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REVIEW

Exploring the interplay of leptin and aging: insights into the role of gut microbiota

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Abstract

Aging, a multifaceted process influenced by genetics, environment, and lifestyle, involves cellular, metabolic, and immune changes. Leptin, a key regulator of appetite and metabolism, contributes to cellular integrity, impacts telomere maintenance, and interacts with insulin and other hormones, influencing metabolic, immune, and neuroendocrine functions. Its role in age-related diseases, such as diabetes, cardiovascular issues, and neurodegenerative conditions, underscores its diverse impact. Studies suggest potential links between altered leptin levels and increased lifespan. Calorie restriction, known to mitigate aging, involves leptin-triggered activation of central SIRT1. The gut microbiome, mediating environmental cues, undergoes age-related shifts, reciprocally affected by leptin. Probiotics may reduce leptin levels, exhibiting anti-obesogenic effects. Bidirectional communication between leptin and the gut microbiome emphasizes their intertwined relationship. Leptin supplementation and lifestyle modifications impacting leptin signaling emerge as potential strategies for healthy aging, offering avenues for future research and intervention.

Keywords: Leptin, microbiota, longevity

Introduction to aging

Aging is a complex and inevitable biological phenomenon characterized by the gradual deterioration of physiological functions over time. It encompasses a spectrum of processes, ranging from molecular and cellular changes to the decline of organ systems and, eventually, the whole organism. Aging is a multifaceted journey influenced by a combination of genetic, environmental, and lifestyle factors [1].

The aging process unfolds in distinct phases. At the cellular level, DNA damage accumulates, leading to alterations in gene expression and protein synthesis. This cellular aging contributes to the decline in tissue and organ function. As individuals age, they experience changes in metabolism, hormonal balance, and immune system function. The culmination of these processes is manifested in the external signs of aging, such as wrinkles, loss of muscle mass, and decreased cognitive function. Nine potential hallmarks encapsulate shared aspects of aging across diverse organisms, particularly emphasizing mammalian aging; these include genomic instability, telomere attrition, epigenetic changes, proteostasis decline, disturbed nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell depletion, and modified intercellular communication [2].

Factors influencing aging

Genetic factors

Genetics plays a pivotal role in determining the rate and trajectory of aging. A correlation is anticipated between the level of DNA damage or mutations and the rate of aging, suggesting that (i) individuals or species with longer lifespans are expected to exhibit a lower damage rate compared to those with shorter lifespans, and (ii) interventions influencing DNA damage and repair capacity should also impact the rate of aging and longevity, and vice versa [3]. Inherited traits can influence the efficiency of cellular repair mechanisms, susceptibility to certain diseases, and overall longevity. While genetic predispositions provide a foundation, their interaction with environmental factors shapes the actual aging experience. Furthermore, various disorders associated with premature aging, such as Werner syndrome and Bloom syndrome, result from heightened accumulation of DNA damage. However, the connection of these progeroid syndromes, including others, to typical aging remains uncertain [4].

Environmental factors

External influences significantly impact the aging process. Environmental factors such as diet, exposure to toxins, and lifestyle choices contribute to wear and tear on the body. Chronic stress, inadequate nutrition, and harmful habits can accelerate the aging process. Conversely, a health-promoting environment, including proper nutrition and regular exercise, can mitigate some of the detrimental effects of aging. Daily habits and lifestyle choices play a crucial role in determining the pace at which aging occurs. Factors such as diet, exercise, sleep patterns, and stress management directly influence the body's ability to cope with the challenges of aging. Adopting a healthy lifestyle can enhance resilience, delay the onset of age-related conditions, and improve overall well-being [5].

Setting the stage for the focus on leptin, it becomes apparent that aging is a dynamic interplay between inherent genetic factors and external influences. In the following sections, we will explore how one specific hormonal player, leptin, intricately participates in this aging puzzle, influencing various aspects of cellular and physiological processes.

The role of leptin in aging

Leptin and cellular processes

Leptin, often recognized for its role in regulating appetite and metabolism, extends its influence to cellular aging. Studies suggest that leptin receptors are distributed throughout various tissues, including those crucial for cellular maintenance. In cell lines and cell culture studies, leptin appears to modulate cellular processes by promoting cell survival and inhibiting apoptosis [6-8] Moreover, in an experimental study, leptin was topically administered to chemical wounds on mouse back skin using a sustained-release absorbable hydrogel, and the wound repair process was histologically observed with measured ulceration over time. The study investigated leptin's impact on human epidermal keratinocytes' proliferation, differentiation,

and migration. Results revealed Ob-R expression in both human and mouse skin epidermal cells, and topical leptin significantly accelerated wound healing. Histological analysis indicated increased blood vessels in the dermal connective tissues of the leptin-treated group, while leptin enhanced the proliferation, differentiation/function, and migration of human epidermal keratinocytes. In conclusion, topically administered leptin demonstrated efficacy in promoting skin wound healing by accelerating key cellular processes and enhancing angiogenesis, suggesting its potential as a treatment for skin wound healing [9]. Leptin may contribute to the repair of damaged DNA, thus participating in the preservation of cellular integrity implying a plausible role in aging. The intricate interaction between leptin and cellular aging involves the modulation of key pathways, including those related to oxidative stress and inflammation [10]. In a study by Kaeidi *et al.*, cell viability of Pheochromocytoma (PC12) cells was evaluated using the MTT test, while cellular reactive oxygen species (ROS) generation was assessed through DCFH-DA analysis. In high-glucose-treated PC12 cells, with and without leptin cotreatment, levels of malondialdehyde (MDA) and glutathione (GSH) were measured. Western blotting was conducted to analyse apoptosis markers, including Cleaved caspase-3 and the Bax/Bcl2 ratio. Elevated glucose levels (100 mmol/L) led to increased intracellular ROS and MDA levels, along with apoptosis in PC12 cells after 24 hours. Leptin administration (12 and 24 nmol/L) mitigated high-glucose-induced cell toxicity, caspase-3 activation, and the Bax/Bcl-2 ratio. Additionally, cotreatment with leptin (12 and 24 nmol/L) significantly reduced oxidative damage, as evidenced by decreased MDA and ROS levels and increased GSH content in PC12 cells under high-glucose conditions. These findings highlight the protective effects of leptin against hyperglycemia-induced neural damage, potentially attributed to the attenuation of oxidative stress and neural apoptosis [11]. In an investigation involving the assessment of serum leptin levels in elderly individuals with diabetic ketoacidosis (DKA), notable differences were observed compared to a control group. Prior to treatment, elderly DKA patients exhibited significantly lower plasma superoxide dismutase (SOD) activity, total antioxidant capacity (TAC), and serum leptin levels in comparison to the control group ($P < 0.05$). Conversely, levels of plasma Malondialdehyde (MDA) and 8-Iso-Prostaglandin F2α (8-iso-PGF2α) were notably higher in elderly patients with DKA before treatment ($P < 0.05$). Following treatment, there was a marked elevation in plasma SOD activity, TAC, and serum leptin levels in elderly DKA patients, while their plasma MDA and 8-iso-PGF2α levels demonstrated a significant reduction ($P < 0.05$). These findings underscore the impact of treatment on oxidative stress markers and leptin levels in elderly individuals with DKA, providing insights into potential therapeutic avenues [12]. By mitigating oxidative damage and reducing inflammatory responses, leptin potentially acts as a guardian against cellular degeneration, offering a unique perspective on its anti-aging properties.

Impact on telomeres

Telomeres, the protective caps at the end of chromosomes, play a vital role in cellular aging. Preserving the integrity of the genome across generations is significantly influenced by the stability of telomeres. The multiple tandem repeats in telomeric regions have the potential for high recombinogenicity. Maintaining telomere stability necessitates processes such as heterochromatin formation, transcriptional repression, suppression of homologous recombination, and protection of chromosome ends. Defects, whether genetic or epigenetic, impacting telomere homeostasis, may lead to length-independent internal damage within telomeric DNA [13].

Research suggests that leptin may have an impact on telomere length maintenance. As telomeres shorten with each cell division, they contribute to cellular aging and consequently, the aging of the entire organism. In a study involving 2,721 elderly participants, the leukocyte telomere length (LTL) and phenotypic markers of obesity were assessed. The baseline analysis revealed a significant association between LTL and various obesity features, such as relative body fat and subcutaneous fat content, but not with BMI or visceral adiposity. After a seven-year follow-up, LTL was linked to a positive change in BMI and percentage of body fat, suggesting that telomere length may predict changes in body composition. Notably, shorter LTL in this study was associated with lower leptin levels [14]. While this aligns with the role of leptin as an appetite-suppressant hormone and higher leptin levels being indicative of a healthier status, it's essential to consider that leptin levels increase with body weight gain, potentially losing their protective function through mechanisms collectively termed as leptin resistance. This was observed in a study which demonstrated a significant negative association between relative telomere length and leptin levels [15]. Leptin's potential role in preserving telomere length adds another layer to its significance in the intricate tapestry of cellular aging.

Interaction with insulin

Leptin's interaction with insulin forms a crucial aspect of its involvement in aging. These hormones share a delicate relationship in regulating metabolism. Leptin, produced by adipose tissue, signals the brain about the body's energy status, influencing appetite and energy expenditure. In tandem, insulin regulates glucose metabolism. Dysregulation in either of these systems can contribute to age-related metabolic disorders [16, 17]. Blüher *et al.* employed the Cre-loxP system to create mice with a specific disruption of the insulin receptor gene in adipose tissue, known as FIRKO mice. In this model, an extension in longevity was observed. FIRKO mice display characteristics such as reduced fat mass, a disturbed plasma leptin-body weight relationship, and resilience against age-related and hypothalamic lesion-induced obesity, as well as obesity-related glucose intolerance, all while maintaining normal food intake. Both male and female FIRKO mice exhibited an increased mean lifespan of approximately 134 days (18%), along with parallel improvements in median and maximum lifespans. The prolonged longevity in FIRKO mice was associated with a shift in the age at which the age-dependent increase in mortality risk becomes evident and a decreased rate of age-related mortality, particularly after 36 months of age. The resistance to obesity in FIRKO mice, despite regular food intake, suggests an elevated metabolic rate rather than a decrease, indicating that the reduction in fat mass may contribute to a decrease in oxidative stress in FIRKO mice [18].

Hormonal balance

Leptin extends its influence beyond insulin to interact with other hormones associated with aging. Growth hormone, cortisol, and sex hormones are among the players in this intricate hormonal orchestra. Analysis of 24-hour leptin, cortisol, and growth hormone (GH) secretions under baseline physiologic conditions indicates a predominant inhibitory influence of the hypothalamic–pituitary–adrenal (HPA) axis on leptin secretion, coupled with a stimulatory effect of leptin on the HPA axis. The association between GH and leptin suggests a positive impact of GH on leptin secretion and a direct negative impact of leptin on GH. The question of whether these observations signify a role for GH and/or cortisol in the physiological regulation of leptin secretion, and conversely, remains to be determined. However, it is evident that leptin serves not only a weight-regulatory function but also plays a crucial endocrine and metabolic role, exerting influences both centrally and peripherally on pathways distinct from the HPA to the GH axis [19].

The cross-talk between leptin and these hormones impacts metabolic, immune, and neuroendocrine functions, collectively influencing the aging process. Exploring these interactions sheds light on how leptin acts as a molecular conductor, orchestrating hormonal harmony or discord that, in turn, shapes the aging trajectory.

Leptin and age-related diseases

Diabetes mellitus

Leptin's intricate relationship with metabolism positions it as a key player in the development and progression of age-related metabolic disorders, particularly diabetes. Studies suggest a complex interplay between elevated leptin levels (hyperleptinemia) and insulin resistance, a hallmark of type 2 diabetes. Leptin resistance, akin to insulin resistance, may impair the body's ability to respond to its signals, contributing to dysregulated glucose metabolism and the onset of diabetes [20]. Additionally, hyperleptinemia is associated with chronic low-grade inflammation, a factor implicated in the pathogenesis of diabetes [21].

Exploring the correlation between leptin levels and diabetes provides valuable insights into potential therapeutic strategies for managing and preventing this prevalent age-related disease. Administration of leptin as a therapeutic intervention has been documented to ameliorate insulin resistance in muscles and the liver among individuals with lipodystrophy [22-24]. Additionally, it has been shown to inhibit liver gluconeogenesis, suppress lipolysis, and mitigate fasting hyperglycemia in animal models with dia-

betes [25].

Cardiovascular diseases

Leptin's impact extends beyond the realm of metabolism, reaching into the cardiovascular system. Elevated leptin levels have been linked to atherosclerosis, hypertension, and other cardiovascular diseases. Leptin receptors are present in vascular endothelial cells and smooth muscle cells, suggesting direct effects on blood vessel function. Leptin manifests physiological impacts that might be unfavourable in conditions of cardiac dysfunction or heart failure. The hemodynamic consequences of leptin, including the elevation of resting heart rate and blood pressure, typically amplify myocardial workload by activating the sympathetic nervous system. Moreover, leptin may collaborate with other factors linked to obesity, such as hyperglycemia, inflammation, and oxidative stress, potentially expediting the onset and advancement of cardiovascular diseases [26, 27].

Neurodegenerative diseases

The brain, a central hub for leptin signaling, is not exempt from the hormone's influence during aging. Emerging evidence suggests that leptin plays a crucial role in maintaining cognitive function and protecting against neurodegenerative diseases. Leptin receptors are abundant in brain regions associated with learning and memory [28]. Leptin has demonstrated protective effects in neurodegenerative models replicating key pathological features of Parkinson's disease and Alzheimer's disease (AD). In the case of AD, where the accumulation of toxic β-amyloid (Aβ) promotes amyloid plaque formation, leptin downregulates the expression of β- and γ-secretase, leading to reduced levels of toxic Aβ through enhanced cleavage of amyloid precursor protein (APP) by α-secretase [29].

Following transient periods of ischemia, the administration of leptin is reported to diminish the size of cerebral infarcts and the extent of brain edema [30]. Leptin treatment induces an increase in adenosine triphosphate (ATP) and phosphorylated Akt (p-Akt) or protein kinase B levels while concurrently reducing lactate dehydrogenase levels, ultimately enhancing overall neuronal cell survival in ischemic stroke models [31]. In examining the connection between leptin and age-related diseases, the complexity of the hormone's impact becomes apparent, reaching far beyond its initial characterization as a regulator of appetite and metabolism. This exploration opens the door to a deeper understanding of how leptin contributes to the aging process and provides valuable insights into potential strategies for promoting overall health and well-being.

Leptin in longevity

A growing body of research suggests a potential link between leptin levels and increased lifespan. Longitudinal studies and experiments involving animal models have provided intriguing insights into the role of leptin in longevity [32-34]. However, lower levels of leptin have also been associated with increased lifespan, raising questions about the intricate balance required for optimal aging [35]. Stenholm *et al*., conducted the Baltimore Longitudinal Study of Aging, this nested case-control study contrasts individuals categorized as "long-lived" (surviving at least 90 years, $n = 41$) with those deemed "short-lived" (deceased between 72–76 years, $n = 31$). Blood samples, collected between ages 58 to 70 years, were analysed for circulating levels of ghrelin, insulin, leptin, interleukin 6, adiponectin, and testosterone. A comprehensive assessment, combining information from five biomarkers (ghrelin, insulin, leptin, IL6, and adiponectin), indicated a borderline significant increase in the global score among long-lived participants compared to short-lived ones ($P = 0.09$ by likelihood ratio and $P = 0.05$ by permutation). This trend persisted even with the inclusion of testosterone in the analysis ($P = 0.22$ by likelihood ratio and $P = 0.05$ by permutation). These findings suggest potential associations between the studied biomarkers and longevity, shedding light on physiological factors that may contribute to extended lifespans in the aging population [32].

In a study by Roszkowska-Gancarz *et al*., the association between extreme longevity and genetic variants of leptin (LEP) and leptin receptor (LEPR) genes was investigated, examining the –2548 G/A and +19 G/A LEP polymorphisms, as well as the K109R, Q223R, and K656N LEPR polymorphisms. Longevity, often linked to good health and delayed onset of age-related diseases, raises questions about the impact of leptin on metabolism and overall organismal functions. The study analyzed the frequencies of these polymorphisms in centenarians, young controls, myocardial infarction patients, and type 2 diabetes mellitus patients using restriction fragment length polymorphism. Results revealed that the GG genotype of –2548 G/A LEP was significantly more prevalent in centenarians compared to young controls, myocardial infarction, and diabetes mellitus groups. Additionally, the AA genotype of the K109R LEPR polymorphism was less frequent in centenarians compared to the aforementioned control groups. These findings suggest a potential role for the leptin pathway in regulating longevity, potentially influencing the susceptibility to myocardial infarction and type 2 diabetes mellitus development. The study provides valuable insights into the genetic factors associated with extreme longevity and their implications for age-related diseases [36].

Calorie restriction (CR), involving a reduction in dietary intake below energy requirements while maintaining optimal nutrition, is identified as the exclusive nutritional intervention known to alleviate aging and potentially increase life span by 1–5 years, concurrently enhancing health span and overall quality of life. The effectiveness of CR lies in its ability to modify intrinsic aging processes through cellular and metabolic adaptations, thereby lowering the risk of developing numerous cardiometabolic diseases [37]. Leptin triggers the activation of central SIRT1, a crucial element for the anorexic effects induced by leptin in hypothalamic POMC neurons. In both leptin receptor mutant db/db mice and leptin-deficient ob/ob mice, there is an absence of SIRT1 activation in the hypothalamus in response to CR [38].

Gut microbiota and leptin

The gut microbiome serves as a mediator of environmental cues, impacting disease risk across diverse age groups and undergoing changes as the host ages. Modifications in the gut microbiome associated with aging result from both intrinsic factors, such as progressive physiological decline, and extrinsic factors linked to lifestyle, including diet, medication, and decreased social interactions [39]. The shifts observed in the gut microbiome during aging and diseases reflect interconnected yet distinct processes. Addressing the signals of 'unhealthy' aging originating from the gut microbiome through personalized or sub-group-specific interventions represents a novel realm of exploration, informed by comprehensive shotgun metagenomics studies and data analytics [40]. In recent years, scientific inquiry has uncovered a fascinating interplay between leptin, aging, and the intricate ecosystem within our digestive tracts known as the gut microbiota [41]. This symbiotic relationship adds a new layer of complexity to our understanding of aging, suggesting that the microbial inhabitants residing in our intestines play a pivotal role in shaping the aging process, with leptin acting as a key mediator.

Probiotics exhibit the potential to reduce circulating leptin levels by modifying the gut microbiota, suggesting anti-obesogenic effects. The study conducted by Cheng *et al.* explored the impact of administering the probiotic bacterium *Lactobacillus rhamnosus* GG (LGG) on gut microbiota and the modulation of leptin resistance in mice. Seven-week-old male Balb/C mice were subjected to a normal diet (ND), high-fat diet (HFD), HFD supplemented with a low dose of LGG (10^8 CFU/mouse/day), or HFD supplemented with a high dose of LGG (10^{10} CFU/mouse/day) for 10 weeks. The HFD-fed mice exhibited a significant increase in body weight, epididymal fat weight, reduced responsiveness to exogenous leptin treatment, and altered villus height to crypt depth ratio compared to ND-fed mice. Additionally, an evident rise in the proportion of Proteobacteria and the Firmicutes/Bacteroidetes ratio in fecal microbiota was observed in HFD-fed mice. However, supplementation of HFD with a high dose of LGG restored exogenous leptin responsiveness, improved the villus height to crypt depth ratio, and reduced the proportion of Proteobacteria in fecal microbiota. These findings suggest that LGG supplementation has the potential to alleviate leptin resistance induced by an HFD, potentially through enhancing the digestive health of the host [42].

In the study by Heiss *et al.*, focusing on the intricate relationship between gut microbiota and leptin, a key observation emerged from studies involving mice lacking a microbiota. These mice exhibited a resistance to diet-induced obesity, shedding light on the protective role of gut microbiota against weight gain. This investigation revealed that wild-type mice with depleted gut microbiota, including germ-free and antibiotic-treated mice, display elevated glucagon-like peptide-1 (GLP-1) levels and are shielded from diet-induced hypothalamic inflammation. Notably, enhanced leptin sensitivity is observed in these mice when subjected to a Western diet. Experiments involving GLP-1 receptor (GLP-1R)-deficient mice underscore the pivotal role of intact GLP-1R signaling in preventing hypothalamic inflammation and improving leptin sensitivity. Furthermore, the expression of GLP-1R in astrocytes and the impact of its deletion in glial fibrillary acidic protein (GFAP)-expressing cells provide insights into the intricate mechanisms involved. This suggests that gut microbiota depletion holds promise in attenuating diet-induced hypothalamic inflammation and enhancing leptin sensitivity through GLP-1R-dependent pathways [43].

Conversely, leptin appears to have a reciprocal effect on the composition and diversity of the gut microbiota. Leptin-deficient mice, characterized by obesity and modified microbiota, are more susceptible to certain intestinal pathogens. Given that Paneth cells secrete antimicrobial peptides (AMPs) and play a significant role in shaping the gut microbiome, in a study by Rajala *et al.* which examined the mRNA expression of gut AMPs, revealed decreased expression in leptin receptor (LepR)-deficient db/db mice. This suggests a potential link between AMP modulation and microbiota composition. To discern whether changes in gut microbiota and AMP mRNA expression in db/db mice result from increased food intake or other leptin action defects, the effects of pair feeding and intestinal epithelial LepRb ablation on AMP mRNA expression and microbiota composition were investigated. Remarkably, phylum-level alterations in fecal microbial content and AMP gene expression persisted in pair-fed db/db mice, indicating that these differences are not solely attributed to hyperphagia. These findings highlight a role for LepRb signaling extrinsic to the intestinal epithelium, independent of food intake, in governing the gut microbiome [44]. This bidirectional communication underscores the intricate relationship between hormonal signaling and the microbial community, with potential implications for aging-related processes.

Leptin supplementation and therapeutic approaches

As we delve deeper into the connection between leptin and these cellular and hormonal dynamics, a clearer picture emerges of how this hormone contributes to the aging process and offers potential avenues for interventions in the quest for healthy aging. Conversely, there is emerging interest in exploring interventions that modulate leptin levels to promote longevity. Leptin supplementation, in some studies, has shown promising effects on metabolic health and may have implications for extending lifespan. However, caution is warranted, as excessive leptin levels or hypersensitivity may lead to leptin resistance and adverse metabolic outcomes. Beyond direct leptin interventions, lifestyle modifications that impact leptin, such as dietary changes and exercise, are also under investigation. These interventions aim to optimize leptin signaling and, by extension, contribute to enhanced metabolic health and potentially increased longevity [45].

Conclusions

Leptin plays a vital role in cellular aging and interacts with hormones, influencing various aspects of our physiological well-being, including metabolic disorders, cardiovascular diseases, and neuroprotection. Exploring challenges and controversies in the scientific literature, we recognize the need for a measured approach in translating leptin-related knowledge for potential anti-aging interventions, considering ethical considerations. Future research avenues include investigating leptin variants, genetic influences, and advanced imaging techniques revealing the brain's response to leptin, offering possibilities for precision medicine, lifestyle interventions, pharmacological strategies, and neurological therapies to promote healthy aging.

In a noteworthy twist, recent research highlights the significant role of gut microbiota in regulating leptin and consequently, the aging process. This symbiotic relationship adds complexity to our understanding of aging, emphasizing the interconnectedness of physiological systems. Concluding our exploration of "leptin and aging," we recognize the intersection of hormones and the microbiome. The intricate dance of leptin with gut microbiota suggests that aging's narrative is shaped not only by hormones but also by the microbial inhabitants within us. This holistic perspective encourages us to redefine the aging landscape, acknowledging the interplay between hormones, gut microbiota, and various contributing factors. The ongoing exploration leads us toward a future where understanding, intervention, and a holistic approach converge to redefine the narrative of aging for generations to come.

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