The Role of Ghrelin in Senescence: A Mini-Review

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Key Words

Aging · Growth hormone secretagogue receptor · Food intake · Glucose homeostasis · Lipid metabolism · Cardiovascular function · Neurodegeneration

Abstract

Ghrelin, a 28-amino acid hormone produced mainly by the X/A-like endocrine cells in gastric mucosa, has a widespread tissue distribution and diverse physiological functions such as hormonal, orexigenic, metabolic, cardiovascular, neurological, and immunological activities. Considerable evidence has suggested that ghrelin plays an important role in organism senescence or aging. The present review provides a comprehensive picture of this new development. We first reviewed the aging (senescence)-dependent reduction of ghrelin signaling, and then highlighted its relationship with the aging-associated alteration in food intake, energy metabolism, cardiovascular function, neurological activity, and adaptive immunity. Our literature review suggests that ghrelin is an innovative and promising agent in the treatment of these pathophysiological conditions associated with senescence.

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Introduction

Ghrelin, a 28-amino acid peptide, was originally identified through a process of reverse pharmacology from gastric extracts as the endogenous ligand for

growth hormone secretagogue receptor 1a (GHS-R1a) by Kojima et al. [1]. The amino acid sequence of ghrelin is highly conserved between species (fig. 1), with its sequence in rodents reported as GSSFLSPEHQKAQQR-KESKKPPAKLQPR. The structure of ghrelin is unique with its third amino acid serine (Ser3) octanoylated. The octanoylation of ghrelin (ser3) is catalyzed by the ghrelin O-acyltransferase (GOAT), a member of membrane-bound O-acyltransferase family. This modification is essential for the binding and activation of its receptor GHS-R1a. Ghrelin is mainly synthesized and stored as round, compact, electron-dense granules in X/A-like endocrine cells in the basal 1/3 of the gastric mucosa. Upon stimulation by either neural or hormonal signals, ghrelin is released into circulation to exert a broad range of functions including: (1) release of hormones such as growth hormone, adrenocorticotrophic hormone, cortisol, and prolactin; (2) conservation of organism energy through its dueling action to increase food intake and to decrease energy expenditure; (3) regulation of gastrointestinal motility and secretion as well as pancreatic function; (4) modulation of glucose and lipid metabolism; (5) attenuation of proinflammatory cascades and stimulation of adaptive immunity, and (6) cellular protection in the cardiovascular system and the central nervous system (CNS). Emerging evidence indicates that ghrelin may also influence organism senescence or aging. This review summarizes our current understanding on the age-dependent reduction of ghrelin signaling, and its relation to senescence-associated alterations in food in-

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Human	G	S	S	F	L	S	P	E	H	Q	R	V	Q	Q	R	K	E	S	K	K	P	P	A	K	L	Q	P	R
Monkey	G	S	S	F	L	S	P	E	H	Q	R	A	Q	Q	R	K	E	S	K	K	P	P	A	K	L	Q	P	R
Rat	G	S	S	F	L	S	P	E	H	Q	K	A	Q	Q	R	K	E	S	K	K	P	P	A	K	L	Q	P	R
Mouse	G	S	S	F	L	S	P	E	H	Q	K	A	Q	Q	R	K	E	S	K	K	P	P	A	K	L	Q	P	R
Dog	G	S	S	F	L	S	P	E	H	Q	K	L	Q	Q	R	K	E	S	K	K	P	P	A	K	L	Q	P	R

Fig. 1. Sequences of ghrelin across species. Asterisk denotes the amino acid Ser3 which is octanoylated.

take, energy metabolism, bone turnover, cardiovascular function, neurological activity, and adaptive immunity.

Age-Dependent Decline in Ghrelin Activity

Early studies in both rodents and humans have demonstrated that the dose dependence of growth hormone release elicited by ghrelin or ghrelin mimetics is attenuated during aging. This alteration in the dose-response curve could be explained by reduced levels of ghrelin, the ghrelin receptor GHS-R1a or less efficient signal transduction.

Alteration of Ghrelin Levels during Aging in Rodents and Humans

Conflicting results have been reported on whether ghrelin levels change during aging. The underlying reason for these discrepancies is unknown, but may be explained at least in part by the differences in body mass index, frailty status, sample size, and assays used to measure ghrelin.

In their studies in rodents, Liu et al. [2] found no correlation between total ghrelin in serum and the age of C57BL/6 mice up to 6 months old. On the other hand, studies by Kappeler et al. [3] showed that total ghrelin levels significantly increased with aging in both Wistar and Lou C/Jall rats. Similar increases in both total and acyl-ghrelin were detected in C57BL/6J mice [4, 5]. Interestingly, no correlation existed between ghrelin activity measured by the ratio of active ghrelin over total ghrelin and age, suggesting that aging is not a significant determinant in the conversion of octanoylated ghrelin to desacyl-ghrelin. Increased levels of plasma ghrelin have been proposed to be attributed to the decline of receptor (and/or post-receptor) functions in senescent animals [4]. This notion contradicts the report showing a decline in gastric

ghrelin mRNA levels in 19-month-old mice [2]. Furthermore, fasting-induced increases in ghrelin were less robust in aging rats despite the basal ghrelin levels being comparable between 4 and 25 months of age [6]. Thus, aging appears to impair either ghrelin expression in the gastric mucosa or the release of ghrelin in response to energy deficiency, although this conclusion is not consistently supported by studies in rodents.

Although Sturm et al. [7] showed no difference in ghrelin levels between young and elderly females, most of the human studies revealed a reduction in circulating ghrelin. Rigamonti et al. [8] reported a decline in fasting ghrelin levels in elderly subjects aged 67–91 years, relative to young controls aged 27–39 years. There exists a negative correlation between the mean fasting plasma ghrelin concentrations and the body mass index and serum insulin levels, but not thyroid-stimulating hormone and insulin-like growth factor 1 (IGF-1) levels in all groups of subjects [8]. Similarly, studies by Nass et al. [9] showed an age-dependent decline in circulating acyl-ghrelin levels in healthy older adults aged 62–74 years relative to healthy young men aged 18–28 years. There is also a significantly lower association between circulating acyl-ghrelin levels and growth hormone secretion in the elderly. However, the reduction in ghrelin levels was found to be independent of the differences in body composition or insulin resistance in this study [9]. Consistent with the rodent experiments, the absence of malnutrition-induced increases in plasma ghrelin levels in elderly subjects has been reported [10].

Changes in Ghrelin-GHS-R1a Signaling during Aging

The efficacy of treating old animals or elderly human subjects with ghrelin or synthetic GHS-R1a agonists suggests that endogenous ghrelin signaling becomes attenuated during aging. Inefficient ghrelin signaling may be a result of reduced GHS-R1a expression or deficits in its signaling. It was demonstrated that pituitary GHS-R mRNA expression decreases in 24-month-old Lou C/Jall rats but remains at similar levels in 3-, 12-, and 24-month-old Wistar rats [3]. In C57BL/6 mice, the GHS-R1a mRNA expression in the pituitary gland and whole brain is stable between 6 and 30 months of age [5]. It is possible that a differential alteration of GHS-R1a expression occurs in distinct brain regions and may not be revealed by assaying the whole brain. Indeed, GHS-R1a mRNA was upregulated in the hypothalamus but downregulated in the hippocampus in dwarf rats [11]. In the dorsal vagal complex, senescent rats demonstrated a significantly lower expression of both GHS-R1a mRNA and protein [12].

The reduction in GHS-R1a is associated with a decrease in parasympathostimulatory neuronal activity [12].

Treatment of old mice with ghrelin or growth hormone was reported to restore the regeneration of hepatocytes [13]. This effect is attributed to the cyclin D3/cdk4/6-dependent attenuation of C/EBP α phosphorylation. The reduced capability of liver regeneration in old animals is attributed to the decline in the amplitude of endogenous GH release, presumably due to the deficient ghrelin signaling in the CNS [13]. In the CNS, compensation for age-dependent reductions in endogenous ghrelin activity in neurons expressing dopamine receptor D1R by administering GHS-R1a agonists may diminish loss of cognitive function in the elderly. This effect is mediated by the amplification of dopamine signaling through the formation of GHS-R1a/D1R heterodimerization [14]. An additional mechanism may involve the increased mitochondrial uncoupling protein-2 (UCP2) induced by ghrelin. Deletion of ghrelin in wild-type and *ob/ob* mice significantly decreases UCP2 [15]. Mitochondrial UCP2 has been proposed to protect aging neurons from the oxidative damage induced by reactive oxygen species [16].

Ghrelin and Age-Associated Impairment in Energy Metabolism

Originally identified as an endogenous growth hormone secretagogue, ghrelin is now considered as a critical hormone with profound effects on energy metabolism. Aging is often associated with a progressive dysfunction in energy metabolism such as obesity, diabetes, and hepatic steatosis. The reasons for the aging-related alteration of energy metabolism are multifactorial. Among these factors, the decline in ghrelin activity plays an important role.

Appetite and Food Intake

Aging is associated with a progressive decrease in appetite and food intake [7]. Deficits in ghrelin activities rather than its plasma concentration have been demonstrated to be linked with the aging-associated reduction in food intake. Overnight fasting stimulates food intake in young mice, but not in senescent mice [4]. Exogenous ghrelin at a dose that stimulates food intake in young mice failed to increase food intake in senescent mice [4]. Further, deletion of GHS-R1a increased meal size and duration while reducing meal frequency in mice aged 12–14 months, although the total daily food intake is similar between wild-type littermates and GHS-R1a null mice.

These effects became less significant in mice aged 24–26 months [17]. This observation suggests that deletion of GHS-R1a causes altered meal patterns with aging.

Thermogenesis and Energy Expenditure

Severe impairment in thermogenesis and energy expenditure is associated with senescence. Previous studies demonstrated that enhanced ghrelin signaling in brown fat tissues contributes to thermogenic impairment associated with aging. Levels of GHS-R1a mRNA increase significantly in brown fat tissues of old mice aged 22 months, relative to 4-month-old young mice [18]. Deletion of GHS-R1a reverses aging-associated decline of thermogenesis and stimulates insulin signaling in brown fat tissue [19]. This effect is mediated by the activation of the thermogenic signaling cascade, its subsequent improvement in mitochondrial biogenesis, and the dynamics of brown adipocytes in old mice. Thus, the antagonism of GHS-R1a to enhance thermogenesis may serve as an alternative approach for treatment of senescence-associated obesity and insulin resistance.

Glucose Homeostasis and Diabetes

Ghrelin contributes to derangement of glucose homeostasis associated with senescence through either a central or a peripheral mechanism. In 10-week-old mice, the pancreatic expression of ghrelin driven by rat insulin II promoter or rat glucagon promoter does not alter pancreatic function or histology, including insulin secretion and glucose metabolism [20]. Similarly, young (12-week-old) mice with overexpression of ghrelin in neurons driven by the neuron-specific enolase (NSE) promoter [21] demonstrate a normal glucose tolerance. However, glucose intolerance develops in old NSE-ghrelin mice aged 32 weeks. Interestingly, insulin levels in NSE-ghrelin mice do not differ from those of wild-type littermates despite the impaired glucose tolerance. These observations indicate a central mechanism for ghrelin-induced glucose dysfunction in senescent mice. The effect of ghrelin on glucose dysfunction during aging may be independent of its action on food intake. Ablation of ghrelin in *ob/ob* mice enhances insulin secretion in response to glucose challenge and improves peripheral insulin sensitivity, while demonstrating no effects on the obese hyperphagic phenotype [15]. Instead, the deletion of ghrelin reduces expression of *Ucp2* mRNA in the pancreas of *ob/ob* mice. Thus, ghrelin may also contribute to the impairment of glucose-induced insulin secretion by the UCP2-dependent mechanism in islet cells.

Lipid Metabolism and Obesity

Aging is often associated with dysfunction of lipid metabolism characterized by increased deposition of fat mass and hyperlipidemia. Despite the report showing that long-term administration of ghrelin reduces body weight and adiposity in aged mice [22], it is generally agreed that ghrelin contributes to obesogenesis during aging. Total cholesterol and triglyceride levels in older GHS-R1a null mice are statistically lower when compared to wild-type littermates [23]. In addition, deletion of GHS-R1a attenuates the age-associated adiposity. In rats, the stimulatory effect of ghrelin on white adipose mass, serum triglyceride, low-density lipoprotein, and cholesterol is more pronounced in older animals relative to peripubertal/young rats [24]. The higher responsiveness to ghrelin-induced increase in lipid metabolite in aged rats is associated with an increase in adrenocorticotrophic hormone and corticosterone levels. Since ghrelin has been documented to increase hypothalamic-pituitary-adrenal axis activity, this observation suggests a central mechanism for ghrelin-mediated increase in fat mass during aging. Other studies suggest a peripheral mechanism through its direct effects on adipose tissue and liver [25, 26]. Thus, antagonism of GHS-R1a may be a novel therapeutic strategy for obesity associated with senescence.

Bone Loss

Ghrelin has been demonstrated to preserve bone mass in animal and in vitro studies. The relationship between ghrelin and bone loss during aging is provocative in animals but inconclusive in human beings. A study by van der Velde et al. [27] demonstrated that ghrelin exerts dual effects on osteoclastogenesis, inhibiting osteoclast progenitors directly and stimulating osteoclastogenesis via a more potent systemic/central pathway. In young mice, the systemic osteoclastogenic activity is suppressed by leptin, thus balancing the two counterregulatory ghrelin pathways which lead to an unchanged bone structure. In aged mice, the systemic/central osteoclastogenic effect of ghrelin is lost, shifting to the direct protective effect of ghrelin on bone structure. This finding is appealing because it suggests that elderly subjects benefit from ghrelin treatment or enhanced GHS-R1a signaling to inhibit osteoclastogenesis and improve bone structure. However, human studies were inconclusive. Studies by Jurimae et al. [28] have found that ghrelin levels are not significantly related to the decrease in bone mineral mass and bone mineral density (BMD) values in elderly women. Further, studies by Weiss et al. [29] showed no evidence for an association with BMD or short-term change in BMD in older adults.

Ghrelin and Reduction of Cardiovascular Function during Aging

Studies in both rodents and humans have shown favorable effects of ghrelin on the cardiovascular function via either growth hormone-dependent or -independent mechanisms. Emerging evidence indicates that ghrelin may be beneficial for the restoration of impaired cardiovascular functions associated with aging.

Cardiac Function and Cardioprotection

Several studies [30] suggest the potential clinical application of ghrelin in improvement of cardiac contractility, decreasing the peripheral resistance and cardioprotection, which are often associated with senescence. Administration of ghrelin to patients with congestive heart failure for 3 weeks significantly improves cardiac functions as demonstrated by increases in left ventricle ejection fraction and left ventricle mass, and decreases in the plasma levels of norepinephrine and left ventricle end-systolic volume [30]. The protective effects of ghrelin on the heart are mediated through its direct action on the heart and blood vessels and/or through the modulation of cardiac autonomic nervous activity [30]. The direct protective effect of ghrelin on cardiomyocytes is mediated by GHS-R1a activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway [30]. The indirect mechanism on autonomic nervous activity is less clear. Peripheral ghrelin may inhibit the renal sympathetic nerve activity by activating GHS-R1a at the cardiac vagal nerve ending, which signals to the nucleus of tractus solitarius [30]. Ghrelin may also act directly on CNS to alter the sensitivity of CNS neurons to other hormones participating in the regulation of sympathetic activity. Exogenous ghrelin reduces the plasma levels of epinephrine and dopamine, thus shifting the balance of autonomic nervous activity toward parasympathetic nervous activity [30].

Endothelium and Angiogenesis

Angiogenesis is impaired in aging individuals. Constitutive expression of ghrelin and GHS-R1a in endothelial cells suggests their role in angiogenesis. Furthermore, exogenous ghrelin increases angiogenesis in cultured neonatal human microvascular endothelial cells (HMVECs) through a mechanism involving the MAPK/ERK2 mitogenic signaling pathway. In senescent HMVECs, ghrelin levels are 3.2-fold lower than neonatal HMVECs. Angiogenesis was significantly reduced in the aged HMVECs, suggesting a cellular senescence in the vascular endothelial

cells. Treatment with exogenous ghrelin markedly reverses the impairment of angiogenesis in aged HMVECs [31]. These findings indicate that ghrelin is a potential therapy for senescence-related impairment of angiogenesis.

Atherosclerosis and Hypertension

Ghrelin may affect key events in atherogenesis. Plasma levels of ghrelin have been reported to correlate with atherogenic lipoprotein [32]. Ghrelin interacts with a species of high-density lipoproteins associated with paraoxonase I (PON I), an esterase which may protect against vascular disease by metabolizing oxidized lipids. If PON I breaks down ghrelin, it may become a target for new drugs to control ghrelin biostability. Ghrelin is also associated with other lipoproteins such as triglyceride-rich lipoproteins, high-density lipoproteins, very high-density lipoproteins, and to some extent, low-density lipoproteins [33]. Ghrelin, along with atherogenic lipoproteins, may serve to predict vascular disease. Ghrelin may also function as an anti-inflammatory molecule in the circumstance of increased inflammation during the more progressed phases of atherogenesis to enhance the binding and removal of oxidized low-density lipoproteins. Another mechanism is the AMPK-dependent attenuation of the inflammatory response and cell proliferation. Ghrelin is thus a potential agent in the treatment of a complex disease like atherosclerosis associated with senescence.

Ghrelin and Neurodegeneration

Chronic neurodegenerative diseases including Alzheimer's, Parkinson's, and Huntington's diseases are strongly associated with metabolic changes. The neuroprotective potential of ghrelin has been demonstrated in animal models of these neurodegenerative diseases and other neuronal injuries such as ischemia or traumatic brain injury, spinal cord injury, and amyotrophic lateral sclerosis. A comprehensive review on the role of ghrelin in neurodegenerative diseases was presented by dos Santos et al. [34] and Stoyanova [35]. Here, we focus on the molecular mechanism of its neuroprotection.

Amplification of Dopamine Signaling

GHS-R1a physically interacts and forms heterodimers with dopaminergic receptor D1R to increase dopamine signaling in the hippocampus, cortex, substantia nigra, and ventral tegmental areas [14]. In addition, GHS-R1a may form a heterodimer with D2R to enhance dopamine release in the striatum [36]. An increase in dopamine signal-

ing by ghrelin results in reduced motor symptoms in Parkinson's disease. Maintenance of efficient dopamine signaling by administration of exogenous ghrelin or GHS-R1a agonist to compensate for age-dependent reductions of endogenous ghrelin activity in dopaminergic neurons may attenuate loss of cognitive function in elderly subjects.

AMPK and Mitochondrial Dysfunction

Mitochondrial dysfunction contributes to neurodegenerative disease by reducing mitochondrial uncoupling [37], increasing free radical production and oxidative stress [38], reducing mitochondrial biogenesis, and impairing calcium buffering [39]. Both pharmacological and genetic studies demonstrate that AMPK is critical for mitochondrial biogenesis. Chronic activation of AMPK by 5-aminoimidazole-4-carboxamide ribonucleotide increases key mitochondrial enzymes in skeletal muscle. Muscle-specific deletion of AMPK subunits β_1 and β_2 induces mitochondrial dysfunction and insulin resistance [40]. In neurons, ghrelin activates AMPK and its downstream targets SIRT1 and PGC1 α , leading to a subsequent increase in mitochondrial biogenesis. The neuroprotective effects of ghrelin may thus be mediated by its activation of AMPK signaling and subsequent enhanced mitochondrial biogenesis. AMPK is also involved in autophagy, including mitophagy and the removal of damaged mitochondria – either through its inhibition of mechanistic target of rapamycin or phosphorylation of serine/threonine-protein kinase ULK1 [41]. Impairment in mitophagy contributes to the development of neurodegenerative diseases. Thus, ghrelin may attenuate neuronal degeneration by increasing mitophagy via an AMPK-dependent mechanism.

Inhibition of Neuronal Apoptosis

Apoptosis contributes to neuronal loss in neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases. Ghrelin inhibits the apoptotic cascade to increase neuronal survival by targeting the Bcl-2 family. Inhibition of caspase-3 by ghrelin has been demonstrated in a variety of brain regions including the temporal cortex, hippocampus, striatum, and medulla [34, 35, 42]. Ghrelin reduces ROS production, preserves mitochondrial inner transmembrane potential, and prevents cytochrome c release in the hypothalamic neurons [34, 35]. Since ghrelin can function to prevent the activation of the apoptotic cascade, treatment with ghrelin may be effective during the early stages of neurodegenerative diseases when the activation of the apoptotic pathway could be prevented.

Fig. 2. Ghrelin and functional changes associated with aging. Downward-pointing arrows denote reduction.

Ghrelin and Age-Related Decline in Adaptive Immunity

The decline in adaptive immunity with senescence is largely attributable to the structural and functional involution of the thymus, which leads to a decline in T-lymphocyte output [43–45]. Reduction of endogenous ghrelin activity in thymus impairs thymopoiesis during aging [43]. Both ghrelin and ghrelin receptor levels in the thymus demonstrate a progressive decline during aging [43]. Administration of ghrelin into old mice rejuvenates the senescent thymus in thymic architecture and thymocyte numbers [43]. Ghrelin increases recent thymic emigrants and improves T-cell receptor diversity of peripheral T-cell subsets by increasing early thymocyte progenitors and bone marrow-derived Lin-Sca1+cKit+ cells [43]. Deletion of either ghrelin or GHS-R1a accelerates thymic involution associated with aging [43]. In addition to its direct effects on thymocyte progenitors, ghrelin may also stimulate the thymopoiesis by regulating critical cytokines and hormones from the thymic microenvironment [44]. Ghrelin and its receptor GHS-R1a are detected in thymic stromal cells. Their expression levels decline with aging. Deletion of ghrelin or GHS-R1a increases adipogenic fibroblasts at the expense of thymic epithelial cells in the thymus. Cellular transitions from thymic epithelial cells to mesenchymal cells that express proadipogenic regulators were detected in the thymus. Loss of ghrelin activity compromises thymic stromal microenvironment by facilitating epithelial to mesenchymal transition and inducing thymic adipogenesis with age. This alteration is

associated with reduced naive T cells. Consistent with this report, administration of ghrelin has been demonstrated to reduce proinflammatory cytokines [45]. Taken together, these findings demonstrate that ghrelin functions in an autocrine and paracrine capacity to regulate the development of T cells. Thus, ghrelin contributes to the regulation of inflammatory aging.

Ghrelin and Aging-Associated Sarcopenia

Sarcopenia, a common complication of aging, is largely due to atrophy-associated reduction in myofibrillar fibers. The decline in growth hormone-IGF-1 signaling contributes to the muscle atrophy associated with aging. As a natural growth hormone secretagogue, ghrelin may thus assume a beneficial effect on the protection of skeletal muscle atrophy in elderly subjects through its activation of GHS-R1a. On the other hand, recent studies [46] have demonstrated that ghrelin may also act on an unidentified receptor to block skeletal muscle atrophy in a growth hormone-independent manner. Both acyl ghrelin and desacyl ghrelin were shown to inhibit dexamethasone-induced skeletal muscle atrophy and atrogene expression through PI3K β -, mTORC2-, and p38-mediated pathways in myotubes. An increase in circulating desacyl ghrelin attenuated skeletal muscle atrophy induced by either fasting or denervation without stimulating muscle hypertrophy and GHSR-1a-mediated activation of the GH/IGF-1 axis. Deletion of GHS-R1a failed to block the protective effects of both acyl

ghrelin and desacyl ghrelin on fasting-induced atrophy. Similarly, studies by Sugiyama et al. [47] showed that ghrelin restores body weight loss and skeletal muscle catabolism in mice treated with angiotensin II. This effect occurs likely through the early restoration of IGF-1 mRNA in the skeletal muscle and the amelioration of nutritional status. Thus, ghrelin has a strong and specific potential for the prevention or treatment of muscle atrophy associated with aging.

Growth Hormone-Dependent versus Independent Effects

Decline in ghrelin secretion or its activity contributes to growth hormone insufficiency during aging. Chronic treatment with ghrelin or GHSR1a agonist restores the decline in amplitude of episodic growth hormone release, leading to a younger phenotype in both old rodents and human subjects. These observations lead to the speculation that ghrelin contributes to loss of vitality, occurrence of frailty, anorexia, central adiposity, cardiovascular complications, deterioration of mental function, and decline in adaptive immunity that occurs with aging through a growth hormone-dependent mechanism. In addition to the growth hormone-dependent actions, current evidence indicates that ghrelin is implicated in the metabolic and functional changes associated with aging through a mechanism independent of growth hormone. For example, ghrelin has been shown to regulate hepatic de novo lipogenesis in a model of growth hormone deficiency, indicating a growth hormone-independent manner [48]. Differences in the activities of immune activation and cytokine expression between growth hormone and ghrelin also indicate a growth hormone-independent action of ghrelin [49]. Furthermore, most of the in vitro studies indicate the distinct functions of ghrelin in the regulation of angiogenesis, adipogenesis, and neural survival through a growth hormone-independent mechanism. The distinct activities of ghrelin may thus aug-

ment the responses when utilized in combination with growth hormone in the restoration of a younger phenotype in elderly subjects.

Conclusions

Senescence, or biological aging, is a series of progressive and phenotypically diverse cellular states acquired during aging. It occurs as a result of cellular senescence and is characterized by the declining ability to respond to stress, the increasing homeostatic imbalance, and the risk of disease. At present, the biological basis of aging remains largely unknown. Here, we have presented an overall picture of the decline in endogenous ghrelin activity during aging and the potential relation with the alteration in food intake, energy metabolism, cardiovascular function, neuronal activity, and adaptive immunity associated with senescence (fig. 2). A deficit in ghrelin activity may contribute to the reduction in appetite, dysfunction of glucose metabolism, increase in adiposity, decrease in the peripheral resistance and cardioprotection, impaired angiogenesis, atherosclerosis, and hypertension, which are often associated with senescence. Further, a decrease in endogenous ghrelin activity during aging may increase the risk of neurodegenerative diseases, decrease adaptive immunity, and increase sarcopenia. The beneficial effects of ghrelin or GHS-R1a agonists may provide a promise for the treatment of these pathologies associated with senescence.

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Disclosure Statement

The authors declare no conflict of interest.

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