Pleiotropic Effects of Growth Hormone and Insulin-like Growth Factor (IGF)-1 on Biological Aging: Inferences From Moderate Caloric-Restricted Animals

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Moderate caloric restriction (60% of ad libitum intake) is an important model to investigate potential mechanisms of biological aging. This regimen has been reported to decrease the number of pathologies and increase life span in all species tested to date. Although moderate caloric restriction induces a wide range of physiological changes within the organism, adaptive changes within the endocrine system are evident and serve to maintain blood levels of glucose. These alterations include an increase in growth hormone secretory dynamics and a decline in plasma levels of IGF-1. These endocrine compensatory mechanisms can be induced at any age, and we have proposed that these alterations mediate some of the beneficial aspects of moderate caloric restriction. Numerous studies indicate that growth hormone and IGF-1 decrease with age and that administration of these hormones ameliorates the deterioration of tissue function evident in aged ad libitum-fed animals, suggesting that the absence of these hormones contributes to the phenotype of aging. Nevertheless, IGF-1 is an important risk factor in age-related pathologies including lung, breast, and prostate cancer. From these studies, we propose that endocrine compensatory mechanisms induced by moderate caloric restriction (including increased growth hormone and decreased IGF-1) decrease the stimulus for cellular replication, resulting in a decline in pathologies and increased life span observed in these animals. These findings have important implications for potential mechanisms of moderate caloric restriction and suggest that neuroendocrine compensatory mechanisms exert a key role on the actions of moderate caloric restriction on life span.

A substantial volume of empirical and scientific evidence has accumulated, demonstrating that biological aging is associated with functional deficits at the cellular, tissue, organ, and system levels (1). Several theories to explain these changes as well as the increased risk of disease with age have been proposed. However, to date, no single explanation has adequately accounted for the diversity of physiological changes associated with age, and it is likely that the decline in tissue function and increased incidence of disease are the result of several interacting factors. Current concepts of aging encompass free radical, somatic mutation, DNA repair, and cellular theories (2). Although there are data to support each of these hypotheses, there is a paucity of evidence to suggest that the natural progression of biological aging can be explained by these classical theories.

The neuroendocrine theory of aging (3) is an alternative hypothesis that was developed to account for physiological changes associated with age. This concept evolved from studies that indicated that (a) the endocrine system has an important role in developmental processes; (b) hormone deficiency results in deterioration of tissue function; and (c) hormones have an important trophic and integrative role in maintaining tissue function. The neuroendocrine system is composed of the hypothalamus and pituitary gland and is under the influence of neurotransmitters and neuropeptides that regulate hypothalamic-releasing and inhibiting hormones secreted into the hypophyseal portal blood (4). The release of these hypothalamic hormones influences the secretion of anterior pituitary hormones that subsequently regulate tissue function. The hypothalamus and pituitary have the capacity to detect humoral secretions from target tissues and adjust hormone production to maintain an optimal internal “milieu” appropriate for normal tissue function. It is well established that the neuroendocrine system has a critical role in regulating tissue growth throughout development and influences: (a) general metabolism of various tissues through the release of growth hormone and thyroid-stimulating hormone; (b) reproductive function through the release of luteinizing hormone, follicle-stimulating hormone, prolactin, and oxytocin; and (c) plasma electrolytes and responses to stress through regulation of vasopressin and adrenocorticotropic hormone. In addition, the hypothalamus has an important role in the integration of parasympathetic and sympathetic activity and can thereby influence a wide variety of functions including heart rate, blood pressure, vascular responses, and glucose metabolism, among others. More recently, the hypothalamus has been implicated in regulation of biological rhythms by its interactions with the suprachiasmatic nucleus and other associated hypothalamic nuclei (5,6). The classification of hormones and their primary function noted above is an overly simplistic view of the neuroendocrine system, as critical interactions occur among hormones that also contribute to the regulation of cellular and tissue function. Because many of the early events of aging include alterations in systems regulated by the neuroendocrine axis, it was hypothesized that age-dependent alterations in the neuroendocrine system have the potential to result in a progressive series of events that contribute to the aging phenotype.

Although the etiology of neuroendocrine changes with age is unknown, it has been proposed that cellular and molecular alterations in specific subpopulations of neurons within the hypothalama...
laminus and pituitary and/or supporting structures within the brain are a contributing factor in the decrease in tissue function (7). The cause of the specific perturbations may be related to loss of neurons, genetic error, or the production of free radicals, which lead to progressive aberrations in tissue function that facilitate biological aging and the progression of disease. Thus, the neuroendocrine theory of aging is unique when compared to other theories of aging in that neuroendocrine alterations are, in many cases, not considered the primary causative factor of biological aging but rather are considered to be mediators of aging initiated by cellular changes in specific subpopulations of neurons or systems that closely interact with hypothalamic neurons.

One of the few manipulations that have been reported to consistently influence the rate of biological aging is moderate caloric restriction. Under this regimen, animals are fed a caloric-restricted diet (60% of ad libitum intake) utilizing a vitamin- and mineral-supplemented diet from an early age (4 months in our studies) throughout life and maintain a stable, albeit lower, body weight than age-matched ad libitum controls. This regimen (generally termed moderate caloric restriction to contrast with studies of acute starvation) increases both mean and maximal life span (8–12), reduces the appearance of pathological lesions (10,13,14), decreases susceptibility to chemical toxicity, and increases DNA repair (15–19) and tissue protein synthetic activity (20–22). Although most of the aforementioned studies are well documented for rodent species, there are recent data that find comparable effects of caloric restriction in nonhuman primates (23–25). By comparing physiological adaptations in the caloric-restricted animal to the ad libitum-fed animal over the life span, this paradigm has been used to identify potential biological mechanisms of aging that could then be pursued in more rigorously controlled studies.

Our interest in pursuing the relationship between moderate caloric restriction and neuroendocrine changes with age was initially based on several lines of evidence: (a) with advancing age, there is an increase in catabolic processes, most notably a decline in cellular protein synthesis (26,27); (b) anabolic hormones such as growth hormone and insulin-like growth factor (IGF-1) decrease with age (28,29), and restoration of these hormones increases cellular protein synthesis in a number of tissues (30,31); (c) moderate caloric restriction increases protein synthesis in tissues, suggesting that catabolic events characteristic of aging are delayed or prevented by this regimen (20–22,32); and (d) growth hormone and IGF-1 are critical for the modulation of glucose homeostasis, and caloric restriction would be expected to induce physiological changes in these hormones to compensate for the reduction in caloric intake (33). From preliminary studies, it was evident that IGF-1 decreased approximately 40% in response to moderate caloric restriction in young animals, but the long-term consequences of dietary manipulation were unknown.

In this review, we present our results on the relationship between moderate caloric restriction and age-related changes in the growth hormone/IGF-1 axis and the neuroendocrine mechanisms that regulate these processes. Age-related changes in the growth hormone/IGF-1 axis are reviewed, and the effects of moderate caloric restriction on the regulation of this axis are presented. Finally, the potential effects of long-term moderate caloric restriction on the regulation of cerebrovascular density and cerebral blood flow are detailed, and its potential mediation by growth hormone and IGF-1 are discussed. From these data and recent publications demonstrating that IGF-1 is a potent mitogenic agent and a risk factor for several types of cancer, we conclude that growth hormone and IGF-1 have pleiotropic effects on aging and propose that neuroendocrine compensatory mechanisms induced by moderate caloric restriction mediate some of its beneficial effects.

The Growth Hormone/IGF-1 Axis and Age

General.—Pure bovine growth hormone was first isolated from the pituitary gland by Li and colleagues (34), and it was subsequently shown to stimulate fatty acid mobilization, amino acid uptake, DNA, RNA, and protein synthesis, and have a role in cell division and tissue hypertrophy. Subsequent studies revealed that growth hormone secretion from the pituitary occurred in discrete pulses that increase after the onset of sleep (35) and see review by Corpas et al. (36)). Although the precise function of this ultradian pattern remains unknown, the pulsatile nature of growth hormone release has been confirmed in every species examined to date and appears to be essential to optimize biological potency of the hormone. Growth hormone binds with high affinity to the growth hormone receptor, which is found in tissues throughout the body; activation of its receptor stimulates the synthesis and secretion of hepatic IGF-1, a small peptide (about 7.5 kD) structurally related to pro-insulin. IGF-1 circulates in the blood at high concentrations and stimulates DNA, RNA, and protein synthesis and is a potent mitogen for many tissues (37). Because of the wide tissue distribution of the growth hormone receptor, growth hormone may also have a role in regulating the synthesis and secretion of IGF-1 from many tissues, thereby directly influencing the paracrine activities of the hormone (38–40). Although it was initially proposed that all of the actions of growth hormone were mediated through IGF-1, several studies have provided relatively convincing data that growth hormone has direct effects on specific tissues, and/or interacts with IGF-1 produced in tissue (41,42); refer to Figure 1).

In humans, growth hormone is released in pulsatile bursts from the pituitary gland with the majority of secretion occurring at night in association with slow-wave sleep (35,43,44). Similar pulses are observed in rodents, except that high-amplitude secretory pulses occur every 3–5 h in males (45) and hourly in females. It was later discovered that the regulation of these pulses involved at least two hormones released by the hypothalamus: growth hormone-releasing hormone (GHRH), which increases growth hormone release (46,47) and somatostatin, which inhibits its release (48). The dynamic interactions between these hormones are responsible for high amplitude, pulsatile growth hormone secretion. It is generally believed that somatostatin tone is dominant during trough periods and that growth hormone is released in response to secretion of GHRH and suppression of somatostatin (49). Both growth hormone and IGF-1 inhibit growth hormone release in a typical feedback relationship either directly at the level of the pituitary or by stimulating somatostatin and/or inhibiting GHRH release (50).

Age-related changes in growth hormone and IGF-1.—Initial studies in elderly humans designed to investigate the relationship between growth hormone and physiological changes as-
associated with age reported a decline in the ability of individuals to secrete growth hormone in response to several stimuli, including insulin-induced hypoglycemia and arginine administration (51). Subsequent studies revealed a loss of the nocturnal surges of growth hormone (35,52) and a decrease in plasma IGF-1 that paralleled the decline in growth hormone pulses (53,54). These early studies in humans have been confirmed by numerous investigators [see review by Corpas et al. (36)]. It is now evident that the decline in high-amplitude growth hormone secretion and plasma IGF-1 concentrations is one of the most robust and best characterized endocrine events that occur with age (Figure 2).

Shortly after the documentation of decreases in growth hormone secretion in humans, studies confirmed that the amplitude of growth hormone pulses decreased with age in rodents (55) and that these changes were associated with a decline in plasma IGF-1 (56). These studies immediately progressed to an investigation of the mechanisms responsible for the decline in growth hormone secretion. Several studies in both humans and animals documented a decline in in vivo pituitary response to GHRH with age (57–59). However, over the next several years, numerous studies attempting to detail the deficits within the pituitary gland produced controversial results that ultimately were attributed to either differential responses of older animals to the pharmacological agents used to suppress endogenous growth hormone pulses during in vivo testing (60,61), or to technical limitations in culturing anterior pituitary cells from older animals (62).

Neuroendocrine regulation.—Research efforts were eventually directed to an analysis of hypothalamic releasing and inhibiting hormones after studies revealed that (a) acute administration of somatostatin antiserum in vivo increased growth hormone release identically in both young and old animals (63); (b) passive immunization with somatostatin antiserum restored the in vivo deficiency in pituitary response to GHRH (64); and (c) stimulation of hypothalamic slices of old animals in a superfusion system released greater amounts of somatostatin than in those of young animals (65). More recently, we have found increased somatostatin peptide concentrations in pituitary extracts from older animals, again suggesting increased release of this peptide from hypothalamic neurons (65). These results provided compelling evidence that increased somatostatin tone may be an important factor in the decline in growth hormone pulses with age. These conclusions were supported by research in humans, where administration of cholinergic agonists or arginine, considered to preferentially inhibit somatostatin release (66), was capable of increasing growth hormone secretion in older individuals (67).

Although the previously mentioned studies did not address the synthesis and release of GHRH, previous studies clearly indicated that a decline in this hormone is another contributing factor in the decrease in growth hormone secretion with age. In a series of experiments, investigators demonstrated that GHRH mRNA decreased with age (68), and that the feedback relationship between growth hormone and hypothalamic neurons is impaired (69). In the latter study, growth hormone increased somatostatin mRNA and decreased GHRH mRNA, but GHRH neurons were nonresponsive in older animals. Thus, the data suggest that decreases in growth hormone secretion with age result from deficiencies within the hypothalamus involving regulation of both GHRH and somatostatin.

Tissue responsiveness to growth hormone.—Although a decline in the amplitude of growth hormone pulses is an important determinant of the decline in plasma IGF-1, more recent studies demonstrate that growth hormone-induced IGF-1 secretion is diminished in elderly individuals and suggest that resistance to the action of growth hormone may be a secondary contributing factor in the low plasma IGF-1 concentrations (70). In

Figure 1. The growth hormone/IGF-1 axis. Growth hormone is secreted from the anterior pituitary gland under the regulation of hypothalamic GHRH and somatostatin. Growth hormone circulates in blood, stimulates the liver to produce IGF-1, and influences the local production of IGF-1 in target tissues. IGF-1 is responsible for the anabolic effects of growth hormone on muscle and many other target tissues. IGF-1 activity is also regulated by several binding proteins and tissue protease activity (not shown).

Figure 2. Age-related changes in plasma IGF-1 in C57/BL6 male mice. Plasma IGF-1 is elevated early in life (maximum levels at 12–15 years of age in humans and 25–60 days in rodents) and decreases substantially with increasing age. As a result, the percent decline in IGF-1 depends on the specific ages compared [adapted from Sonntag et al., 1992 (22)].
rodents, a twofold increase in growth hormone receptors has been observed with age, but this fails to compensate for the reduction in growth hormone secretion (71,72). A more detailed investigation revealed that the $K_d$ and apparent size of the growth hormone receptor were not altered, whereas the capacity of growth hormone to induce IGF-1 gene expression and secretion was $40\%$--$50\%$ less in old than in young animals. These results demonstrated that an impairment in growth hormone receptor signal transduction contributes to the decline in IGF-1 in both animals and humans.

The growth hormone receptor belongs to the cytokine family of receptors, and its activation facilitates the association of the receptor with JAK2 into a complex with subsequent phosphorylation of both proteins (73–76); see review by Roupa and Herington (77). Several other intracellular proteins are subsequently phosphorylated, including mitogen-activated protein kinase (MAP kinase), S6 kinase, and the STAT proteins (signal transducer and activator of transcription). The result of growth hormone receptor activation is an increase in c-fos, c-jun, serine phosphatase inhibitor-1, and IGF-1 gene expression (78). Although diminished signal transduction has been described for the insulin and IGF-1 receptors in aged animals (79,80), no study had addressed alterations in growth hormone receptor signal transduction with age. Studies by Xu and colleagues (72) reported that phosphorylation of JAK2 and the growth hormone receptor complex were suppressed in aged rodents in response to growth hormone, and that these decreases were accompanied by a decline in MAP kinase activity. More recent studies demonstrate that growth hormone-induced STAT3 activation and nuclear translocation are also decreased with age (81). Although these studies did not address the etiology of the decrease in JAK2 activity, they clearly indicated that diminished growth hormone receptor signal transduction is a contributing factor in the functional alterations in tissues with age.

Because the specific deficits in growth hormone signal transduction with age appear to be an early event in receptor signaling, we postulated that production of splice variants that are resistant to phosphorylation or a decrease in turnover of the growth hormone receptor, perhaps resulting from oxidative damage to the receptor molecule, contribute to the signaling deficit in old animals. However, recent data from our laboratory demonstrate that growth hormone receptor turnover in vivo increases with age, and there are no obvious changes in receptor mRNA structure analyzed by RT-PCR (Xu and Sonntag, unpublished data). Other mechanisms that potentially contribute to the decline in growth hormone receptor signaling with age include point mutations, post-translational modifications in receptor protein, and enhanced phosphotyrosine phosphatase activity. Although the specific mechanisms for the decline in growth hormone signal transduction are poorly understood, the deficiency in growth hormone signal transduction together with concomitant decreases in growth hormone secretion appear to be the major factors involved in the decline in plasma IGF-1 with age.

Moderate Caloric Restriction and the Growth Hormone/IGF-1 Axis

IGF-1.—Since protein synthesis is one of the intracellular processes regulated by IGF-1, the hypothesis that increases in protein synthesis observed in animals maintained under conditions of moderate caloric restriction were mediated by attenuating the age-related decline in plasma IGF-1 was assessed. Our initial studies demonstrated that caloric restriction decreased IGF-1 approximately $40\%$ in young animals and, with continued restriction, the age-related decline in IGF-1 was attenuated (82). However, contrary to our initial hypothesis, no differences in plasma IGF-1 levels were observed between old ad libitum-fed and restricted animals (Figure 3). These results clearly indicate that the increases in protein synthesis observed in caloric-restricted animals were not dependent on the concentrations of plasma IGF-1 alone, and that other mechanisms for the increase in protein synthesis in caloric-restricted animals (including type I IGF receptor density and insulin-like growth factor binding proteins [IGFBP] levels) need to be pursued.

Subsequent analysis of type I IGF receptor density in tissue revealed no consistent changes in ad libitum-fed animals with age, but in response to caloric restriction there was a $1.5$--$2.5$ fold increase in receptors in liver, heart, and skeletal muscle from caloric-restricted compared to ad libitum-fed animals. Because increases in receptor expression are generally associated with increases in tissue response, it was suggested that part of the mechanism for increased protein synthesis in response to moderate caloric restriction was related to enhanced tissue response to IGF-1 (83) or alterations in the regulation of paracrine (tissue) IGF activity.

IGF-1 paracrine activity at the tissue level is regulated by (a) the local production of IGF-1 (84–89), (b) concentrations of IGF receptors, and (c) the activity of binding proteins and specific proteases that degrade binding proteins releasing IGF-1 to interact with its receptor. In preliminary studies, we have found that caloric restriction prevented the age-related decline in tissue levels of IGF-1 analyzed after saline perfusion to remove plasma IGF-1 (Sonntag and colleagues, unpublished data). Unfortunately, few data are currently available on the levels of IGFBPs or protease activity in caloric-restricted animals.
Nevertheless, the results of studies to date are consistent with the hypothesis that there is a differential regulation of tissue and plasma IGF-I in response to caloric restriction (e.g., local expression of IGF-1 is maintained whereas plasma IGF-1 is substantially reduced). The specific consequences of the shift in the source of IGF-1 from the plasma to the tissue compartment are not immediately apparent. Certainly, it has been demonstrated that tissue maintenance and repair are facilitated by the paracrine expression of IGF-1 and, therefore, the paracrine expression of IGF-1 into old age may be an important factor contributing to the maintenance of normal tissue function in response to specific stimuli. Concurrently, the reduction in plasma IGF-1 may be sufficient to diminish a generalized mitogenic stimulus and thus influence the initiation and progression of age-related pathologies (refer to Pleiotropic Effects section).

Growth hormone.—As noted previously, the age-related reduction in plasma IGF-1 and cellular protein synthesis in ad libitum-fed animals results in part from a decrease in the levels of growth hormone secreted from the anterior pituitary gland (55,57). Because of the decline in IGF-1 in response to moderate caloric restriction observed in previous studies and the close association of IGF-1 with growth hormone concentrations (90), the secretory dynamics of growth hormone in animals maintained under conditions of caloric restriction were not assessed in our initial studies. However, our results demonstrating an increase in protein synthesis in caloric-restricted animals coupled with increases in the number of tissue type 1 IGF receptors suggested that alterations in growth hormone secretion and the actions of growth hormone directly on paracrine IGF-1 potentially could be an important mediating factor in the effects of moderate caloric restriction. Consistent with previously reported studies, it was found that the amplitude of growth hormone secretory pulses decreased with age in ad libitum-fed animals and, as expected, the short-term consequence of caloric restriction in young animals was a decline in the amplitude of growth hormone pulses (Figure 4).

Nevertheless, in older caloric-restricted animals, growth hormone pulses were similar to those in young, ad libitum-fed animals. The rise in plasma levels of growth hormone in old caloric-restricted animals was unexpected, but both the number of growth hormone pulses detected and the mean growth hormone concentrations increased substantially. From these studies, we concluded that after a period of adaptation to caloric restriction, animals exhibit increases in high-amplitude growth hormone secretion that are maintained into old age. Because plasma concentrations of IGF-I were diminished in the presence of increased tissue protein synthesis in these animals, the studies again suggested the possibility that increased amounts of circulating growth hormone may act directly at the tissue level to maintain paracrine IGF-I activity. In either case, the studies demonstrated that increased growth hormone secretory dynamics are associated with longevity and may be part of the mechanisms that enable these animals to maintain tissue function into old age.

Neuroendocrine regulation.—The aforementioned effects of caloric restriction on growth hormone secretory dynamics led us to use these animals as a model to assess potential neuroendocrine mechanisms for the decline in growth hormone with age. In ad libitum-fed old animals, there was substantial evidence for increased somatostatin secretion, but further analysis indicated a reduction in somatostatin mRNA in the hypothalamus of several strains of rats (91,92). These results raised an important question regarding the mechanisms for the increase in somatostatin secretion. To be translated into protein, mRNA must attach to polysomes, and several lines of evidence suggested that this process can be regulated by specific intracellular proteins. In subsequent studies, we observed an increase in somatostatin mRNA precipitating with the polysomal fraction and an increase in the ratio of polysomal/total somatostatin mRNA. The changes in somatostatin mRNA initially occur during mid-age, when growth hormone pulse amplitude decreases. Compared to the ad libitum-fed condition, the moder-

![Figure 4. Examples of growth hormone secretory dynamics in young ad libitum-fed (left), old ad libitum-fed (center), and old moderate caloric restricted (right) Brown Norway rats. Blood samples were taken at 20-minute intervals from 0920 to 1640 h. Data indicate a significant reduction in growth hormone pulse amplitude with age that is ameliorated by moderate caloric restriction [from Sonntag et al., 1995 (92)].](https://academic.oup.com/biomedgerontology/article-abstract/54/12/B521/605623)
ate caloric-restricted animals did not demonstrate a decline in total somatostatin mRNA levels; when the fraction of somatostatin bound to the polysome was calculated, no age-related increase was apparent. The results of our studies again support the conclusion that factors that regulate somatostatin gene expression have an important role in the regulation of growth hormone secretion in aging animals. Furthermore, increased association of somatostatin mRNA with the polyribosomal fraction was closely related to a decline in growth hormone secretion in ad libitum-fed animals; caloric restriction, by delaying age-related changes in the translational regulation of somatostatin mRNA, appeared to maintain normal growth hormone secretory patterns (Figure 5).

The regulation of growth hormone secretion is an excellent example of a complex neuroendocrine feedback mechanism compromised during normal aging. In young animals, in response to decreases in plasma growth hormone and IGF-I, total somatostatin mRNA and peptide secretion decrease and GHRH increases, resulting in the restoration of normal growth hormone levels (50,93-95). The decrease in somatostatin mRNA in old ad libitum-fed animals in the presence of diminished growth hormone and IGF-1 concentrations is consistent with the hypothesis that hypothalamic neurons from old animals are capable of detecting the low levels of growth hormone and attempt to compensate by inhibiting somatostatin transcription (resulting in the decrease in total somatostatin mRNA). However, our previous studies on the regulation of growth hormone release in aged animals suggested that diminished transcription of somatostatin alone is insufficient to inhibit the synthesis and release of the peptide; therefore, other mechanisms must be considered. These data led us to conclude that intracellular factors regulate the association of somatostatin mRNA with polysomes, and that altered regulation of these processes with age results in increased synthesis of somatostatin. Although our studies were not designed to address the specific molecular mechanisms for the increased translational efficiency with age, several possibilities exist: (a) there may be increased synthesis and degradation of somatostatin mRNA with nascent mRNA favored for translation; (b) aging animals may exhibit diminished levels or activity of proteins or factors that normally inhibit mRNA association with polysomes; and/or (c) there may be increases in cytosolic facilitory factors that regulate association of somatostatin mRNA with polysomes. In recent studies, several investigators have identified both cis and trans acting regulatory elements in the 5’ untranslated region of ferritin as well as other mRNAs that are important for the translational regulation of gene expression (96-105). These factors appear to facilitate or inhibit ferritin mRNA association with polyribosomes, thus serving as an important regulatory site for the synthesis of protein. Although there is no information currently available on regulation of translational efficiency in neuroendocrine systems, preliminary analysis of total and polyosome-associated somatostatin mRNA in response to hypophysectomy or CNS active drugs (Sonntag and colleagues, unpublished observations) suggests that translational regulation of somatostatin mRNA may be an important component of somatostatin synthesis and subsequently growth hormone secretion in adult animals.

![Figure 5. Polyribsome-associated (left), total (center), and polysomal/total (right) somatostatin RNA in ad libitum-fed (Δ) and moderate caloric restricted (●) aging rats. The hypothalamus was dissected from each animal, homogenized in buffer, and aliquots separated for analysis of total and polyosome-associated somatostatin mRNA. Results indicated a decline in total somatostatin mRNA and an increase in polyosomal mRNA in 25-month as compared to 6-month-old ad libitum-fed animals (p < .05). Data for polysomal/total were calculated after correction to mRNA concentrations/tissue and are expressed as a percentage. A substantial increase in polyosomal/total somatostatin mRNA was observed in 25-month as compared to 6- or 16-month-old ad libitum-fed animals (p < .05). The differences in somatostatin mRNA were not observed in moderate caloric restricted animals. Data represent means ± SEM for 10 animals/group (from Sonntag et al., 1995 (92)).](https://academic.oup.com/biomedgerontology/article-abstract/54/12/B521/605623)
**Growth hormone signal transduction.**—Because of our interest in the signal transduction properties of growth hormone in older animals, we also assessed the effects of caloric restriction on JAK2 and growth hormone receptor phosphorylation induced by growth hormone (Figure 6). Our results indicated that moderate caloric restriction restored the deficient JAK2 and growth hormone receptor phosphorylation, MAP kinase activity, IGF-1 mRNA levels, and IGF-1 secretion in vitro in response to growth hormone (106). These studies did not address the specific mechanisms responsible for the beneficial effects of caloric restriction, but rather provided the first demonstration that growth hormone signal transduction could be improved by this regimen. These results raise the possibility that moderate caloric restriction acts not only by increasing growth hormone pulse amplitude, but also improves growth hormone signal transduction resulting in enhanced growth hormone regulation of IGF-1 paracrine activity.

**Short-term caloric restriction of old animals.**—Although previous studies demonstrated that caloric restriction beginning at 4 months of age could prevent the age-related decline in growth hormone pulse amplitude, the effects of short-term moderate caloric restriction of aging animals remained unknown. Our rationale for these studies was to assess whether the age-related decrease in growth hormone secretion was the result of permanent alterations in the function of hypothalamic neurons. We therefore analyzed growth hormone secretory dynamics in older animals that were initiated to the caloric restriction regimen at 26 months of age and had demonstrated a reduction in both growth hormone and IGF-1 levels and a decrease in insulin sensitivity. In response to 3 months of moderate caloric restriction, body weight in these animals decreased by 30%. Concurrently, growth hormone secretory dynamics increased to levels indistinguishable from young animals, whereas no increase in plasma levels of IGF-1 was observed (Figure 7). Similar improvements were found for insulin sensitivity (Table 1). Older ad libitum-fed animals exhibited increased insulin levels compared to young animals during a glucose tolerance test, whereas old animals maintained for 3 months under conditions of moderate caloric restriction demonstrated marked improvements in insulin levels and demonstrated increased insulin sensitivity. These studies demonstrated that (a) hypothalamic centers that regulate growth hormone secretion are not permanently impaired in old ad libitum-fed animals, and (b) age-related impairments in insulin sensitivity can be reversed by caloric restriction. Although several possibilities exist (including decreases in oxidative stress), one potential interpretation of these findings is that the reduction in adipose tissue mass decreases the secretion of factors that actively suppress growth hormone and insulin sensitivity. Cytokines such as tumor necrosis factor-α (TNF-α), for example, have been shown to suppress both growth hormone signal transduction (107) and insulin sensitivity (108–112) in young animals. With increasing age, we have evidence that TNFα secretion is increased (Xu and colleagues, unpublished data) and, if such factors can be shown to directly regulate the secretion of growth hormone, important insight into one of the actions of moderate caloric restriction would be attained (e.g., the reduction in adipose tissue and the corresponding reduction in secretory products from this tissue remove the inhibition of growth hormone levels and hormone signal transduction).

**Growth Hormone and IGF-1 as Mediators of the Age-Related Decline in Tissue Function**

**General.**—Limited studies in rodents over a decade ago revealed that administration of growth hormone increases IGF-1 and restores tissue protein synthesis in old animals to levels normally found in young animals (22,57), suggesting that the age-related decline in skeletal muscle mass and function was not solely related to intrinsic deficits within the tissue. Other reports were published demonstrating that growth hormone or IGF-1 administration could partially reverse the decline in immune function (113,114), increase the expression of aortic elastin (115), and increase life span in rodents (114). The results from these studies were the first to indicate that the decrease in the concentration of growth hormone has clinical significance and may be responsible for the generalized catabolic state that accompanies normal aging.

A number of investigators recognized the potential significance of decreases in growth hormone and have studied the effects of replacement therapy to older adults (116–118). Although the specific populations under study were quite varied, it has generally been reported that administration of growth hormone increases IGF-1, lean body mass, muscle mass, and skin thickness and reduces total body fat content in elderly humans. In addition, there are some reports of elevations in serum osteocalcin (an osteoblast-produced marker of bone formation), urinary hydroxyproline (a marker for bone resorption), and nitrogen retention (a marker of protein synthesis), raising the possibility that growth hormone treatment may delay osteoporosis. Interestingly, aerobic exercise training by elderly adults for 1 year increases the amount of growth hormone secreted over a
Figure 7. Example of growth hormone secretory dynamics in young ad libitum-fed (left), old ad libitum-fed (center), and old short-term moderate caloric restricted (right) Brown Norway rats (n = 6/group) initiated to caloric restriction at 26 months of age for 3 months. Blood samples were taken at 20-minute intervals from 0920 to 1640 h and growth hormone was analyzed as described by Sonntag et al. (92). Data indicate a significant reduction in growth hormone pulse amplitude with age that is ameliorated by short-term moderate caloric restriction [from Sonntag et al., 1996 (214)].

Table 1. Effects of Short-Term Caloric Restriction on Glucose Tolerance

<table>
<thead>
<tr>
<th>Glucose Sum</th>
<th>Insulin Sum</th>
<th>Insulin Response</th>
<th>Insulin Peak</th>
<th>Insulin Fasting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young ad libitum</td>
<td>1340.00 ± 144.82</td>
<td>275.03 ± 27.68</td>
<td>119.26 ± 9.26</td>
<td>70.13 ± 6.76</td>
</tr>
<tr>
<td>Old ad libitum</td>
<td>1194.25 ± 92.58</td>
<td>372.00 ± 26.15</td>
<td>145.00 ± 9.65</td>
<td>84.05 ± 6.09</td>
</tr>
<tr>
<td>Old restricted</td>
<td>1269.57 ± 89.10</td>
<td>232.60 ± 20.07*</td>
<td>114.51 ± 19.87</td>
<td>67.63 ± 5.83*</td>
</tr>
</tbody>
</table>

Notes: Blood samples were taken from 6 mo and 28 mo (ad libitum and moderate caloric restricted) Fischer 344×BN (F1) males at -2 and 5, 10, 15, 20, 30, and 40 minutes after infusion of 0.5 g/kg dextrose. Measurements for glucose sum are in milligrams per deciliter (mg/dl). Measurements for insulin are in microunits per milliliter (µU/mL).

*p < .05 compared to old ad libitum-fed animals.

Cerebrovasculature and aging.—Previous studies indicate that cerebral blood flow and capillary density decrease with age in rodents, nonhuman primates, and humans and have the potential to be important contributing factors in brain aging (120–126). Although the etiology of the decrease in cerebral blood flow has not been determined, the decline did not appear to be related to alterations in mean arterial pressure, as pressure remains constant or increases with age. However, increases in vascular resistance due to an age-related increase in arteriolar vessel segment length between branches has been reported (127). Hutchins and colleagues (128,129) demonstrated a decline in the total number of arterioles between the ages of 3 and 30 weeks in skeletal muscle, suggesting that a reduction in arteriolar density contributes to the decrease in blood flow. Because an age-related decline in arteriolar density (or an increase in vessel segment length) has the potential to decrease perfusion pressure and tissue blood flow, we hypothesized that the decline in cerebral blood flow observed in aged animals may be related to a decline in arteriolar density. This hypothesis has been supported by our recent data demonstrating that an age-related decrease of arteries, arteriolar-to-arteriolar anastomoses, and venules occurs on the surface of the brain in rodents (Figures 8, 9). In each case, we observed a decrease between 20% and 50% when young (4–6 months old) and old (25–32 months old) animals were compared. Because vasculature on the surface of the brain has been demonstrated to be generally representative of vasculature in other brain regions (130), we concluded that the decline in blood flow with age resulted from a decrease in the number of microvessels supplying blood to the brain.

The maintenance of arteriolar density is a complex process involving a number of growth factors. We and others have proposed that both growth hormone and IGF-1 have an important regulatory role in blood vessel growth and repair (89,131–133). For example, blood vessels have receptors for growth hormone and IGF-1, and several studies indicate that immunoreactive IGF-1 within vessels increases during periods of vessel growth and repair (134,135). Furthermore, IGF-1 has been shown to potentiate the actions of several vascular growth factors (136). Although it is well known that both plasma growth hormone and IGF-1 decrease and contribute to the decline in protein synthesis and vascular compliance that occurs in aged animals (56,82,115,116), the role of these hormones in the age-related...
decrease in vascular density had not been assessed. Because the decrease in cerebral blood flow appears to be an important factor in brain aging, the regulation of vascular density by these anabolic hormones has the potential to have therapeutic importance for both vascular repair and brain function.

Both growth hormone and IGF-I have been reported to stimulate endothelial cell proliferation, tube formation, and angiogenesis in a number of tissues. Growth hormone, for example, has been shown to stimulate angiogenesis in choioallantoic membranes of the chick embryo (133), whereas IGF-I has been reported to stimulate the growth of endothelial cells in the retina (137) and the proliferation of omental microvessel endothelial cells (136). Similarly, IGF-I increases angiogenesis and migration of endothelial cells in both rat aorta rings and bovine carotid artery cells. Tube formation of carotid artery cells also has been reported in response to IGF-I (138,139). In addition to the apparent ability of IGF-I to stimulate vascular growth independent of age-related decline in vascular density.

In our recent studies, the effects of growth hormone on vascular changes within the aging brain were assessed by administration of growth hormone to old animals for 30 days. As expected, vehicle-treated young and old animals exhibited no changes in vascular density during this period. However, a substantial increase in vascular growth in older animals treated with growth hormone was observed (Figure 10). Although the vascular growth observed in these animals represented only small arterioles, and a complete restoration of vascular density was not evident, the results provide compelling evidence that growth hormone (and/or IGF-I) participate in the regulation of vascular growth and contribute to the age-related decline in vascular density.

Obviously, vasculature has a crucial role in nutrient and metabolic exchange with tissues. However, several laboratories have reported the presence of specific growth factors that are produced in the peripheral vasculature, suggesting that the vasculature exerts a trophic influence on surrounding tissues. (89,140,141). In our own studies, we have observed that the microvasculature throughout the brain is a major site of IGF-I production (Figure 11). With age, total IGF-I concentrations in brain decrease by 30%-40% and, because of the high concentrations of IGF-I in the microvessels, we have proposed that the reduction in vessel density is one of the factors that contribute to the decline in brain IGF-I levels. The production of these growth factors by the vasculature may have important implications for the regulation of brain function during aging. Because of the important interrelationships between brain function and cerebrovasculature and the presence of IGF-I as a potential mediator in both neuronal and vascular function, detailed analysis of the mechanisms responsible for the age-related decline in vascular function merits further investigation.

Moderate caloric restriction and microvasculature.—Comparison of vascular density on the surface of the brain between ad libitum and moderate caloric-restricted animals revealed that the age-related decline in vascular density was almost completely ameliorated by moderate caloric restriction. The effects of chronic caloric restriction were also evident on local cerebral blood flow. Using [14C]iodoantipyrine, analysis indicated an age-related decrease in blood flow in most areas of cortex and hippocampus (approximately 30%), and this decrease was partially prevented by moderate caloric restriction. Preliminary data also suggested that moderate caloric restriction prevented the age-related decline in brain IGF-I levels. Although the specific consequences of maintenance of vascular density into old age are unclear, we suspect that the increase in vascular density results in a rise in regional blood flow and vascular-derived IGF-I that has the potential to have trophic effects on the brain.

The vascular effects of moderate caloric restriction were also evident when older animals were fed 60% of the ad libitum diet for 30 days (Figure 12). During this period, there was a growth of small arterioles that was similar to that observed in response...
Figure 9. Summary of arteriolar (left), arteriole-to-arteriole anastomotic (center), and venular endpoint (right) density in male Brown Norway rats. Data represent mean ± SEM for 18 young, 14 middle-aged, and 13 old animals. Results indicate that arteriolar and arteriolar-arteriolar anastomotic density decreases with age ($p < .05$) [from Sonntag et al., 1997 (210)].

Figure 10. Effects of bovine growth hormone (25 µg/kg, twice daily) or vehicle administration for 35 days on changes in arteriolar density in 30-month-old Fischer 344 × Brown Norway rats. Data are expressed as the percent increase in arteriolar density from baseline and represent mean ± SEM of 10 (growth hormone-treated) and 7 (saline-treated) animals/group. No vascular growth was observed in 8- or 30-month-old saline-treated animals [from Sonntag et al., 1997 (210)]. *$p < .01$.

Suggest that some of the effects of caloric restriction may be mediated by growth hormone. Although this relationship is correlation at the present time, further studies to assess the relationship between these factors are clearly warranted.

CNS function.—Although data on growth hormone’s direct action on neuronal function are extremely limited, many investigators have provided convincing evidence that IGF-1 and IGF-2 have an important role in this regard (86,88,142). IGFs have been reported to stabilize tubulin mRNA (143), stimulate DNA and RNA synthesis (142,144–146), stimulate neurite formation (147–149), enhance oligodendrocyte proliferation (150–153), increase survival of neurons and glia in culture (154), increase neuromuscular synaptogenesis (155), and have an important role in neuronal repair (156). More recent evidence suggests that IGF-1 participates in the regulation of calcium and increases the expression of the proto-oncogene c-fos (157,158). Although there is a large volume of data supporting a role for IGF-1 in brain function, there are few in vivo studies of the actions of IGF-1, in part, because of the lack of appropriate models to manipulate IGF-1 levels.

While growth hormone and plasma IGF-1 appear to have a role in brain function [see review by Hepler and Lund (159)], the sources of IGF-1 that influence the brain are less clear. The majority of evidence suggests that growth hormone does not cross the blood-brain barrier although it is known that hypophysectomy (which decreases both growth hormone and plasma IGF-1) decreases IGF-1 mRNA in brain, and concentrations can be restored by growth hormone administration (160). In addition, recently published studies suggest that administration of growth hormone raises brain concentrations of IGF-1 (161), and peripheral injections of IGF-1 have been shown to protect neurons from cell death after ischemic injury (162). Evidence
PLEIOTROPIC EFFECTS OF GH AND IGF-1

Supports the conclusion that plasma IGF-1 is actively transported through the blood brain barrier (163), but the specific mechanism for this process is poorly understood. Because IGF-1 is also produced in endothelial and smooth muscle cells (87,89,140), the possibility exists that both plasma IGF-1 and vascular-derived IGF-1 (possibly under the regulation of growth hormone and/or IGF-1) are important sources of IGF-1 in the brain.

As a large body of evidence supports the conclusion that IGF-1 is an important neurotrophic factor that decreases with age, we undertook studies to assess the effects of intracerebroventricular IGF-1 replacement on learning and memory as well as several biochemical measures linked to cognitive ability. Our studies revealed that administration of icv IGF-1 for 28 days to old animals increased both working and reference memory using the Morris water maze (Figure 13; (164)). In addition, preventing the age-related decline in growth hormone pulse amplitude and plasma IGF-1 by daily injections of [D-Ala²]GHRH for 18 months prevented the age-related decline in reference memory. In fact, performance of old [D-Ala²]GHRH animals on the reference memory task was indistinguishable from young animals. Although the specific mechanisms for the improved performance in response to these anabolic hormones are still under investigation, we have found that aged animals exhibit a decrease in specific subtypes of the NMDA receptor (NMDA R2a-c), and that IGF-1 reverses these age-related deficits (165). Similarly, IGF-1 appears to reverse the age-related decrement in D²-induced receptor activity that is evident in older animals (166). Because both NMDA and dopamine receptors have been strongly implicated in the process of memory acquisition (167-171), it is tempting to speculate that the behavioral improvement noted in response to IGF-1 is based, in part, through effects on these neurotransmitter systems.

The effects of moderate caloric restriction on brain levels of IGF-1, cerebrovascular density, and blood flow led us to compare reference memory between caloric-restricted and ad libitum-fed aged animals. We observed that moderate caloric restriction prevented the age-related decline in reference memory, which is in close agreement with several other studies indicating that this regimen prevents the age-related decline in sensorimotor function and cognitive ability in mice(172, 173). Although the studies conducted to date do not allow us to draw definitive conclusions, the importance of cerebral blood flow and the trophic actions of vascular-derived IGF-1 lead us to speculate that modest deficiencies in blood flow to the aging brain resulting from a rarefaction of vasculature may contribute to the reduction in neurological function and possibly age-related pathologies (refer to Figure 14 for a general summary of the effects of age on the growth hormone/IGF-1 axis).

### Pleiotropic Effects of Growth Hormone/IGF-1

**General.**—As previously noted, the increase in growth hormone in moderate caloric-restricted animals provides access to the energy source of free fatty acids stored in adipose tissue. Growth hormone and other hormones including cortisol and circulating catecholamines stimulate hormone sensitive lipase and increase the availability of nutrients for tissues—representing an important physiological adaption to moderate caloric restriction. Similarly, the decline in anabolic hormones such as...
IGF-1 is adaptive in that cellular growth is minimized while limited nutrients are targeted for essential cellular functions, including tissue maintenance and repair. Thus, the condition of moderate caloric restriction produces unique alterations in the endocrine system—not only in the regulation of growth hormone and IGF-1, but also in the regulation of cortisol, insulin, catecholamines, and numerous other factors that regulate homeostasis (174).

**Growth hormone/IGF-1 and the physiological manifestations of aging.**—Research over the past 15 years has clearly demonstrated that administration of growth hormone and/or IGF-1 reverses many of the physiological changes in tissue function, and we have proposed that the aging phenotype results, in part, from chronic, multiple hormone deficiencies. Although the concept of aging as hormone deficiency has not been readily accepted, the capacity of estrogen replacement to ameliorate the age-related increase in cardiovascular disease, the decrease in bone mass, and most recently the decreases in cognitive function in women clearly suggests that hormone deficiency is an important contributing factor in many age-related processes. The ability of growth hormone to increase intracellular protein synthesis, cognitive function, skin thickness, bone mass, immune function, and vascular density in older animals and humans again provides compelling evidence that the decline in these hormones has important physiological consequences for the development of the aging phenotype. As intriguing as the possibilities are, however, the long-term beneficial effects of replacement therapy have been questioned because increases in anabolic hormones have the potential to increase the risk of pathology and therefore may decrease, rather than increase, life span.
Growth hormone/IGF-1, tissue pathology and life span.—

An excellent example of anabolic hormones increasing risk of pathology is recent studies that have provided a link between the incidence of a number of cancers and the expression of IGF-1. Using in vitro models, it has been recognized for some time that IGF-1 is a potent mitogenic factor that increases the transition from G1 to S phase in the cell cycle. In cell culture, serum supplementation is generally necessary for cell survival. Serum contains high quantities of IGF-1, and antibodies against IGF-1 are able to inhibit the ability of 5% serum to stimulate DNA synthesis in Balb/c-3T3 cells (175). In addition, Balb/c-3T3 cells transfected with IGF-1 and the type 1 IGF receptor grow in serum-free media (176), and antagonists to the IGF receptor inhibit cellular growth (177). It also appears that other growth factors, including platelet derived growth factor (PDGF) and epidermal growth factor (EGF), increase cellular IGF-1 synthesis, and it has been proposed that their effects may be mediated in whole, or in part, through the IGF-1 system.

Similar stimulatory effects of IGF-1 on cellular growth have been reported in vivo. Numerous human cancers and transformed cell lines produce IGF-1 or its receptor [see review by Werner and LeRoith (178)], and overexpression of the type 1 IGF receptor in 3T3 fibroblasts leads to the formation of tumors in nude mice (179). As expected, passive immunization with antibodies against the type 1 IGF receptor inhibits the proliferation of numerous cell types and cancers (180–188). As expected, transgenic rodents expressing high levels of human growth hormone and subsequently plasma IGF-1 exhibited an increase in mammary tumors; however, degenerative changes that appear to resemble aging were also apparent (189). In humans, elevated IGF-1 levels have been demonstrated to be a risk factor in breast cancer (190–193), lung cancer (194–197), and prostate cancer (198). These studies demonstrate an important link between plasma IGF-1 and the appearance of tissue pathologies and raise the possibility that a reduction in IGF-1 or IGF-1 activity may induce a selective advantage by delaying or preventing age-related pathologies.

It is interesting to note that the substantial decrease in IGF-1 observed in caloric-restricted animals early in the life span is associated with a decline in the number of pathologies compared to ad libitum-fed animals. Comparison of pathological changes in various cohorts appears to indicate that the beneficial effects of caloric restriction are detectable early in the life span (14). Additionally, one of the strongest predictors of life span is body weight at 10 months of age, which is known to be highly dependent on circulating levels of IGF-1. Although more research will be required to establish a link between the decline in IGF-1 and decreased pathological risk in moderate caloric-restricted animals, the implication of these results is that early exposure to high concentrations of IGF-1 or a cumulative exposure to IGF-1 during the early phase of life initiates pathological changes in tissues that are manifest at later ages (Figure 15). The potential of IGF-1 as a risk factor for a number of age-related pathologies raises the question as to whether IGF-1 has a role in determining life span of the organism. However, studies designed to assess this relationship are difficult to interpret in part because of the close relationship between growth hormone and IGF-1 and inherent difficulties with all of the models. For example, studies in mice suggest that immune function and life span could be improved by administration of low doses of growth hormone that result in mildly elevated IGF-1 levels (199). However, subsequent studies by Kaluz and colleagues (200) using several strains of mice and rats suggested that administration of physiological doses of human growth hormone to animals beginning at 17 months of age (resulting in a modest increase in plasma IGF-1) did not result in a general increase in life span. At the same time, they did not observe an increase in the number of pathologies or a shortening of life span. Both of these studies used human growth hormone in rodent models that is known to exhibit both somatomatogenic and prolactogenic properties (201–204). In our own laboratory, we have observed that chronic injections of [D-Ala6]GHRH to increase endogenous levels of growth hormone in rodents have little effect on life span or age-related pathologies (205). In another study, which used transgenic animals producing aphysiological hormone levels, it has been suggested that high concentrations of growth hormone and IGF-1 shorten life span in a dose-dependent manner (189). In addition, low levels of growth hormone and IGF-1 (as seen in dwarf mice) are associated with increased life span. The latter results are somewhat limited in that the dwarf mice used in the study were deficient in several hormones including growth hormone, prolactin, and thyroid-stimulating hormone (206,207). Nevertheless, these studies are consistent with previous results indicating that high levels of IGF-1 are a contributing factor in age-related pathologies, and they raise the important issue related to interactions of body size with life span (possibly independent of the contribution of growth hormone and IGF-1). Obviously, further research is necessary to resolve the specific role of these hormones in the onset of age-related pathologies and life span. Future studies will require the development of transgenic models that isolate the actions of each hormone and use concentrations that are physiologically relevant for aging studies.
Conclusion

There is a large body of evidence that alterations in the regulation of the growth hormone/IGF-1 axis have significant effects on age-related alterations in physiological function, pathology, and eventually life span. With age, both growth hormone and IGF-1 decrease and administration of these hormones ameliorates the effects of aging on numerous tissues including the central nervous system (reversing the age-related decline in cerebrovascular density and cognitive function). In response to moderate caloric restriction, important endocrine compensatory mechanisms are invoked that represent an important adaptive process to maintain blood levels of glucose. These adaptations include an increase in growth hormone pulse amplitude, a decline in plasma levels of IGF-1, and possibly a shift to increase the paracrine activity of IGF-1. These alterations in the growth hormone/IGF-1 axis can be induced in young or old animals and appear to have important physiological effects on tissue at any age.

Although the age-related decreases in growth hormone and IGF-1 contribute to the aging phenotype, IGF-1 is also linked to a number of pathologies and appears to be an important risk factor for breast, lung, and prostate cancer. The relationship between IGF-1 and tissue pathology has led us to speculate that the decrease in plasma IGF-1 in response to moderate caloric restriction minimizes the mitogenic stimulus to tissues and contributes to the reduction in age-related pathologies and increased life span observed in this model. Because IGF-1 has also been demonstrated to be an important trophic factor for tissue maintenance and repair, the rise in growth hormone, which may drive paracrine IGF-1 activity, may be equally important. On the contrary, studies indicating that cellular replicative potential is reduced in transgenic mice overexpressing growth hormone and IGF-1 (212) and that moderate caloric restriction increases replicative potential (213) provide additional associations between the effects of IGF-1 and biological aging. At the present time, it is unknown whether high levels of IGF-1 during specific periods in the life span or throughout life contribute to the induction of age-related pathologies and the regulation of cellular replicative potential.

The plethora of effects induced by moderate caloric restriction suggests that other endocrine and nonendocrine systems may also contribute to the beneficial effects of this regimen on age-related pathologies and life span. Alterations in plasma levels of cortisol, catecholamines, and insulin, as well as other peptide hormones including leptin and neuropeptide Y, may be critical in mediating the response of these animals to fasting and thus potentially have a role in the effects of moderate caloric restriction. Similarly, the decline in blood levels of glucose and the reduction in oxidative stress have been demonstrated in response to caloric restriction of a number of species and may provide independent or overlapping mechanisms that contribute to the health of these animals. Nevertheless, compensatory changes in the endocrine and neuroendocrine systems appear to have a key role in the processes of moderate caloric restriction and underscore the significance of age-related changes in the neuroendocrine system.

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