastrointestinal, musculoskeletal and reproductive systems [11].

The importance of leptin is derived from many experimental and clinical studies. Mice homozygous for mutations in the leptin (*ob*) gene, which prevent leptin production or lead to the secretion of an inactive leptin molecule (*ob/ob*), exhibit hyperphagia, insulin resistance, early-onset obesity, diabetes, fatty liver and several neuroendocrine abnormalities, all of which can be improved by exogenous leptin administration [10,11]. A similar phenotype is exhibited in *db/db* mice and *fa/fa* (Zucker) rats, which have dysfunctional LepR due to homozygous mutations; however, as expected, leptin treatment does not improve the observed metabolic or non-metabolic abnormalities in *fa/fa* rats [10,11].

The discovery of leptin has also prompted a better characterization and deeper pathophysiologic understanding of lipodystrophy, a clinically heterogeneous and difficult-to-treat disease, characterized by the complete or partial loss of adipose tissue, and resulting in numerous metabolic and neuroendocrine derangements [14,15]. The abnormal adipose tissue metabolism, a hallmark of lipodystrophy, leads to either loss of subcutaneous adipose tissue (lipoatrophy) or extra-adipose (i.e., hepatic, pancreatic, etc.) accumulation of fat (lipohypertrophy). Lipodystrophy is associated with varying degrees of insulin resistance, dyslipidemia, hyperglycemia or T2DM, and NAFLD, and can be congenital or acquired. Congenital forms of lipodystrophy are rarely seen, whereas the most common form of acquired lipodystrophy is that associated with human immunodeficiency virus (HIV) infection and highly active antiretroviral therapy (HAART) [16]. Patients with congenital or acquired lipodystrophy have complete or relative leptin deficiency, which implies that leptin replacement could be a rational therapeutic option [16,17]. Recently, the US Food and Drug Administration (FDA) and the Japanese Pharmaceuticals and Medical Devices Agency have approved recombinant human methionyl leptin (metreleptin) replacement therapy for the treatment of congenital generalized or acquired generalized (non-HIV-associated) lipodystrophy, on the basis of uncontrolled, non-randomized, open-label studies [18–20]. For safety reasons, metreleptin is currently available only through the Myalept Risk Evaluation and Mitigation Strategy (REMS) Program, which requires monitored enrollment of patients and the training of prescribers and pharmacists.

The discovery of leptin had initially born expectations for the treatment of common obesity [11], but clinical trials have demonstrated no or minimal effects of leptin on obesity [21,22]. This fact is mainly attributed to leptin tolerance/resistance and the generation of anti-leptin antibodies. Most patients with obesity and associated co-morbidities, including T2DM and NAFLD, have hyperleptinemia, presumably in response to leptin tolerance/resistance, and thus, the normal actions of leptin are impaired [21]. Therefore, despite initial expectations, recombinant leptin administration in obese and hyperleptinemic individuals has not been associated with significant weight loss or significant reductions in metabolic complications [11,23].

3. From Current Knowledge to Future Directions

Although the discovery of leptin has opened new windows into human pathophysiology and therapeutics, many other pieces of the energy homeostasis and endocrine function of adipose tissue puzzles remain unknown. First, although a receptor-mediated transportation of leptin has been proposed, it is unclear how leptin produced by adipose tissue crosses the blood–brain barrier (BBB) to affect central nervous system functions. LepR on astrocytes have been proposed to actively regulate leptin transport across the BBB, a finding consistent with evidence that central regulatory changes of LepR during obesity and inflammation often occur in astrocytes [24]. Leptin transport through the BBB has been shown to be saturable [25] and decreased in obese rats, thereby potentially enhancing leptin tolerance/resistance [26], although other studies have reported similar transport capacities in lean and diet-induced obese rats [27]. Lipopolysaccharide, which is known to increase circulating leptin levels and to affect the passage of other regulatory proteins across the BBB, also decreases leptin transport through the BBB in a dose-dependent manner [28]. On the other hand, chronic alcohol ingestion, which is known to decrease appetite, has been shown to increase leptin permeation across the BBB [29]. Interestingly, a cholecystokinin-1 receptor agonist was also shown to increase leptin permeability through the BBB [30]. The above evidence highlights not only the complexity of leptin transport through the BBB, but also the need for a deeper knowledge and understanding, which may lead to therapeutic techniques and pharmaceutics which could diminish leptin tolerance/resistance, if indeed limited leptin transportation to the brain may partially underlie leptin tolerance or resistance.

Leptin is mainly produced by white adipose tissue, but it may also be expressed in tissues other than the adipose tissue, including the brain [31], bone [32], macrophages [33], thyroid [34], breast [35], placenta [36], and even the dental pulp [37]. Under normal conditions, the extra-adipose leptin production is minimal. However, this production increases in certain pathological processes, including inflammation and malignant transformation. For instance, low birth weight and premature delivery have also been linked to lower leptin levels in newborns [38]. More studies are needed to elucidate the role of leptin in certain diseases, including distinct cancers, atherosclerosis, osteoarthritis, pregnancy complications and even periodontitis, and subsequently to determine whether leptin has any therapeutic potential for these conditions.

Another important field for further research is the proinflammatory actions of leptin and the cross-talk between leptin and other adipokines, myokines and extra-adipose tissue hormones, including insulin and thyroid hormones. Leptin administration restores Th1/Th2 balance and is part of feedback loops along with several cytokines. For example, TNF-α activates leptin expression [39] and upregulates the LepR [40], whereas leptin increases tumor necrosis factor (TNF)-α expression [41]. TNF-α also suppresses adiponectin transcription, secretion and action [42,43]. In turn, there is evidence that adiponectin inhibits leptin [44,45] and TNF-α [42,43] signaling. Overall, it seems that there is a positive loop between leptin and TNF-α, which may be negatively regulated by adiponectin.