All Sciences Proceedings

3rd International Conference on Innovative Academic Studies

September 26-28, 2023 : Konya, Turkey

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Leptin Effects on Brain Function and the Immune System

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Abstract – The leptin hormone not only examines its effects on energy balance and weight control but also delves into its profound impacts on brain functions and the immune system. The receptors and neuronal pathways of leptin in the brain, along with their effects on mental functions and cognitive abilities, will also be addressed. Furthermore, the regulatory role of leptin in the immune system, its contributions to inflammatory processes, immune responses, and disease processes will be discussed in detail. Leptin hormone is significant not only in terms of body composition and energy regulation but also in its comprehensive effects on brain functions and the immune system.

Leptin, primarily known as a protein hormone produced by fat cells, has long been associated with regulating nutrition and body fat storage. However, recent research indicates that the effects of leptin are not limited to the traditionally focused hypothalamus region. Leptin serves as a versatile hormone that influences different areas and has various effects on intelligence, motivation, learning, memory, neuroprotection, and more.

Keywords – Leptin Hormone, Energy Balance, Brain Functions, Immune System, Cognitive Abilities

I. INTRODUCTION

While leptin hormone is often associated with body composition and energy balance, recent research indicates that its effects extend to a broader spectrum. This hormone not only impacts energy regulation and weight control but also has profound effects on brain functions and the immune system. In this article, we will examine the effects of leptin hormone's receptors and neuronal pathways in the brain on mental functions and immune responses, allowing us to better understand the significance of this versatile hormone.

II. LEPTIN HORMONE

Leptin, a hormone weighing 16 kDa, is encoded by the obesity gene (OB) located on chromosome 7 in humans. This gene transcribes a peptide consisting of 167 amino acids, including a 21-amino acid signal sequence at the amino-terminus [1], [2]. After removing the N-terminal signal peptide, the mature form of the hormone consists of 146 amino acids [3], [4]. Leptin is primarily produced in adipose tissue, although not exclusively, and its circulating levels are directly correlated with the percentage of body fat [5]. Once released into the bloodstream, leptin crosses the blood-brain barrier and binds to its receptor (ObR) in hypothalamic centers [6]. This binding regulates the body's energy balance and helps maintain stable energy stores [7], [8]. Leptin's interaction with ObR activates various intracellular signaling pathways that control different cellular functions. Leptin signaling also takes place in sensory circumventricular organs (CVOs), such as the subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT), which lack the typical blood-brain barrier. These organs have fenestrated capillaries that allow circulating leptin direct access to neurons in this central nervous system region, enabling it to regulate energy balance and control cardiovascular and metabolic functions [9], [10], [11], [12], [13].

Leptin is a hormone derived from adipocytes with cytokine-like properties, acting both centrally and peripherally. While it plays a crucial role in energy metabolism, it also serves as a significant regulator of various physiological and pathological processes, including immune system activation and cancer progression [14], [15]. Leptin can also be produced by tissues other than adipocytes, exerting its influence on several physiological processes in peripheral organs through paracrine, endocrine, and autocrine mechanisms [16,17,18,19]. Beyond its adipostatic function, leptin can regulate the differentiation and proliferation of hemopoietic cells and macrophage function [20], promote angiogenesis [21], enhance wound healing [22], and impact immune and inflammatory responses [23], [24].

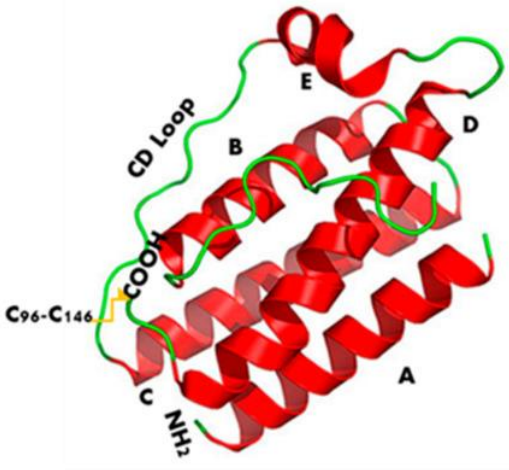

Fig 1 illustrates the three-dimensional structure of leptin, comprising four antiparallel α-helices labeled as A, B, C, and D. These helices are interconnected by two elongated crossover links, AB and CD, and a shorter loop known as BC. Together, they form an up-up-down-down helical bundle. Additionally, within the CD loop, there exists a fifth helix referred to as E [25].

Leptin hormone serves multiple endocrine functions and plays a role in regulating various physiological processes, including immune and inflammatory responses, bone formation, initiation of human puberty, hematopoiesis (the formation of blood cells), angiogenesis (the development of new blood vessels), and wound healing [26], [27], [28], [29].

A. Leptin Hormone Function

Over the past two decades, our comprehension of the likely role of leptin has evolved significantly. Instead of merely being a "hunger hormone" that suppresses appetite, leptin is now recognized as a guardian of body weight. It operates as a feedback mechanism, signaling crucial regulatory centers in the brain to curb food intake and maintain body weight and energy balance. This concept has been substantiated by numerous studies conducted in rodents [30], [31]. Individuals who lack leptin tend to gain weight because their brains lack the signal indicating sufficient body fat, leading them to continue eating. Leptin conveys to the brain that there is an adequate energy reserve stored in the fat cells, enabling normal metabolic processes. To put it differently, when leptin levels reach a specific threshold unique to each person, likely influenced by genetic factors, having leptin levels above that threshold signals to the brain that there is enough energy available for regular metabolic functions, allowing for normal eating habits and exercise routines [32].

Additionally, leptin hormone serves various endocrine functions and plays roles in regulating immune responses, inflammatory processes, bone formation, initiation of human puberty, hematopoiesis (the production of blood cells), angiogenesis (the formation of new blood vessels), and wound healing [33], [34], [35], [36]. Mutations in the leptin gene or its regulatory regions are associated with severe obesity, morbid obesity accompanied by hypogonadism, and the development of type 2 diabetes mellitus [37].

Leptin and the gut peptide cholecystokinin synergistically cooperate to enhance the satiation process. Although this interaction may occur at multiple levels within the nervous system, prior research suggests that leptin can specifically amplify the satiation effect of cholecystokinin by influencing subdiaphragmatic vagal afferent neurons [38].

In essence, leptin shares similarities with insulin in that just as some individuals exhibit resistance to insulin's signals (insulin resistance), necessitating increased insulin production, others are resistant to leptin's signals. Leptin resistance is most pronounced in obese individuals, making them more prone to hunger and less adept at recognizing when they are satiated. This complicates the application of leptin as a remedy for obesity. Leptin resistance implies that regardless of how much leptin is introduced into the system, the body continues to perceive leptin levels as "low." Individuals who lack leptin receptors in the brain, another rare medical

condition, experience obesity akin to those who do not produce leptin.

B. *Effects of Leptin Hormone on Brain Functions and Immune System*

Leptin, primarily released from fat cells, is known to impact various physiological processes, including reproduction, glucose regulation [39], bone formation, and immune function [40], [41], [42]. It exerts its metabolic effects by interacting with receptors present in both the central nervous system and peripheral tissues, such as the lungs, kidneys, liver, heart, pancreas (endocrine part), adrenal glands, uterus, ovaries, testes, hematopoietic cells, skeletal muscles, among others [43]. The primary site of action for leptin receptors is within the hypothalamus, where they play a role in appetite control, reproduction, and growth [44].

Leptin, often described as a signaling factor originating from adipocytes, elicits a multifaceted response upon binding to its receptor. This response encompasses the regulation of body weight, energy expenditure, and significant contributions to reproduction and neuroendocrine signaling. Leptin also influences the functioning of the cardiovascular and urinary systems. Beyond its critical role in maintaining physiological balance, leptin is actively involved in regulating food intake, managing energy balance, controlling the onset of puberty, influencing hypothalamic-pituitary functions, and impacting insulin resistance [43], [45].

Leptin exerts both central and peripheral effects on a wide range of functions, including appetite control, energy expenditure, thermogenesis, cardiovascular function, neuroendocrine regulation, growth hormone modulation, thyroid function, adrenal system regulation, immune system function, and reproductive processes [48], [49], [50]. Additionally, it plays a role in hematopoiesis, sympathetic nervous system activation, gastrointestinal function regulation [51], angiogenesis [52], osteogenesis, carbohydrate and fat storage, and metabolism [53].

Furthermore, leptin is associated with the modulation of immune function. Apart from stimulating the synthesis of white blood cells, leptin enhances the effect of erythropoietin on red blood cells [54]. Similar to bacterial antigens, leptin activates macrophages, enhancing their ability to engulf foreign particles and stimulating the secretion of both proinflammatory and anti-inflammatory cytokines by macrophages [55].

Leptin is recognized for its role in regulating oxidative stress and promoting the process of phagocytosis by binding to its receptors on macrophages and monocytes within the immune system. Additionally, it induces the synthesis of eicosanoids, nitric oxide (NO), cytokines, and surface markers in these immune cells [56]. In the context of the acquired immune response, leptin is reported to enhance the maturation of thymocytes and the proliferation of naive T cells, while also preventing apoptosis in these cells, as well as in memory T cells and B cells [57], [58].

Gender is one of the factors that influence leptin levels. Women tend to have higher leptin levels compared to men, influenced by variables like body mass index, body fat percentage, total fat tissue mass, skin thickness, and age [59]. In women, the greater fat percentage and distinct fat distribution contribute to higher leptin levels, while in men, testosterone plays a role in suppressing leptin levels [45], [60].

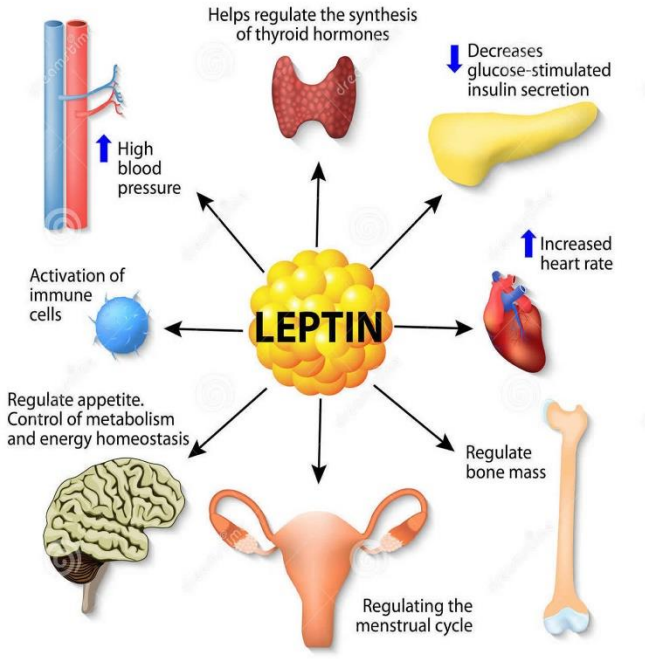

Fig 2 Leptin Function [61]

III. IMMUNE SYSTEM

The immune system functions as a protective mechanism consisting of a wide array of biological components and processes [62]. Its primary objective is to shield the organism from bacteria, viruses, and parasites [63]. This system can be divided into two main components: the innate and adaptive immune systems. The innate immune system serves as the initial line of defense against invading microorganisms that enter the human body. Although it triggers an inflammatory response, it does not provide complete protection [64], [65], [66]. The innate immune system responds to infectious microorganisms by releasing cytokines and chemokines and mobilizing specialized cells like killer cells, dendritic cells, and phagocytes [67]. In cases where the innate immune system falls short in eradicating these pathogens, the adaptive immune system is activated. This system displays exceptional sensitivity and generates a specific response by recognizing distinct pathogens [68]. The primary actors in the adaptive immune system, T and B lymphocytes, collaborate to eliminate the infectious agents [69].

The human body utilizes a range of strategies to protect itself from bacteria, viruses, and foreign agents. These defensive mechanisms include physical barriers, specialized phagocytic cells found in both the bloodstream and tissues, as well as a variety of molecules within the bloodstream. These protective mechanisms can be categorized into two closely linked defense systems: the innate immune system and the adaptive immune system [70].

III-a. Innate Immunity

The first stage of the defense system, known as the non-specific immune system, distinguishes between self and non-self within the organism but does not differentiate between different types of pathogens [71]. Innate resistance consists of two general lines of defense. When microorganisms are exposed to the mucous membranes in our skin's epithelial tissue, respiratory tract, gastrointestinal tract, and urogenital tracts, they encounter the first line of defense [72].

III-b. Acquired Immunity

Acquired immunity develops over an individual's lifetime, distinguishing between the body's own elements and foreign invaders, and generating targeted responses to various pathogens and alien substances. Key players in specific immune defense are a group of white blood cells called lymphocytes. These lymphocytes consist of T lymphocytes, contributing to cellular immunity, and B lymphocytes, which play a role in humoral immunity. Cellular immunity encompasses the production of cytotoxic T cells (TC cells) with the ability to eliminate cells carrying antigens. In contrast, humoral immunity involves the transformation of B cells into plasma cells that produce antigen-specific immunoglobulins [76].

C. Effect of Leptin Hormone on the Immune System

Within the innate immune system, leptin has been observed to modulate oxidative stress and promote the phagocytic process when it binds to its receptors on macrophages and monocytes. Furthermore, leptin triggers the production of eicosanoids, nitric oxide (NO), cytokines, and the expression of surface markers in these cells [77]. Regarding the adaptive immune response, there are reports indicating that leptin enhances the maturation of thymocytes and the proliferation of naive T cells while also preventing apoptosis in these cells, as well as in memory T cells and B cells [78].

D. Effects of Leptin Hormone on Brain Functions

Research indicates that leptin expression levels and signaling pathways may have connections to various neurological conditions, including but not limited to Parkinson's disease, epilepsy, ischemic stroke, migraine, cognitive decline, and dementia [79], [80].

Parkinson's disease, among the most prevalent neurodegenerative disorders, is commonly linked to the reduction of dopaminergic neurons in the substantia nigra [81]. There are suggestions that leptin could play a role in regulating the homeostasis of this nigrostriatal pathway [82].

Leptin has been proposed as a potential candidate for stroke therapy due to its potential neuroprotective effects against neuronal damage resulting from ischemic stroke. It appears to stimulate neurogenesis and angiogenesis in both in vitro and in vivo experimental models [83], [84]. Zhang and colleagues have reported that leptin's neuroprotective impact during cerebral ischemia is associated with the activation of the PI3K/Akt signaling pathway [85].

In the case of individuals suffering from migraines, studies have revealed notably lower

leptin levels, which tend to increase after treatment [86], [87].

While animal model studies are somewhat limited, research conducted in the elderly population suggests that individuals with elevated leptin levels may be at a reduced risk of experiencing cognitive decline and dementia [88], [89].

Furthermore, the hippocampus has been identified as a region potentially mediating leptin's antidepressant-like effects [90]. Garza and colleagues have demonstrated that chronic leptin treatment in rats exposed to unpredictable chronic mild stress (CUMS) can mitigate decreased hippocampal neurogenesis and depressive behaviors resulting from stress [91]. Following the application of CUMS in rat models, depression-like behaviors were induced, and it was observed that serum leptin levels decreased along with hypothalamic leptin receptor mRNA expression [92].

In a study comparing leptin levels between patients diagnosed with borderline personality disorder, who exhibit aggressive behaviors and suicide attempts, and a healthy control group, it was revealed that leptin levels were significantly lower in the patient group [93], [94].

IV. Results

To sum up, it is evident that leptin, recognized for its involvement in a wide range of physiological and pathophysiological mechanisms, should be recognized as a pivotal hormone in the management and prognosis of diverse medical conditions, encompassing neurological and psychiatric disorders.

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