REVIEW

Central effects of the somatotropic system

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Abstract

The somatotropic axis interacts with the central nervous system (CNS) on several levels. Growth hormone (GH) and insulin-like growth factor-I (IGF-I) receptors are expressed in many brain areas including the hippocampus, pituitary and hypothalamus. GH and IGF-I can pass the blood-brain barrier by an as yet not completely understood mechanism. They can also be produced in the brain and thus act via paracrine/autocrine mechanisms. GH and IGF-I are important factors in the development and differentiation of the CNS and have protective properties in dementia, and in traumatic and ischemic injury of the CNS. An improvement in cognitive functioning in GH-deficient patients by GH substitution has been shown. Significant results could, however, only be achieved with supraphysiological doses. In some studies, a correlation between IGF-I and cognitive function in the elderly has been found. GH has an important impact on mood and well-being with GH secretory capacity being reduced in depression. Pulsatile GH secretion is closely related to slow wave sleep (SWS) with SWS being stimulated by GH releasing hormone and rapid eye movement (REM) sleep by GH.

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Introduction

The positive effects of growth hormone (GH) substitution on metabolism, the cardiovascular system and body composition have been described (1–6). Recently, the effects of the somatotropic axis on the central nervous system (CNS) have come to be the focus of interest. However, it remains largely unclear whether these effects are mediated directly by GH or by its mediator – insulin-like growth factor-I (IGF-I) or, in some cases, by the hypothalamic neuropeptide growth hormone releasing hormone (GHRH). It is also unclear which functions are influenced by the above-mentioned hormones of the somatotropic axis.

In humans, GH binding sites, indicative of GH receptors (GH-R) can be found in most areas of the CNS. They are detected in their highest concentrations in the choroid plexus, but are also found in relevant amounts in the hippocampus, putamen, thalamus, pituitary and hypothalamus (7–9). GH-R messenger ribonucleic acid (mRNA) has also been detected in samples of human fronto-parietal and temporal cortex (10). A reduction in GH binding sites in the brain is seen with increasing age (7, 8).

The question as to whether GH can pass the blood-brain barrier (BBB) is still a subject of discussion. In acromegalic patients with excessive GH levels in the plasma, some authors have found normal GH levels in the cerebrospinal fluid (CSF) (11), whereas others have found increased levels (12). When GH is applied

externally for GH substitution, there is an increase in GH levels in the CSF (13, 14). In rats, GH has been found in the cortex, hippocampus, thalamus and amygdaloid nucleus (15, 16). Active transport mechanisms, similar to the ones known for leptin and insulin, have been proposed (8, 17). It has been shown that a transport mechanism across the BBB exists for prolactin, whereby prolactin receptors in the choroid plexus act as transport molecules (18). GH binding sites are also found in highest concentration in the choroid plexus, so it is possible that they act as a transport mechanism in a similar fashion. In addition, GH mRNA can be found in the CNS, suggesting that GH also acts via autocrine/paracrine mechanisms (19).

Similarly, IGF-I receptors are found predominantly in the hippocampus and parahippocampal areas, but also in the amygdala, cerebellum and cortex (20). There is evidence that IGF-I is transported across the BBB via transcytosis (17). In rat brain neurons, uptake of IGF-I could be shown (21). A relevant amount of IGF-I is produced in the brain with IGF-I mRNA being found predominantly in the brain stem and cerebellum in adult rats (22). GHRH receptors have been found in abundance in the cortex and brain stem of rats (23).

GH release occurs in a pulsatile fashion with most being secreted during the early hours of night sleep in males, but in a more variable pattern and with a higher output during the day in females (24). GH secretion underlies the regulation of GHRH and somatostatin, as well as ghrelin, the newly discovered

natural ligand of the GH secretagog receptor (GHS-R) (25) (see Fig. 1). GHRH stimulates (26) and somatostatin inhibits (27, 28) GH release. Ghrelin is a peptide hormone that is mainly produced in the stomach (25). The GHS-R is expressed in the hypothalamus (29) and in the pituitary (30), and ghrelin mRNA is found in the pituitary (30). Ghrelin is a potent stimulator of GH release (31–34) and acts synergistically with GHRH on GH release (34, 35). Additionally, it appears to be an important stimulus of appetite and food intake (36–39) that might be mediated by stimulation of agouti-related protein expression in the hypothalamus (29), and correlates negatively with body weight (40, 41). IGF-I is mainly produced in the liver and is stimulated by GH, but a certain amount is also directly produced in the target tissues. Additionally, it underlies the regulation of the feeding state. In anorexia IGF-I is reduced and correlates positively with body mass index (42) whereas in obesity a slight reduction in IGF-I and a negative correlation with body mass index has been found (43, 44). Central functions that can be influenced by GH, IGF-I and GHRH include sleep, cognitive functions, mood, and neuroprotection. The aim of this review is to give an overview of the impact of the somatotropic axis on these functions with a focus on clinical symptomatology.

Neuroprotection

Growth hormone

The somatotropic axis plays a central role in the development and growth of the CNS. The distinction between GH- and IGF-I-mediated effects is often difficult; however, transgenic mouse models have shown that GH and IGF-I may exert distinct effects on the nervous system. For example, in transgenic mice overproduction of GH induces an increase in body size and motoneuron size. On the other hand, overproduction of IGF-I only induces an increase in body size, with the motoneuron size remaining unchanged (45).
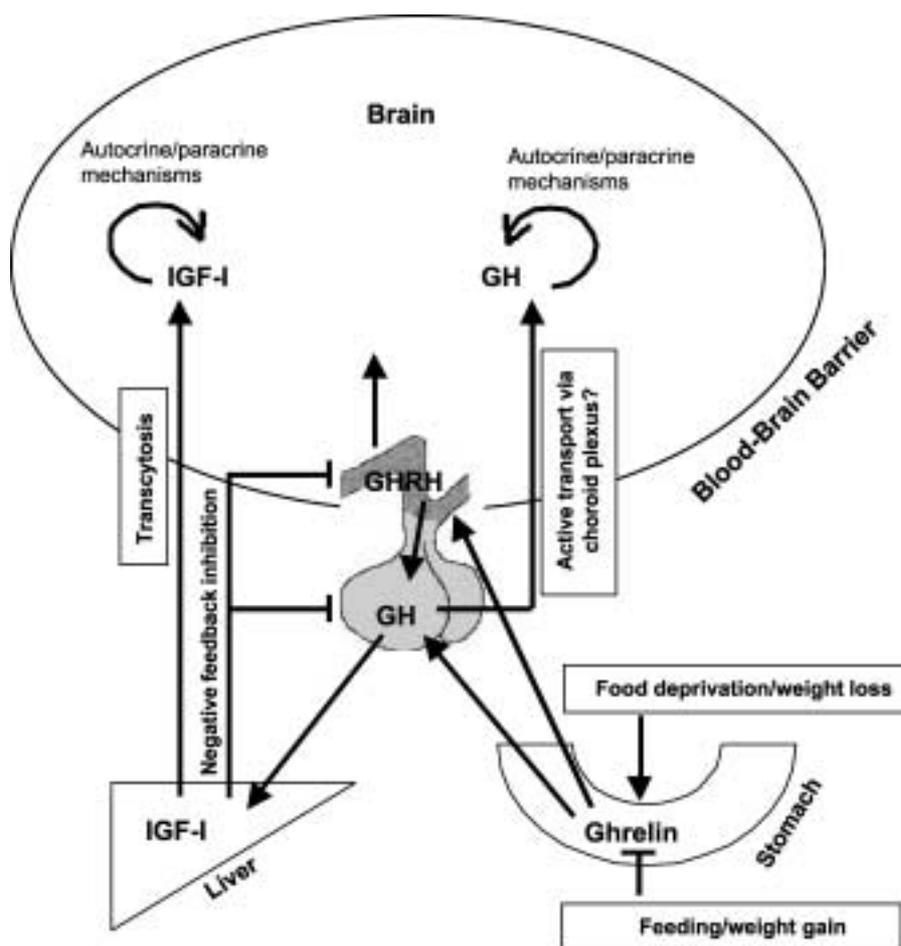
Figure 1 Modes of action on the brain and regulation of the somatotropic system. GHRH stimulates GH release. GH release is also stimulated by the natural GH secretagog ghrelin synergistically with GHRH. GH stimulates IGF-I release in the liver that exerts a negative feedback on GHRH and GH. Both IGF-I and GH may pass the blood-brain barrier and exert distinct effects in the brain. Both hormones are also produced directly in the brain and might act via autocrine/paracrine mechanisms.

In spinal chord injuries a decreased production of GH and IGF-I can be found (46). In rats with spinal chord injuries the application of GH improved neurological functions and reversed the traumatic suppression of evoked potentials in the spinal chord (9). Scheepens *et al.* (47) studied rats with hypoxic brain damage: in areas with strong cell loss, they found pronounced immunoreactivity for GH. By intracerebroventricular application of GH the amount of neuronal loss could be reduced in the frontoparietal cortex, hippocampus and dorsolateral thalamus, but was left unchanged in the striatum. This matches the regional distribution of GH receptors and thus supports the hypothesis that these particular neuroprotective effects are mediated directly by GH, and not by IGF-I.

Insulin-like growth factor-I

IGF-I supports the myelinization of the CNS by stimulating proliferation and differentiation of oligodendrocytes. It is involved in the differentiation of neurons to specific cell types; it can increase levels of neurotransmitters, neurotransmitter receptors and proteins of the cytoskeleton; it can inhibit apoptosis in neurons (22) and it stimulates dendrite growth (48). Disruption of the IGF-I gene leading to loss of function induces neuronal loss in the hippocampus and striatum (49). In animal models it has been shown that IGF-I has a positive influence on markers of Alzheimer's disease such as cholinergic dysfunction, amyloid toxicity, tau-phosphorylation, and glucose metabolism (50).

In some regions of the mammalian brain, for instance in the dentate gyrus of the hippocampus, there is lifelong neurogenesis. With increasing age, the rate of neurogenesis decreases. This decrease is dependent on environmental factors, hormones, and growth factors such as IGF-I. It has been shown that in aged rats a 60% reduction in the differentiation of new cells to neurons occurs. This reduction could be reversed by the intracerebroventricular application of IGF-I (51). This is particularly interesting as IGF-I production and IGF-I receptor density also declines with increasing age. Thus, it can be speculated that the age-dependent decline of IGF-I and IGF-I receptors might be a possible factor contributing to the development of cognitive deficits seen in the elderly.

In experimental infarction by occlusion of the medial cerebral artery in rats, a 60% reduction in infarct volume and an improvement in neurological functions could be achieved by intranasal application of IGF-I (52, 53). Recently, the Torres-Aleman group has published some very interesting results. They studied the effects of treadmill running and IGF-I application in rats. They found that both exercise and IGF-I application elevate IGF-I levels in the cerebrospinal fluid and induce an increase in neuronal c-fos expression and hippocampal brain-derived neurotropic factor (BDNF) (21), and exercise also induces an increase in neuron number in the hippocampus (54). In addition, exercise prevents neuronal loss in toxic damage of the hippocampus and the brain stem and has the ability to reverse neurological deficits (55). All effects of exercise and IGF-I could be reversed by blocking IGF-I or the IGF-I receptor.

These results show that both IGF-I and exercise have neuroprotective abilities, that the neuroprotective potential of exercise is mediated by IGF-I, that IGF-I can pass the BBB under physiological conditions, and that c-fos and BDNF are possibly involved in the mediation of the neuroprotective effects of IGF-I.

These data show that GH and IGF-I are not only important factors for the growth and development of the CNS but also exert neuroprotective effects throughout life. However, the clinical relevance of these findings has scarcely been investigated and clinical studies in humans are advisable.

Cognitive functions

The question of the influence of the somatotropic system on cognitive functions has been the subject of debate for a long time. In healthy volunteers it could be shown that a single dose of GHRH improves memory function (56). Neuroprotective properties of GH and IGF-I, especially in the hippocampus, support the assumption that the somatotropic axis has effects on cognitive abilities. An increase in aspartate, the ligand of the N-methyl-D-aspartate (NMDA) receptor has been found in the CSF of GH-deficient patients after GH replacement (57). NMDA receptor activation has been implicated both in memory function (58) and in attentional performance (59).

Growth hormone deficiency

A higher incidence of school under-achievement in short-statured children, independent of etiology has been reported (60). However, it remains unclear whether this is due solely to psychosocial or physiological reasons, or is also dependent on GH deficiency (GHD). In 1996, Sartorio *et al.* published a review on the relationship of growth hormone and body size to cognitive abilities (60). Short children are often low achievers in reading, spelling and arithmetic, despite a normal IQ. Children with GHD show learning and attention deficits (60) and disturbance in visual-motor integration (61) in spite of a normal IQ. In a study comparing children with GHD to short children with normal GH secretion, no differences in a multifactorial intelligence test and several personality questionnaires could be found (62). This supports the assumption that other factors besides GHD play an important role in the occurrence of school under-achievement in short-statured children.

However, other studies underline the role of GH in cognitive function and life achievements. In adult patients with GHD there is an increased rate of unemployment

even though these patients show normal intelligence and scholastic achievements (60). An impaired social status in patients with childhood-onset (CO)-GHD has been reported compared with short (63) and normal controls (64). Impairment in memory and executive function has been found in patients surgically treated for pituitary tumors (65), and women with untreated GHD exhibited lower scores in neuropsychological tests than healthy controls (66).

Deijen *et al.* examined cognitive functioning in 31 men with multiple pituitary hormone deficiency (MPHD), 17 men with isolated CO-GHD and in a healthy control group (67). They found reduced cognitive abilities in many fields in MPHD patients compared with controls, but in patients with isolated GHD only an impaired memory function was found. This shows that GHD appears to have a direct influence on memory function whereas other cognitive impairments are due to additional hormone deficiencies.

Effects of growth hormone substitution

In recent years some very interesting studies of GH substitution on cognitive function in GH-deficient subjects have been conducted (see Table 1). Deijen *et al.* studied the effects of three different doses of GH (1, 2, and $3\,IU/m^2/day$) compared with a placebo treatment over six months, and afterwards in an open-label phase over 18 months. In the first phase, they found improvements in memory function (associate recognition task, associate learning task) compared with placebo only in the groups with high GH doses leading to supranormal IGF-I levels. In the open-label phase, after one and again after two years, they found improvements in memory functions at all doses (68). This study confirmed the positive findings of GH substitution on cognitive abilities in previously conducted studies with small patient numbers (69, 70).

In nine patients with GHD treated with GH (0.25 IU/kg/week) or placebo for 6 months and then with only GH for another 6 months, a significant improvement in measures of attention (digit backwards, verbal fluency, cognitive efficiency) could be shown (71). This is consistent with results from our institute. We conducted a double-blind placebo-controlled trial with 18 GHD patients (16 adulthood-onset (AO)-GHD, two CO-GHD, six women, 12 men). In the first phase, patients received either GH (0.25 IU/kg/week) or placebo for 6 months. In the second phase, all patients received GH for another 6 months. Patients treated with GH showed continuous improvement over 12 months in attention trials (digit cancellation test, trail-making test, see Fig. 2) but no differences in verbal short-term or long-term memory were noted (72).

Baum *et al.* studied adult patients with AO-GHD in a double-blind placebo-controlled GH replacement study (0.042–0.126 IU/kg/week, adjusted to IGF-I) over

18 months (73). Tests for intelligence, language, memory, abstract thinking and personality showed normal results. Mild impairments in verbal learning and visual memory were found but these were still in the normal range. In none of the measured parameters was there an effect of GH compared with placebo (73). In another trial by Degerblad *et al.* conducted in a cross-over design with six patients over 12 weeks, no effects of GH substitution (0.5–0.6 IU/kg/week) could be shown (74).

Overall, these results are very interesting, but some of them are rather conflicting. It is possible that there is a difference between CO-GHD and AO-GHD which could explain the different results found by Deijen and Baum. It can be speculated that the occurrence of GHD during a more vulnerable phase or the longer duration of GHD in CO-GHD or a combination of both of these leads to more pronounced cognitive deficits in CO-GHD than in AO-GHD patients.

Another possible explanation is that the effects seen depend on the dose of GH. It is quite striking that in the study of Baum *et al.* (73), GH doses were much lower than in all other studies cited above. Baum's study was the only one in which the GH doses were adjusted to IGF-I levels. In all the other studies the applied doses were three to ten times higher, which often led to supraphysiological IGF-I levels. In the placebo-controlled phase, Deijen *et al.* (68) could only find cognitive improvement with doses which led to supranormal IGF-I levels, and in the open-label phase a placebo effect cannot be excluded. Degerblad *et al.* (74) found no effects even though they used a very high dose. It is possible that either GH does not exert an effect on the assessed cognitive functions or that the duration and the power of the study were too low to measure any existing effects. Deijen *et al.* (68) found improvements in learning and recognition but, like Oertel *et al.* (72), no changes in short-term and long-term verbal memory. Taking the above-mentioned data together, it is quite possible that effects on cognitive functions can only be achieved with supraphysiological GH doses. On the other hand, it cannot be ruled out that in some studies the duration of the study was too short to show any effects. There is still a need for placebo-controlled trials with large case numbers in which the effects of physiological GH doses on different aspects of cognition, sex and etiology of GHD can be studied.

## Growth hormone, insulin-like growth factor-I and cognition during aging

In the elderly, GH secretion and serum IGF-I levels decrease (75–77) and there is a reduced expression of GH receptors in the brain (7). Normal aging is accompanied by slight decreases in some aspects of cognitive function (78–80). In patients with dementia, decreased serum IGF-I levels can be found (81, 82). It has been a subject of debate as to whether there is a

Table 1 Influence of GH substitution on cognitive function in GH-deficient patients.

Reference	Date	*n*	**Dose** (IU/kg/week)	Design	Results
Almqvist *et al.* (69)	1986	5	~0.34	Adults with CO-GHD, DBPC, cross-over GH for 4 weeks	Improvement in face recognition
Degerblad *et al.* (74)	1990	6	0.5−0.6	DBPC, cross-over GH for 12 weeks in GHD	No objective change in cognitive function
Sartorio *et al.* (70)	1995	8	0.5	Adults with CO-GHD, open-label GH for 6 months	Improvement in symbol-number association (cognitive, visual-motoric and procedural speed)
Deijen *et al.* (68)	1998	48	~0.175, 0.35 or 0.525	Men with CO-GHD: 6 months PC with 3 different doses, 18 months open-label	In first 6 months improvement of memory (associate learning task, associate recognition task) compared with placebo only with supraphysiological doses. After 1 year improvement in all treatment groups
Baum *et al.* (73)	1998	40	0.042−0.126, adjusted to IGF-I	Men with AO-GHD: 18 months DBPC	No effect of GH on cognitive functions
Soares *et al.* (71)	1999	9	0.25 adjusted to IGF-I	DBPC 6 months GH, followed by 6 months open-label GH in adults with GHD DBPC	Improvement in attentional parameters (digit backward, verbal fluency, vocabulary, picture arrangements, comprehension)
Oertel *et al.* (72)	Unpublished data	18	0.25	GH for 6 months DBPC, followed by 6 months open-label; 16 AO-GHD, 2 CO-GHD	Improvement in attention (digit cancellation test, trail making test). No effect on verbal memory or nonverbal intelligence

The applied GH doses are shown in IU/kg/week. For Almqvist *et al.* (69) and Deijen *et al.* (68) the values were approximated. In Almqvist *et al.* (69) all probands received 8 IU GH 3 × /week independently of body weight. This corresponds to 0.34 IU/kg/week in a 70 kg proband. In Deijen *et al.* (68) 3 different does with 1, 2, and 3 IU/m^2 /day were administered. The values shown were calculated for a man of 80 kg and 180 cm.
GHD, growth hormone deficiency; CO-GHD, childhood-onset GHD; AO-GHD, adulthood-onset GHD; GHRH, growth hormone releasing hormone; GH, growth hormone; IGF-I, insulin-like growth factor-I; PC, placebo-controlled; DBPC, double-blind placebo-controlled.
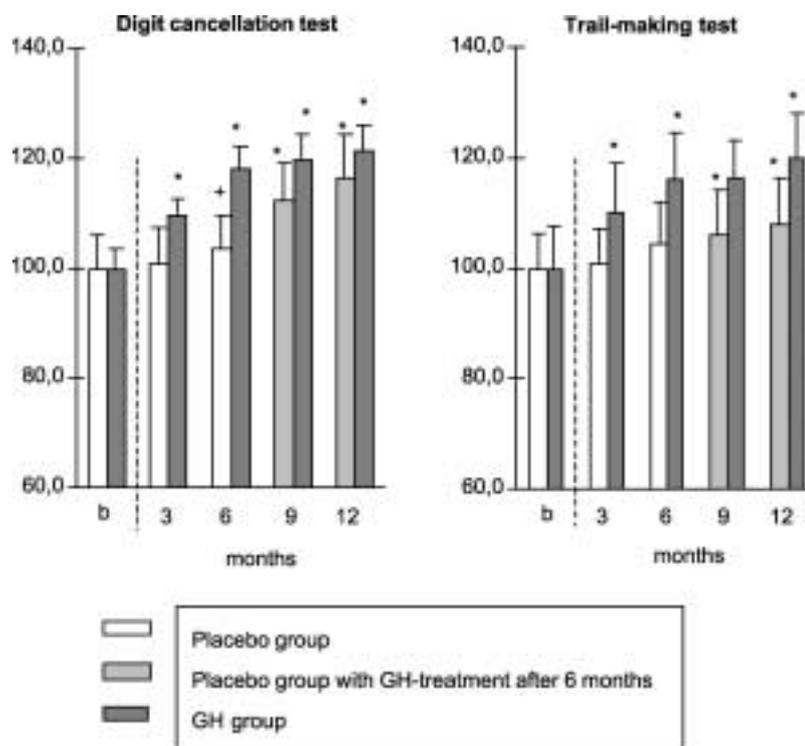
Figure 2 Effect of GH replacement on measures of attention. In the digit cancellation test, the subjects were asked to search for the target letter 'd' with two dashes above and/or below it, among 'ds' with different numbers of dashes or 'ps' with two dashes. The test variable was the number of correctly cancelled items per minute. In the trail-making test subjects had to connect numbers from 1 to 90 in an ascending order. The number of items correctly connected per minute was used as the test variable. Tests were standardized to baseline. Values are shown as means±S.E.M., expressed in % of baseline. *$P < 0.05$, indicates significant improvement in the GH group compared with baseline (tests with contrasts); +$P < 0.05$, indicates significant differences between groups (tests of simple effects). In both tests, patients showed significant improvements only under GH substitution and not under placebo treatment. After 6 months, patients under GH substitution showed significantly better scores in the digit cancellation test than patients under placebo treatment, whereas the differences between the GH and the placebo group in the trail-making test remained not significant. Data modified from (72).

relation between the decline of the somatotropic axis and cognitive function during normal aging.

Table 2 shows an overview of the studies that have examined the relationship between cognition and the somatotropic system during aging. In 104 elderly men, Papadakis *et al.* found a correlation between age and cognitive status, but no association of IGF-I with cognition independent of age (83). On the other hand, Morley *et al.* found a correlation between measures of cognitive function and both IGF-I and the ratio of IGF-I to GH in 65 healthy men between the ages of 20 and 84 years (84). However, in this trial, the correlation of IGF-I to cognitive function was less strong than the correlations of IGF-I to age, and cognitive function to age. It is therefore possible that both IGF-I and cognitive function only show a correlation to each other due to their close association to aging rather than being independently related. Further studies with smaller case numbers have also shown independent correlations of IGF-I and cognition (85–87). Paolisso *et al.* (87) examined the ratio of IGF-I to IGF-binding protein-3 (IGFBP-3) as IGF-I is bound mainly to IGFBP-3 in the serum and thus

IGF-I/IGFBP-3 reflects serum levels of active, bioavailable IGF-I. After adjustment for age, they found a positive correlation of both IGF-I and IGF-I/IGFBP-3 molar ratio with cognitive function in groups of elderly individuals of 75–99 years of age and in centenarians. Moreover, in a large prospective study it was found that with high levels of IGF-I as well as IGF-I/IGFBP-3 there is a low risk of cognitive decline over 2 years (89).

Effects of growth hormone or insulin-like growth factor-I therapy during aging

Not many studies on the effects of GH or IGF-I treatment on cognition in normal aging subjects have been conducted. In a placebo-controlled trial, Papadakis *et al.* examined the effects of GH administration for 6 months (0.27 IU/kg/week) in healthy elderly men (mean age 75 years) with low IGF-I levels (90) and Friedlander *et al.* studied the effects of IGF-I in postmenopausal women over 60 years of age for one year in a placebo-controlled study (91). In both trials, no effect

Table 2 GH, IGF-I and cognitive function in the elderly.

Reference	Date	*n*	Design	Results
Papadakis *et al.* (83)	1995	104	Cross-sectional, healthy men 74–94 years	No independent correlation between IGF-I and cognitive function
Morley *et al.* (84)	1997	65	Cross-sectional, healthy men 20–84 years	Correlation of IGF-I and IGF-I/GH with age and cognitive parameters, negative correlation of IGF-I with age
Paolisso *et al.* (88)	1997	96	Cross-sectional, healthy probands *n* = 30 21–49 years, *n* = 30 75–99 years, *n* = 19 centenarians	IGF-I/IGFBP-3 higher in centenarians than in probands 75–99 years of age. Independent correlation of IGF-I and IGF-I/IGFBP-3 with MMSE in centenarians and in probands 75–99 years of age
Rollero *et al.* (85)	1998	22	Cross-sectional, healthy probands 65–86 years	Independent correlation of MMSE with IGF-I
Aleman *et al.* (86)	1999	25	Cross-sectional, healthy men 65–76 years	Independent correlation of IGF-I with digit symbol test and concept shifting task
Aleman *et al.* (87)	2000	17	Cross-sectional, healthy men 66–76 years	Negative correlation of GH secretory capacity (GHRH-GHRP-6 test) and positive correlation of IGF-I with cognitive function
Kalmijn *et al.* (89)	2000	186	Prospective over 1.9 years, healthy probands, 55–80 years	Correlation of IGF-I and IGF-I/IGFBP-3 with reduced cognitive decline
Arai *et al.* (81)	2001	49	Cross-sectional, centenarians	Higher prevalence of dementia in persons with low IGF-I
Murialdo *et al.* (82)	2001	25	Cross-sectional, 25 patients with Alzheimer's disease, 12 control persons	IGF-I decreased in Alzheimer's disease
Papadakis *et al.* (90)	1996	52	DBPC, healthy men over 69 years (mean age 75 years), GH for 6 months	No effect of GH on cognitive abilities
Friedlander *et al.* (90)	2001	16	DBPC, IGF-I for 12 months in postmenopausal women over 60 years	No effect of IGF-I on mood and memory

GHRH, growth hormone releasing hormone; GHRP-6, growth hormone releasing peptide-6; GH, growth hormone; IGF-I, insulin-like growth factor-I; IGFBP-3, IGF-binding protein-3; DBPC, double-blind placebo-controlled; MMSE, mini mental state examination.

on mood, memory or other aspects of cognitive function could be found.

Overall, there is some evidence that the somatotropic axis may have an influence on cognitive abilities even in the physiological range, although there are probably many other factors. However, a positive effect of GH or IGF-I therapy on cognitive function in the elderly has not been shown. The underlying mechanisms for the decline in IGF-I seen in GHD and normal aging are not the same and the effects of replacement therapy may, therefore, be different. It is possible that the lack of effectiveness of GH application in the elderly is due to the fact that during aging not only do GH secretion and IGF-I levels decline but so does GH receptor expression in the brain, thus reducing central sensitivity to GH. Moreover, the fact that IGF-I is positively correlated with cognitive function, and that low IGF-I levels are found in dementia does not necessarily imply that low IGF-I levels are the reason for impaired cognitive function. And finally, it should be considered that during normal and pathological aging changes in other hormonal systems such as a decline in dehydroepiandrosterone (DHEA), DHEA sulfate, and sex steroids and an increase in nocturnal cortisol levels, may occur. These hormones may also exert neurotropic actions and additionally may influence cognitive changes during aging. For the present, it cannot be ruled out that low IGF-I is simply a side-effect of cognitive decline without any functional significance. Further studies are needed.

Quality of life

Growth hormone deficiency

Adults who were substituted with GH for childhood GHD showed impaired emotional status, physical mobility and social isolation after discontinuation of GH replacement (92). Reduced quality of life (QoL), assessed with the quality of life-assessment in growth hormone deficiency in adults (QOL-AGHDA), a questionnaire specifically designed for evaluation of QoL in GHD, was found in a study of more than 900 untreated GH-deficient patients (93). In a prospective trial over two years it was found that patients showed a decline in general scores of QoL and higher scores of depression and anxiety after termination of GH substitution (93). On the other hand, in other studies it could be shown that the degree of impairment of QoL is also dependent on the functioning of other pituitary axes (67, 95). GH-deficient subjects showed an increased incidence of social phobia (96), depression and fatigue (97) and decreased self-esteem and QoL in self-rating questionnaires (97–99). In 86 patients with AO-GHD worse scores for energy, social isolation, emotional reaction and sex life were described in the Nottingham Health Profile (NHP) (99). On the other hand, in a study of 48 patients with pituitary disease with at least two

hormone deficiencies and low IGF-I, no differences compared with controls were found in the assessment of QoL using two questionnaires, the Short Form 36 and the General Well-Being Schedule (100). It has been found that patients with AO-GHD show higher impairments in QoL than patients with CO-GHD (101, 102).

Effects of growth hormone replacement

Improvement in QoL after GH substitution in GH-deficient subjects has been found in an open-label study as assessed with the NHP and the Psychological General Well-Being Schedule (PGWB) (103) and in several placebo-controlled trials with the NHP (101, 104–106), the Comprehensive Psychological Rating Scale (107), the Kellner Symptom Questionnaire (108), and the Hopkins Symptom Checklist (HSCL) (104). However, other placebo-controlled trials showed no impact of GH substitution on QoL assessed with the NHP, the PGWB and the Minnesota Multiphasic Personality Inventory-2 (73), the HSCL and the Profile of Mood States (68) and the Disease Specific Questionnaire, the Symptom Checklist-90 and the Social Adjustment Scale (109). There are several possible reasons for these different findings. First, not all authors used the same questionnaires. Different methods may have led to different results. As mentioned above the GH dose given in the study of Baum *et al.* (73) was lower than in the other studies. In the study of Florkowski *et al.* (109) a cross-over design with a three-months active period was chosen and it is possible that this period was too short to produce measurable effects. Indeed, many studies showed continuous improvement in QoL over 1 or 2 years (101, 105). On the other hand, in these studies, both of which were placebo-controlled for the first 6 months and open-label afterwards, in some aspects, positive findings could only be shown after a longer period. Thus, it cannot be excluded that some of the positive findings are simply due to a placebo effect. A further reason for negative findings could be a lack of specificity of the questionnaires used.

As a consequence, specific questionnaires to evaluate successful treatment of GH substitution have been developed. The questionnaires existing at the moment are the modified impact scale (IS), the modified life fulfillment scale (LFS) (110), the growth hormone deficiency questionnaire (GHDQ) (106), the QOL-AGHDA (111), and the Questions on Life Satisfaction Modules-Hypopituitarism (QLS^M-H) (112).

Interestingly, in one trial, placebo-controlled for 6 months and open-label for another 6 months, that evaluated the effectiveness of GH substitution using the NHP and the GHDQ, significant improvements were seen in some aspects of the NHP but no change in scores were seen for the GHDQ (106). The GHDQ, which was specifically developed for that trial, consisted of 30 questions related to the three subscales of energy,

mood, and sleep, each answered on a 10-cm visual analog scale on a portable computer.

The LFS is a self-assessment questionnaire consisting of 12 items divided into two subscales: personal fulfillment and material fulfillment. It consists of two questionnaires, the first one dealing with the importance of and the second one dealing with satisfaction with various aspects of life. The IS consists of ten items dealing with the impact the disease has on different aspects of life. Both questionnaires have been tested for reliability and validity (110) and used in a 12-month trial with a 6-month phase being placebo-controlled and another 6-month phase being open-label for the efficacy of GH replacement in a group of 32 patients (105). Here, no significant change in the LFS but an improvement in the IS was shown.

The QOL-AGHDA is the best validated questionnaire at the present time (102, 113–120). It is a questionnaire containing 25 items that can be answered dichotomously ('yes' or 'no'). The score is calculated by adding all the items answered with 'yes', with a high score indicating poor QoL. It exists in five languages and has shown good reliability and validity in each language version. Moreover, it is used in an international database monitoring the effects of GH replacement (111).

The QLS^M-H consists of nine items. Each item can be rated according to its importance to the individual as well as the individual's satisfaction with it on a 5-point scale, with low scores implicating low QoL. The questionnaire was designed to have a high specificity for hypopituitarism and, additionally, provides the opportunity to weight each item according to its relative importance to the individual. In an open-label trial with 717 GHD patients and 2700 control individuals it showed a high reliability and validity and significant improvements in QoL during GH substitution (112).

Taken together, data on the effects of GH on QoL are still controversial. If GH substitution has an effect on QoL, the LFS and the the GHDQ appear to lack the sensitivity to measure it. The IS has shown improvements in a placebo-controlled trial, but it has not been studied in a large sample. The QOL-AGHDA has been used in many trials and in a large database and the QLS^M-H has also been tested with a large population. However, both of them lack results from placebo-controlled studies. This is particularly important, as a subjective measure such as QoL is highly susceptible to a placebo effect. Therefore, testing of these questionnaires in long-term, placebo-controlled studies is needed to evaluate their real usefulness.

Mood and depression

Healthy young men with high depression and anxiety scores show a reduced or no increase in GH secretion after physical exercise (121). In depressive patients, reduced nocturnal and 24-h GH secretion have been found (122–124), but other authors have found unchanged (125) or even increased 24-h GH secretion due to elevated daytime levels (126, 127). The GH response to stimulation testing is reduced (122, 128) but elevated levels of IGF-I have been observed (125, 129). In depressed children, a decreased response to dynamic testing has also been found (130, 131). In addition, in children and adolescents who are not depressive but have a high genetic risk of depression, a reduced increase in GH in response to stimulation testing was found (132).

Since well-being appears to be affected by GH and the somatotropic axis is altered in mood disorders, it can be speculated that GH or IGF-I affect brain areas or neurotransmitter systems that are related to mood and well-being. In fact, an increase in beta-endorphin in the CSF could be shown after GH substitution in GH-deficient adults (13), and in rats after intracerebroventricular GH administration (9). Beta-endorphin is an endogenous opioid that can stimulate dopamine secretion in the brain reward system (133, 134). In the mammalian brain, this consists of synaptically interconnected neurons associated with the medial forebrain bundle, linking the ventral tegmental area, nucleus accumbens, and ventral pallidum. Electrical stimulation of this circuit supports intense self-stimulation in animals and, in humans, produces intense pleasure or euphoria. This circuit is strongly implicated in the neural substrates of drug addiction as well as in the pleasures produced by natural rewards such as food and sex (135). Burman *et al.* found no change in beta-endorphin in the CSF after GH substitution but a decrease in free thyroxine (T4) and homovanillic acid (HVA) and an increase in aspartate levels (14, 57). A reduction in HVA levels in the CSF can also be seen after successful treatment of depression with antidepressant agents. HVA reflects the dopamine metabolism in the brain whereas aspartate, as discussed above, is a ligand of the NMDA receptor that has been implicated in memory (58) and attentional function (59) of the mammalian brain. A possible reason for decreased T4 is an increased conversion into tri-iodothyronine in the brain (57).

Sleep

GH secretion is associated with sleep rhythm. In young men the GH peak at sleep onset is normally the most reproducible peak. In middle-aged and elderly men this is often the only phase during which measurable GH secretion takes place. In premenopausal women the GH peak at sleep onset also occurs but does not normally constitute the main part of the 24-h secretion. In shifts of sleep onset the GH peak still normally occurs at sleep onset (136), but in about 25% of young men a GH peak occurs before sleep onset (137). The somatotropic axis interacts with sleep on many levels: there is a close relationship between the

Table 3 Influence of the somatotropic system on sleep and hormone secretion during sleep.

Hormone administered	Reference	SWS	REM sleep	GH	Cortisol
GHRH	146–148	↑	↑/–	↑	↓
GH	142, 143	↓/–	↑/–	↑/n.a.	n.a.
GH-secretagogs	153–156	↑ (Ghrelin, MK-677)–(GHRP-6)	↑ (MK-677) – (Ghrelin, GHRP-6)	– (MK-677) ↑ (Ghrelin, GHRP-6)	– (MK-677) ↑ (Ghrelin, GHRP-6)
Somatostatin	146, 150, 151	↓ (old pr.), – (young pr.)	↓ (old pr.), – (young pr.)	–	n.a.
CRH	157, 159	↓	↓	↓	↑
ACTH	158	–	↑	↑	↑
Cortisol	158, 160	↑	↑		

↑, increase; ↓, decrease; –, unchanged; pr., probands; n.a., not assessed; SWS, slow wave sleep; GHRP-6, growth hormone releasing peptide-6; CRH, corticotropin releasing hormone; ACTH, adrenocorticotropin.

occurrence of slow wave sleep (SWS) of the sleep phases III and IV, and pulsatile GH secretion. In addition, with increasing age, a parallel exponential decline in SWS duration and nocturnal GH secretion occurs (138). Therefore, a common cause for SWS and the regulation of pulsatile GH secretion has been assumed (139). In Table 3, an overview of the effects of different components of the somatotropic axis and its functional antagonists on sleep structure is shown. In patients with isolated GHD an increase in total sleep time and reduced SWS have been found (140, 141). In healthy individuals, GH has been found to reduce SWS and increase rapid eye movement (REM) sleep duration (142), or to exert no changes in sleep pattern (143). In GH-deficient adults, on the other hand, increases in SWS and REM sleep have been found after GH substitution (144), whereas in children with GHD a decrease in stage III sleep after GH replacement has been described (145).

When GHRH is applied in a pulsatile fashion during the first half of the night, an increase in SWS and GH secretion and a suppression in cortisol can be seen (146). Other authors found enhanced REM sleep after a bolus injection of GHRH but an increase in SWS only after sleep deprivation or when GHRH was given in the third REM sleep period (147). When comparing pulsatile GHRH injections to continuous GHRH infusions, a more pronounced effect of pulsatile GHRH administration on sleep promotion and GH secretion was found (148). During aging the response of GH and SWS to GHRH declines (149). Somatostatin decreases SWS in elderly subjects (150), whereas in young individuals no effect of somatostatin on sleep EEG can be found (146, 151). In the young it is possible that GHRH tonus is high enough to antagonize the sleep disturbing effects of somatostatin, while this effect vanishes with a decrease in GHRH tonus due to aging.

In normal and hypophysectomized rats GHRH stimulates non-REM sleep. REM sleep is also stimulated by GHRH in normal rats but not in hypophysectomized rats (152). Thus non-REM sleep appears to be directly stimulated by GHRH, whereas REM sleep seems to be mediated by GH but not by GHRH. The fact that GHRH stimulates non-REM sleep both in normal and hypophysectomized rats implies that GHRH directly stimulates non-REM sleep. On the other hand, both GHRH and GH increase REM sleep and GH reduces SWS which implies that REM sleep is stimulated by GH (139) and that the decrease in SWS by GH is induced by a negative feedback mechanism on GHRH. Pulsatile administration of ghrelin, the natural GH secretagog receptor ligand, leads to enhanced SWS and stimulation of GH and cortisol secretion (153). A single dose of GH releasing peptide (RP)-6, a synthetic GH secretagog, induces an increase in phase II sleep (154, 155). Oral administration of MK-677, another GH secretagog, over one week leads to an increase in REM and phase IV sleep (156).

In some respects the adrenocorticotropic system appears to act as an antagonist of the somatotropic system. Corticotropin releasing hormone (CRH) reduces nocturnal GH secretion (157), and CRH, adrenocorticotropin and cortisol decrease REM sleep duration (158); SWS duration is reduced by CRH (159) and increased by cortisol (158, 160). This implies a central inhibition of SWS by CRH and an inhibition of REM sleep by cortisol. During normal aging and in depression sleep becomes shallow, SWS and the activity of the somatotropic system decreases, and the activity of the adrenocorticotropic system increases, so that the balance between the two systems shifts towards the adrenocorticotropic system (139).

In summary, these data show that neuropeptides, particularly GHRH and CRH play an important role in the regulation of sleep and act as functional antagonists. However, it has also been shown that both GH and cortisol can also exert direct effects on sleep structure.

Conclusions

Data on the effects of GH, IGF-I and GHRH on brain function have been accumulating in recent years, but understanding is still lacking as to exactly how GHRH, GH, and IGF-I interact with the brain. Putative mechanisms include local production of hormones, transport via the BBB, influence on levels of neurotransmitters, and the regulation of genes such as BDNF and c−fos.

Both GH and IGF-I appear to exert neuroprotective effects in pathological brain damage, as well as in normal brain aging. However, most results have been obtained in animal studies and evidence for a possible clinical application is scarce. Cognitive impairments can be seen in GHD and some studies have shown improvement after GH replacement. As some studies have produced conflicting results, further evaluation is needed. An impact of GH on mood and well-being has been found with GH-deficient patients showing a reduced quality of life and a reduced sense of well-being. Specific questionnaires that have been developed to assess the efficacy of GH replacement still need to be evaluated in placebo-controlled trials. In depression, a changed GH secretion has been found, the meaning of which still remains to be elucidated. Both GHRH and GH seem to influence sleep structure and sleep is altered in GHD.

Acknowledgements

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