Human Ageing and the Growth Hormone/Insulin-Like Growth Factor-I (GH/IGF-I) Axis - The Impact of Growth Factors on Dementia§

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Abstract: There is clear evidence that human ageing is associated with reduced activity of the growth hormone (GH)/insulin-growth factor-I (IGF-I) axis, the so called “somatopause”. Although this condition is likely to contribute to age-related changes in body composition, structure functions and metabolism, we are now in face of the paradox of lifelong GH/IGF-I deficiency or resistance resulting in prolonged life expectancy. This evidence questions whether GH deficiency is or is not a beneficial adaptation to ageing. On the other hand, neuroendocrine studies provided evidence that brain ageing is associated to peculiar age-related alterations in the control of GH/IGF-I axis, mostly including GHRH deficiency and SS hyperactivity, reflecting the age-related cholinergic impairment. This hormonal pattern is present in normal and demented elderly subjects, and a neuroendocrine distinction among these conditions is impossible. This review will focus on the age-related decline in the activity of GH/IGF-I axis as a function of either normal or pathological brain ageing. Particularly, the influence of GH/IGF-I axis on cognitive functions and related disorders will be discussed.

Keywords: GH, IGF-I, ghrelin, ageing, dementia.

INTRODUCTION

There is clear evidence that human ageing is associated with diminished activity of the growth hormone (GH)/insulin-growth factor-I (IGF-I) axis that is probably the most impressive example of decreased hormonal activity as function of age-related changes in the neural control of endocrine functions [1-5].

Although mechanisms underlying the age-related decrease of GH release include peripheral influences, age-related changes in hypothalamic neuropeptides and neurotransmitters leading to growth hormone-releasing hormone (GHRH) hypoactivity and absolute or relative somatostatin (SS) hyperactivity seem to play a major role; they, in turn, are likely to reflect age-dependent changes in supra-hypothalamic functions [1-5]. The well known cholinergic impairment in the ageing brain involves hypothalamic pathways and contributes to the disrupted GHRH/SS interplay, leading to a decreased function of the GH/IGF-I axis in normal as well as in demented elderly subjects [6-9]. Also age-related variations in the ghrelin system, a gastric hormone discovered as a strong natural GH Secretagogue (GHS) and acting within the central nervous system (CNS), including the hypothalamus, could play a role in the decreased GH secretion that connotes ageing [10-13].

It is well known that ageing is associated with several abnormalities in body composition, metabolic and psychological functions, involving reduced lean mass, increased adiposity, decreased bone mass and protein synthesis, cognitive and affective disorders [1] and it is impressive how these alterations are similar to those in young adults with GH deficiency (GHD) [14-16]. This evidence, together with the demonstration of the age-related declining activity of the GH/IGF-I axis, led to coin the neologism “somatopause”, that indicates a potential link between the age-related decline in GH and IGF-I levels and “frailty” in ageing. The following hypothesis was that it would be possible to counteract the age-related changes in body composition and metabolism by restoring GH and IGF-I levels to young levels, similarly to what happens in young GHD patients [15-17]. On the other hand, GH and IGF-I also play remarkable actions in the CNS, affecting cognitive function and exerting neurotrophic, neuroprotective and metabolic effects [18-24]; thus it was hypothesized that GH and/or IGF-I could positively affect also age-related CNS impairment.

As the age-related decline in the function of GH/IGF-I axis is reflecting central alterations, somatotroph function in ageing could be more appropriately restored by GHRH and/or ghrelin-mimetics [25-31]; these molecules, in turn, possess pleiotropic actions including central activities and this evidence added further complexity and opportunities of research.

This review will focus on the age-related changes in the activity of GH/IGF-I axis as function of either normal or...
pathological brain ageing. Moreover, the influence of GH/IGF-I axis on cognitive functions and related CNS disorders will also be considered. Given the well known positive influence of GH/IGF-I on body composition, structure functions and metabolism, potential clinical implications will also be discussed taking into account evidence showing that a certain deficiency in GH/IGF-I has been demonstrated associated to prolonged lifespan.

AGE-RELATED CHANGES IN ACTIVITY OF GH/IGF-I AXIS: FOCUS ON NORMAL AGEING (FIG. 1)

In both animals and humans GH secretion undergoes clear age-related variations that are generally mirrored by IGF-I levels, the best marker of GH status [1,3-5]. Spontaneous GH secretion is high in newborns, then decreases in childhood and maintains constant levels up to the onset of puberty, when it is clearly enhanced, particularly in term of pulse amplitude [3-5]. Mean 24 h GH secretion then declines from puberty to adulthood, persisting more marked in women than in men [32,33]. A further progressive fall in 24 h GH secretory rates occurs with ageing (approximately 14% per decade); this is due to decline in both day- and night-time GH secretory burst number and amplitude, particularly in women, so that in ageing no gender-related difference is present [32,33]. The reduced GH levels observed in ageing mostly reflect an age-related decrease in GH production rate; in fact, while during puberty the diurnal GH production rate varies between 1.0-1.5 mg/day, elderly subjects can produce as little as 50 µg/day of GH, showing an hormonal secretion similar to that in hypopituitary GHD patients [1,3,4,14].

IGF-I levels generally reflect the GH status, at least in well nourished subjects, therefore showing a progressive decline in ageing, very often overlapping with those recorded in adult GHD patients [1,3,4,14]. Interestingly, total IGF-I levels continue to progressively decline with advancing age despite no further worsening of somatotroph insufficiency [1,34]. Nutritional alterations, that frequently occur in aged people, are associated with peripheral GH resistance and low IGF-I synthesis and they could account for the progressive reduction of IGF-I levels [34-36]. In fact, a report suggested some peripheral GH resistance whereby a the IGF-I response to GH in elderly subjects was found to be impaired [37]. However, preserved IGF-I and IGFBP-3 responses to very low rhGH doses in the elderly was clearly demonstrated later on, ruling out the presence of GH
resistance during ageing process, at least in well nourished subjects [38]. In agreement with this assumption, free IGF-I levels have been reported to be increased in the elderly [39], although the possibility that the reduced GH release during ageing could be due to exaggerated negative IGF-I feedback has not been ruled out [40].

The mechanisms underlying GH/IGF-I hypofunction in ageing are not completely clear, although changes in either neural control of somatotroph cells secretion or in peripheral factors have been hypothesized.

Most of the common stimuli of GH release, such as hypoglycemia, activation of α2-adrenergic, cholinergic, opioid and galaninergic pathways, showed a reduced stimulatory effect on GH release in ageing [1-5]. Even the GH responsiveness to GHRH has generally been reported to be reduced in the elderly, although about 30% of them still have a preserved GH response to the peptide [1-5]. Nevertheless, it has clearly been demonstrated in both animals and humans that the pituitary GH releasable pool is not reduced with advancing age [1,2]. However, either a reduction in hypothalamic GHRH release or an impairment of pituitary GHRH receptor and/or post-receptor mechanisms has also been demonstrated to contribute to the decrease in GH secretion in aged animals and humans [1,2,41-42]. In accordance with an age-related impairment of GHRH release and/or action in aged subjects, prolonged treatment with GHRH was shown to be capable of restoring GH pulsatility and increase IGF-I levels to young levels [25], while theophylline, a phosphodiesterase inhibitor, restored the GH response to GHRH [42].

Absolute or relative hyperactivity of hypothalamic SS neurons has been reported in ageing that, in turn, could lead to further intra-hypothalamic suppression of GHRH-secreting neurons [1-5]. In fact, the GH response to GHRH is clearly enhanced in the elderly by neuroactive substances acting via inhibition of hypothalamic SS release, e.g. cholinergic and catecholaminergic agonists, and even restored by arginine, an amino acid endowed with a strong GH-releasing effect mediated by SS inhibition [43].

Cholinergic agonists, such as pyridostigmine, increase but do not restore the GH response to GHRH in aged subjects [44-46], suggesting the existence of an hypothalamic cholinergic hypactivity leading to SS hyperactivity and dampened GH secretion, thus confirming the well known “cholinergic hypothesis of brain ageing” [7].

Although there is evidence for a reduced central catecholaminergic activity in brain ageing [3], studies focusing on adrenergic effects on somatotroph function in elderly subjects show controversial results.

Clonidine, a central α2-adrenergic agonist, has been reported to restore spontaneous and stimulated GH secretion in aged dogs [47], while in aged humans this drug enhanced but did not restore somatotroph function [48]. Similarly, galanin, a neuropeptide which stimulates GH secretion via concomitant activation of GHRH- and inhibition of SS-secreting neurons [3], enhances but does not restore GH response to GHRH in elderly subjects [46]; the same effect is shared by metenkephalin, an endogenous opioid [49], though the role of opioids in the control of somatotroph function is not definitively clarified [3].

Interestingly, arginine, an amino acid [43], shares with cholinergic agonists the same effects on GH secretion, with the notable exception being ageing [50]. In fact, this amino acid, fully restores the GH responsiveness to GHRH in elderly subjects through inhibition of hypothalamic SS rather than via nitric oxide (NO)-mediated mechanisms [43], making the response overlapping to that in young subjects and even in normally growing children [50]. This evidence indicates that the GH releasable pool is basically preserved in the aged pituitary and that SS hyperactivity is likely to have major role in the age-related decline of somatotroph function.

Age-related variations in the ghrelin system could play a role in the decreased GH secretion that connotes ageing. Ghrelin, a 28-amino acid peptide predominantly produced by the stomach, possess strong and dose-related GH-releasing effect both in humans and in animals [10], by acting at the pituitary and mainly at the hypothalamic level via GHRH-secreting neurons [10]. The GH-releasing effect of ghrelin undergoes marked decrease with ageing [10-12], probably reflecting variations in GHRH- and SS-activity [1-5]. However, the reduced GHS receptor number in the aged human hypothalamus suggested that an age-related decline in the ghrelin system could play a direct role in the age-related decline of GH [10,11]. Some reports have found a negative association between plasma ghrelin levels and age [13,51], whereas others did not find such correlations in either men or women [52,53]; moreover, an age-related variation in ghrelin gene expression has also been reported [54].

Peripheral factors are also known to influence the GH/IGF-I axis in the elderly, with a particular role exerted by the increase of adiposity and the decrease in gonadal steroids [1-5].

GH concentrations during 24 h are negatively correlated with body mass index, percentage of body fat, particularly abdominal visceral fat, which is known to increase in ageing; noteworthy, age and body mass independently affect somatotroph function [55,56].

Although some reports have demonstrated that both endogenous and exogenous gonadal steroids are able to modulate the GHRH/SS interplay and to affect IGF-I synthesis and secretion [33,37,39,57-59], there is no clear evidence supporting the hypothesis that the age-related decline in the function of GH/IGF-I axis is mostly dependent on the age-related change in the gonadal steroid milieu.

The strong clinical similarity between adult GHD and normal ageing, together with the evidence that patients with severe GHD benefit from GH replacement [15-17] and that elderly subjects present decreased activity of the GH/IGF-I axis [1-5], have raised the question whether or not aged people could benefit by a restoration of the GH and IGF-I levels to young levels. Despite the attention that GH therapy has received as a potential “anti-ageing” treatment option,
the results of different trials were not as exciting as those in adult GHD, yielding controversial results [60,61] (Table 1).

GH therapy is able to increase IGF-I levels and to improve some parameters of body composition in healthy elderly, including an increase in lean body mass and muscle mass and a reduction of total body fat [60-66]; moreover, a decrease in total cholesterol has been reported [65]. However, no positive effects on other clinically important outcomes, such as functional ability, muscle strength, bone mass and glucose metabolism, have ever been clearly demonstrated by such intervention [60,61,64,67]. Moreover, GH administration in healthy elderly individuals very frequently caused adverse effects, generally dose-dependent, similar to those found in GHD young adults, probably reflecting over-dosage and/or wide inter-individual variations in GH sensitivity [60,61]. The main side effects included soft tissue edema, arthralgia, carpal tunnel syndrome and gynecomastia [60,61]. Of note, there was also an increase in glucose and insulin concentrations, resulting from differing degrees of insulin resistance [60,61]. A serious concern about GH therapy in the elderly relates to the potentially increased risk for developing cancer or leading to cancer progression [61], but no very long-term studies are available to clarify this crucial issue (Table 1).

Alternatively to GH, treatment with GHRH, generally given in short-time studies and in a few patients, has been shown to restore spontaneous GH secretions and IGF-I in the elderly [25], and this effect could be enhanced by co-administration of arginine [26]. Some authors also reported slight but significant positive effects on body composition [28-30], while neither increase in physical performance scores nor a synergism with the positive effect of physical exercise were demonstrated by GHRH therapy [28,29].

Treatment with ghrelin-mimetics had also been proposed as anabolic anti-ageing intervention in frail elderly subjects. Indeed, prolonged treatment with orally active, non peptidyl GHS such as MK-0677 has been shown able to restore spontaneous GH pulsatility and IGF-I levels in aged humans [30], while no significant increase in muscle strength or function has been reported.

Besides the effects on body composition and metabolism, it has recently been demonstrated that GH and IGF-I are able to exert important actions on the CNS, affecting cognitive, neurotrophic, neuroprotective and metabolic actions [18-24]. This evidence implied the obvious hypothesis that GH replacement would be effective in elderly subjects with pathological conditions associated with brain impairment.

GH and IGF-I act within the CNS at various levels, in agreement with GH and IGF-I receptors expression in many CNS areas, including cerebral cortex, hippocampus and hypothalamus [18,21,68]. IGF-I and probably GH cross the blood brain barrier, but these hormones are also produced within the CNS, where they could act via autocrine/paracrine mechanisms [69]. Particular emphasis has been given to the actions of IGF system within the CNS where IGF-I exerts neurotrophic, neuroprotective and metabolic effects, meantime contributing to the negative feedback regulation of somatotroph function [20-22,24]. In addition to IGF-I and IGF receptors, IGF binding proteins (IGFBPs), which are expressed in CNS, play a relevant role by either modulating IGF-I activity or exerting direct actions [70].

Although several studies focused on the relationship between GH/IGF-I axis and parameters of CNS function, whether there is a link between the decline in GH/IGF-I axis activity and cognitive function during normal ageing is still matter of debate.

Although GH and IGF-I receptors have been reported to be decreased as function of age in brain areas playing a critical role in cognitive processes, such as hippocampus [18,22,68,71], several authors have reported that IGF but not GH levels positively correlate with cognitive performance in elderly subjects. Some studies also reported a positive correlation between total IGF-I levels or IGF/IGFBP ratio and cognitive functions in elderly individuals [72], although these findings have not confirmed by others [73-76].

An important question is whether low IGF-I levels are predictive of cognitive decline. The results of three studies addressed to solve this question [77-79] have suggested that circulating IGF-I levels may have a predictive value with regard to cognitive functioning later in life.

It is therefore of interest to know whether targeting the GH/IGF-I axis can improve cognition and hence support a causal role for the somatotrophic axis in higher brain function. At present, there is no evidence that treatments with GH or IGF-I improve cognitive parameters, memory or mood in normal elderly subjects, as reported by a few studies (Table 1) [60,61,64,80]. Similarly to GH/IGF-I therapy, treatment with GH-releasing molecules such as GHRH and ghrelin-mimetics, induced no significant improvement in cognitive function in aged people. Nonetheless, some authors have reported beneficial effects of six month GHRH treatment above all for tests involving problem solving, attention/mental processing speed and working memory [29]. The negative results in ageing are in contrast with those in young GHD patients, in whom a positive effect of GH replacement therapy on cognitive function, quality of life and well-being have clearly been demonstrated [81,82].

The different mechanisms underlying the hyposomatotropism of GHD and normal ageing is likely to explain the different impact of GH replacement on cognitive function in normal elderly and adult GHD. In fact, ageing is connoted not only by decline in GH and IGF-I levels but also in GH binding sites that are reduced in many central areas, particularly in those devoted to the control of cognitive functions; the decline in central GH receptors is, therefore, likely to reduce central GH actions. Finally, many other hormonal changes occur during advancing age, namely reduction in dehydroepiandrosterone sulfate (DHEAS) and gonadal steroids coupled with an increase in hypothalamus-pituitary-adrenal axis activity [83-85]; as these hormones are known to possess neurotropic actions, their age-related variations would contribute to the cognitive impairment observed in the elderly.
GH/IGF-I AXIS AND LIFESPAN

Although somatopause contributes to the changes in body composition, structure functions and metabolism that connote the “frailty” in elderly subjects, the impact of GH and IGF-I axis on lifespan is, at present, controversial. In fact, we are in facing of the paradox of lifelong GH/IGF-I deficiency or resistance resulting in prolonged life expectancy and GH replacement at advanced age probably exerting anti-ageing effects. Moreover, GHD is associated with features commonly seen in ageing and increased mortality. These findings question whether GH deficiency is or not a beneficial adaptation to ageing.

Reduced GH/IGF-1 effects are associated with prolonged lifespan in several animal models, not only primitive organisms such as worms [86] but also invertebrates such as flies and nematodes, and vertebrates such as rodents and mammals [87-104]. Some data in humans too support that GH/IGF-I deficiency may be associated with increased longevity [105-109].

The short lifespan of invertebrate models make them useful systems to study molecular pathways that may influence longevity. Mutants in both Caenorhabditis elegans and Drosophila melanogaster have revealed that a reduction in intracellular signaling pathways homologous or similar to that induced by insulin or IGF-1 increases longevity [91,92].

Moreover, several mouse models with reduced GH and or IGF-1 signaling have been shown to have extended lifespan as compared to control siblings. Mice homozygous for targeted disruption (knockout, KO) of the gene encoding the GH receptor/GH binding protein (Ghr-KO) are GH resistant, as demonstrated by profound suppression of hepatic IGF-1 expression, peripheral IGF-1 levels, somatic growth and adult body size [93], but they live 40-50% longer and show no decline of cognitive functions in comparison to normal siblings [94,95].

Snell and dwarf mice, homozygous for a defect in the Pit-1 (pituitary specific transcription factor 1) gene or in the PROP-1 (prophet of Pit1 or paired-like homeodomain transcription factor in the Prop-1) [96-98], lack GH, prolactin, and thyroid stimulating hormone producing cells; they show female sterility and severely reduced circulating levels of insulin, IGF-1, glucose, and thyroid hormones. Despite these hormonal abnormalities, they exhibit a major (40-65%) extension of lifespan associated to reduced immune, collagen and cognitive ageing [99-101]. Similarly, Lit/Lit mice with a missense mutation in the extracellular domain of the GHRH receptor as well as mice with a complete GHRH gene deletion are dwarf, showing severe GHD but increased longevity [100]. Again, female mice heterozygous for the IGF-1 receptor gene disruption do show a 33% increase in lifespan, while male mice show no statistically significant increase in longevity [102]. Interestingly, the female mice have an increased lifespan and are not dwarf, unlike the previous mentioned models, suggesting that dwarfism is not a requirement for the extended lifespan.

Not all mouse models with reduced GH or IGF-1 levels exhibit improvements in longevity. Mice that express a transgene for a growth hormone antagonist, a molecule that competes with endogenous GH for GHR binding resulting in marked reduction of GH-induced intracellular signaling, are dwarf and, with low IGF-1 levels, but they do not show extension in lifespan as compared to littermate controls [103].

While the majority of lifespan data in vertebrates has been generated from mice, several studies have focused on other rodent models. Data from rats are controversial, although some data support that repression of this axis may be beneficial for ageing. For example, in GH antisense transgenic rats longevity is extended in heterozygotes that have moderate reduction in IGF-1 levels but is shortened in homozygotes showing marked suppression of IGF-1 synthesis and secretion [104].

Differently from animals, the role of the GH/IGF axis in modulation of lifespan in humans is controversial. In fact, both severe GH deficiency and GH excess have been found associated with reduced life expectancy, although these alterations in lifespan would simply reflect the increased risk of malignancy or cardiovascular diseases, rather than the acceleration of ageing process [14-17, 110-112]. Moreover, as most cases of GHD occur in panhypopituitary patients, it remains yet unclear whether this increased mortality results from untreated GHD or from other hormonal deficiencies or conditions.

Recently, in centenarians, Suh et al. [108] have identified an overrepresentation of heterozygous mutations in the IGF-I receptor gene that cause reduction of intracellular signaling, confirming that genetic alterations in this system can confer increased longevity; on the other hand, Aguilar-Oliveira et al. [109] have reported that the longevity in isolated GHD subjects with a homozygous mutation in the GHRH receptor was not different from their siblings. These data do not seem to support the concept that isolated GHD compromises longevity in humans and seem to confirm a positive role of GH deficiency on lifespan, as reported in animals.

The influence of diet on longevity and age-related disease is a new relevant field of research. Energy restriction has been shown to significantly increase lifespan and reduce age-related diseases compared with “ad libitum” feeding, at least in animals. A negative correlation between adult body size and lifespan has been demonstrated in animals [113-115] and in several studies in humans [116-118]. Caloric restriction is associated with a clear reduction in GH and IGF-I secretion, with the consequent suppression of growth and adult body size, and it has been shown to delay both ageing and the onset of age-related diseases, to prolong lifespan in several animal models [116]. Indirect similar effects of caloric restriction in humans have been demonstrated, in agreement with the results obtained in animal experiments [116-118].

Putative mechanisms linking reduced IGF-I with delayed ageing and prolonged longevity in animal models probably
include reduced insulin release and/or enhanced insulin sensitivity. In fact, decreased insulin sensitivity facilitates neuronal damage and accelerates ageing process. Moreover, a reduced glucose utilization impairs repair processes in the brain, which are normalized by the improvement in glucose metabolism [119,120]. The association of reduction of GH/IGF-I activity, improvement of insulin signaling and prolonged longevity in animal models seems, however, in contrast with human findings showing that in normal ageing and in adult GHD the reduced activity of GH/IGF-I axis is associated with hyperinsulinism and insulin resistance [14-16].

**GH/IGF-I AXIS ACTIVITY IN DEMENTIA: FOCUS ON ALZHEIMER’S DISEASE (FIG. 2)**

Alzheimer's disease (AD) is the most common cause of dementia worldwide in the elderly, characterized by cognitive and memory deterioration, progressive impairment of language, and a variety of neuropsychiatric symptoms and behavioral disturbances, leading to inexorable progression of impaired self-sufficiency [9]. The global burden of disability associated with dementia in the elderly is believed to be higher than in stroke, musculoskeletal disease, heart disease and cancer.

AD involves a complex pathological cascade that is characterized by two hallmarks: extra-cellular amyloid plaques (diffuse or neuritic), consisting of deposits of insoluble β-amyloid (Aβ) peptide, and intra-cellular neurofibrillary tangles [9,121]. Accordingly to the “amyloid cascade hypothesis” the increase of deposit of Aβ in several areas of CNS leads to several secondary events including hyperphosphorylation of the microtubular protein tau and generation of neurofibrillary tangles, inflammation, oxidation, and excitotoxicity [9,121]. Amyloid plaques are also observed in the brain of normal aged individuals and do not correlate with progression of dementia, while neurofibrillary tangles are deposited in a hierarchical and systematic fashion that correlates closely with cognitive decline in AD [121]. Oxidative stress and free radicals, by altering glucose metabolism and mitochondrial functions, have been shown to contribute to Aβ production and to the accumulation of senile plaques [122-126]. In addition, the AD brain shows extensive atrophy, due to a dramatic loss of neurons and synapses, and several neuroinflammation areas [9].

All of these morphological alterations are responsible for impairment of neural pathways in several cerebral areas, including cerebral cortex and limbic area, which play a

Fig. (2). Pathological mechanisms in Alzheimer’s disease.
crucial role in the modulation of cognitive function and mood. Indeed, a dramatic impairment of cholinergic activity, particularly in the cortical and hippocampal areas, and to a lesser extent of catecholaminergic, dopaminergic and serotoninergic activity, occurs in AD being more pronounced that in normal brain ageing [7,8,121,127].

Increasing evidence points to a crucial role of IGF system as protective factor against neurodegenerative processes, including those observed in AD.

As a pleitropic neuroprotective agent, IGF-I has proven to be a potent anti-apoptotic signal for neurons and this is probably one of the mechanisms underlying its positive effects on the neurodegenerative alterations of AD [128-131]. In addition, when Aβ levels are abnormally high and become neurotoxic, IGF-I has also been reported to specifically protect neurons from neurotoxicity, being IGF-I able to influence metabolism and clearances of Aβ peptides [130-134].

Moreover, interactions between IGF system and neurotransmitter pathways affected in AD have been demonstrated, such as IGF-I-induced increase in enzyme activities increasing cholinergic, catecholaminergic and dopaminergic functions [130-132, 134, 135]. Particularly, IGF-I has a positive effect on neuronal survival and acetylcholine release in hippocampal and cortical cholinergic neurons, areas deeply affected in AD [7,8,127].

More recently, the interaction between IGF system with insulin and glucose metabolism within the CNS received great attention considering the hypothesis that central metabolic alterations might contribute to accelerate neurodegenerative processes, facilitating the processes leading to AD [119-123, 136,137]. In fact, as GH-IGF-I axis and insulin are two anabolic systems that are interlinked at many levels, abnormalities in one of these systems effect the other causing disordered metabolic homeostasis. Patients with type 2 diabetes mellitus have a two- to three-fold increased risk for AD [137]. Vascular complications might explain partially the increased incidence of neurodegeneration in patients with type 2 diabetes mellitus. Alternatively, neuronal resistance for insulin/IGF might represent a molecular link between type 2 diabetes mellitus and AD, characterizing AD as "brain-type diabetes". According to this hypothesis, brains from AD patients showed substantially downregulated expression of the insulin receptor, the IGF-I receptor, and the insulin receptor substrate proteins [137]. Finally, a central anti-inflammatory effect of IGF-I would be another mechanism explaining the IGF-I protecting action against cerebral AD alterations [138-140].

These data point toward a strict link between cerebral degenerative alterations of AD, cognitive and neurohormonal impairment, including the GH/IGF-I axis.

Based on this evidence and taking into account the age-related derangement in the neuroregulation of somatotrope function leading to a decline in GH and IGF-I levels, several authors focused on the relationships between neurodegenerative alterations, cognitive impairment and hormonal functions in AD, with particular attention to GH/IGF-I axis. Like normal ageing, AD is connoted by a GH hyposecretory state [141-144]. However, studies comparing GH and IGF-I secretion in AD with that in normal elderly subjects provided conflicting results [141-147].

Increased or unchanged GH levels were reported in AD patients compared to age-matched controls [141-144], while the majority of studies reported IGF-I increased in the early stages of AD and reduced at later stages [141-147], although others showed IGF-I levels in AD lower than in age-matched controls independently from the stage of the disease [148]. Slight age and/or nutritional differences as well as a more pronounced impairment of insulin sensitivity and/or glucose metabolism between AD and normal elderly subjects have been hypothesized to account for these controversial data [137,144].

GH responsiveness to provocative stimuli has also been evaluated in order to disclose potential neuroendocrine markers of AD possibly correlated to clinical parameters.

The GH response to GHRH has been reported similar, increased or reduced in AD in comparison with age-matched controls [141-143,149-155], and a delayed GH response to GHRH was observed by some [150] but not by other authors [142,152]. On the other hand, other studies focusing on the effects of other neuroactive drugs able to stimulate GH secretion, such as clonidine, pyridostigmine and apomorphine, generally confirmed that AD shows a GH response similar to that in normal elderly subjects [141, 142, 152-156].

Based on the evidence of a central cholinergic impairment in AD [7,8,121,127], the evaluation of the effects of cholinergic agonists, such as pyridostigmine or rivastigmine, on the GH response to GHRH gave particular attention. Indeed, cholinergic agonists are able to increase both spontaneous and GHRH-induced GH secretion in AD patients [142, 152-154, 156] without any difference with normal elderly [142,153], although both responses are reduced compared with normal young subjects [142]. These findings, therefore, confirmed the presence of neuroendocrine cholinergic derangement in the ageing brain but demonstrated that, at least at hypothalamic level, cholinergic pathways are not more impaired in AD than in normal elderly. However, the GH-inhibitory effect of cholinergic antagonists is preserved in both AD and normal aged people, indicating that the activity of tuberoinfundibular SS neurons within the hypothalamus is indistinguishable in normal and pathological ageing [153]. On the other hand, the GH responsiveness to GHRH combined to arginine is normal in AD [142], indicating that the hyperactivity of hypothalamic SS neurons probably reflects peculiar impairment of the cholinergic control of hypothalamic SS release. Actually, this hypothesis disagrees with the evidence that both SS immunoreactivity and receptors are reduced in many brain areas of AD patients [157-159].

Taking all together, the main message coming from the neuroendocrine studies in AD is that it is impossible to clearly differentiate patients with AD from normal elderly
subjects, possibly due to the poor sensitive experimental approaches used to test the neuroendocrine functions, namely the neuroendocrine control of GH/IGF-I axis. Moreover, there is no evidence, at present, supporting the hypothesis that some histopathological alterations in AD are associated with peculiar neuroendocrine impairment. This assumption implies that treatments with GH or GH secretagogues in AD would be considered simply on the basis that these patients, likely normal elderly subjects, would benefit by restoring the activity of GH/IGF-I axis at a younger level, that is, at present, not demonstrated. In this context, a recent randomized clinical trial showed that the administration of the growth hormone secretagogue MK-677 stimulates growth hormone and raises serum IGF-I levels but it has no clinical effects in AD patients [160].

On the other hand, given the relationship between brain alterations in AD and IGF-1/insulin signalling, the possibility exists that both peptides and/or their analogues could become candidates for drug therapy in neurodegenerative disorder. In fact, although heavily supported by the pharmaceutical industry, all marketed drugs for AD have no major clinical impact and the notion of a therapeutic “cocktail” in AD is now emerging, suggesting IGF-1/IGF-1 and insulin mimetics as possible components. In this context, some experimental studies suggest that small molecule insulin mimetics with better penetration into CNS as well as IGF-1 analogs with very high affinity for IGFBPs, able to increase “free” IGF-I levels, might represent therapeutic tools for the treatment of neurodegenerative disorders, including AD [140,161].

GH/IGF-I AXIS IN DOWN’S SYNDROME: A CLINICAL MODEL OF ANTICIPATED AGEING OF THE GH/IGF-I AXIS

Down’s syndrome (DS) is the most common cause of genetically-defined intellectual disability and congenital growth retardation. The disorder is caused by trisomy of chromosome 21 and it is associated with many neurological complications, including cognitive deficits, seizures, early-onset dementia that resembles AD, and neurological complications of systemic disorders [162].

On the other hand, short stature is a classical somatic feature of DS patients, which has been reported, at least partially, responsive to treatment with exogenous GH [163-165].

Early onset AD occurs with extremely high incidence in DS patients and is causally-related to overexpression of Aβ, which is one of the triplicated genes in DS [166-168]. Cholinergic alterations, impairment of cognitive functions, such as learning or memory, as well as sleep disturbances are common in DS as well as in ageing and AD [7,8, 166,167]. Moreover, hypothalamic alterations in DS have been reported, including a neuronal loss in the arcuate and ventromedial nuclei, which are brain areas involved in the neural control of GH secretion [169].

As GH/IGF-I axis is essential not only for body growth but also for development and maintenance of the CNS [18-24], attention has been paid to the role of GH/IGF-I axis in DS.

Some authors reported reduction of IGF-I levels in DS patients, without any age-related differences, to an extent similar to that in GHD patients [165, 170-172], while others showed a progressive decrease during advancing age, although within the age-related normal range [173]. Nutritional, lifestyle and/or social differences may explain these controversial findings. Both hepatic and cerebral IGF-I receptors seem preserved in DS that, in fact, show normal IGF-I sensitivity to exogenous GH administration as well as normal GH binding proteins [163, 170, 172].

Data concerning spontaneous and stimulated GH secretion in DS are controversial, as both reduced and normal somatotropic responsiveness to several stimuli have been reported.

Low GH response to L-DOPA and clonidine, two indirect GH-releasing agents, have been shown in prepubertal DS patients, while normal arginine- as well as GHRH-induced GH rise was reported in DS children [171-176]. Normal GH response in DS children was also observed after maximal provocative stimuli, such GHRH combined with pyridostigmine or arginine, as well as after hexarelin, a synthetic GH secretagogue mimicking ghrelin action [173, 176, 177]. Treatment with GH is generally not allowed in patients with DS, notable exception being DS patients in whom concomitant severe GHD is demonstrated. On the other hand, adult DS patients show reduction of the GH response to GHRH to an extent similar to that in normal elderly subjects and in AD patients [173]. As anticipated, precocious brain ageing has been shown in DS, likely including anticipated impairment in the neural pathways controlling GH release, namely cholinergic neurons [166,167,178]. The early brain ageing in DS, involving alterations in hypothalamic cholinergic pathways, probably induces SS hyperactivity and this could explain the overlap observed between the neuroendocrine behavior in DS, AD and normal elderly subjects. In fact, in adult DS patients the reduced GH response to GHRH is enhanced but not restored by pyridostigmine [173], similarly to what observed in both normal and demented elderly subjects [142]. Once again, differently from pyridostigmine, arginine was shown to completely restore the reduced GH response to GHRH in adult DS patients, making this similar to that in young as well as in normal children [176].

In all, these data demonstrate that, like normal and demented elderly subjects, adult patients with DS have a preserved pituitary releasable GH pool across lifespan but at the same time precocious derangement of neural pathways, i.e. cholinergic and somatostatinergic neurons. The early neuroendocrine ageing in DS disclosed by neuropharmacological tests is fascinating from the pathophysiological point of view indicating that GH/IGF-I axis in adult DS is already super imposable to that in normal and demented elderly subjects. However, the usefulness of anti-brain-ageing drug interventions with GH, GHRH and/or GH-secretagogues to treat adult DS patients is still to be demonstrated.
CONCLUSIONS

Studies in adult GHD have shown that GH is more than simply a "growth hormone", so that it should more appropriately be renamed "somatotropic hormone". Its strong influence on body composition, metabolism and CNS functions has definitely been demonstrated by improvements in GHD patients during GH replacement.

Whether somatopause is simply a physiologic evolution is still a matter of debate. Although somatopause is likely to contribute to age-related clinical impairment, GH cannot be recommended for use by the healthy elderly, bearing in mind that GH decline with age may represent a beneficial adaptation to ageing.

Neuroendocrine studies provided evidence that brain ageing is associated to peculiar age-related alterations in the control of GH/IGF-I axis, mostly including GHRH deficiency and absolute or relative SS hyperactivity which, at least partially, reflect the age-related cholinergic impairment. This picture is present either in normal or demented elderly subjects and Down’s syndrome patients and neuroendocrine distinction among these conditions is, at present, not possible. Whether the available neuroendocrine knowledge is simply descriptive or anti-neuroendocrine-ageing interventions may provide benefit to human beings is, at present, unknown.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

REFERENCES


Table 1. Long-Term Clinical Trials by Using GH, IGF-I or GHRH in Healthy Elderly Subjects Focusing on Cognitive Functions

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects (Age)</th>
<th>Intervention</th>
<th>Duration</th>
<th>Cognitive Effects</th>
<th>Main Positive Effects</th>
<th>Main Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papadakis 1996 [64]</td>
<td>52 men (69 yrs)</td>
<td>GH 30 µg/kg 3 X/wk</td>
<td>6 months</td>
<td>unchanged</td>
<td>↓ fat mass ↑ lean mass</td>
<td>oedema arthralgia</td>
</tr>
<tr>
<td>Friedlander 2001 [80]</td>
<td>16 women (70 yrs)</td>
<td>IGF-I 15 µg/kg 2 X/day</td>
<td>12 months</td>
<td>unchanged</td>
<td>↑ IGF-I</td>
<td>fatigue oedema headaches</td>
</tr>
<tr>
<td>Vitiello 2006 [29]</td>
<td>44 men, 45 women (68 yrs)</td>
<td>GHRH 14 µg/kg /day</td>
<td>6 months</td>
<td>improved</td>
<td>↑ IGF-I</td>
<td>none</td>
</tr>
</tbody>
</table>


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