AGE (2006) 28:173–180
DOI 10.1007/s11357-006-9005-9

The aging brain: is function dependent on growth hormone/insulin-like growth factor-1 signaling?

B. A. Forshee

Received: 1 January 2006 / Accepted: 1 February 2006

Abstract The role of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in normal brain function is not well understood. Studies looking at cognition in humans with GH deficiency have produced controversial results. Experiments in which GH is administered to rodents have shown an apparent improvement in learning and memory. However, studies in which GH deficient or resistant mice were tested in learning and memory tasks reveal that these animals have normal cognitive performance and that their neural function does not deteriorate with age at the same rate as their normal siblings. Further research into this phenomenon revealed that these animals have elevated GH and IGF-1 expression in the hippocampus compared to normal animals. Additional studies with GH deficient and resistant mice suggested that these mutants experience a delay in age-related decline in locomotor activity and exploratory behavior. Data indicate that GH/IGF-1 deficiency and resistance do not impair neural function and instead may offer some degree of protection that results in delayed cognitive and motor aging.

B.A. Forshee (✉)
Lake Erie College of Osteopathic Medicine,
1858 W. Grandview Blvd.,
Erie, PA 16509, USA
e-mail: bforshee@lecom.edu

Key words aging · cognition · delayed aging · dwarfism · growth hormone · learning and memory

Abbreviations

GH	growth hormone
IGF-1	insulin-like growth factor-1
GHRKO	GH receptor knockout
PRL	prolactin
TSH	thyroid stimulating hormone

Growth hormone (GH) levels vary with age from high prepubertal expression to a gradual decline from adulthood to death. This age-related reduction in GH is believed to result in a loss of muscle mass, bone density and energy levels, and an increase in adiposity (Rudman 1985; Meites 1988). Indeed, several reports indicate that GH replacement can reverse many of these conditions as well as improve an individual's "quality of life" (Rudman et al. 1990; Degerblad et al. 1990; Jorgensen et al. 1991; Almkvist et al. 1986; McGauley et al. 1990; Binnerts et al. 1992). While these initial reports suggested that recombinant GH could be a new anti-aging drug, there are now concerns about whether GH treatment is actually harmful due to potential side effects (Laron 2005). The adverse reactions reported are consistent with those present in humans and animals with high levels of GH, such as hyperinsulinemia and glucose intolerance, arthritis, hypertension, edema, congestive heart failure

and possibly increased tumorogenesis (Vance 1990; Marcus et al. 1990; Moon et al. 1950; Cullen et al. 1990). Animal studies looking at GH treatment during aging found improvements in microvascular blood supply and partial reversal of age-related bone marrow loss and thymic regeneration (Sonntag et al. 2000; French et al. 2002). Further, it was reported that injections of GH prolonged life in mice but not in rats (Kalu et al. 1998; Khansari and Gustad 1991). Although GH is used in middle-aged and elderly patients to improve physical and mental well-being, the harmful side effects make its use and value controversial.

While it is documented that GH expression decreases with age, the relationship between GH and longevity remains controversial. The pulsatile secretion of GH and the sensitivity to growth hormone releasing hormone (GHRH) stimulation decrease with age in both animals and humans (Muller et al. 1993). However, studies attempting to determine how GH directly affects longevity have been troubled by the interference of other physiological alterations. For example, mice with elevated GH have a shortened lifespan (Steger et al. 1993a). These animals overexpress insulin-like growth factor-1 (IGF-1) as expected, but they are also hyperinsulinemic, have elevated corticosterone levels and decreased cellular replication (Balbis et al. 1992; Cecim et al. 1996; Pendergast et al. 1993). In addition, hormone levels for several reproductive and neuroendocrine hormones are altered (Steger et al. 1993b; Bartke et al. 1994). As a result, it is very difficult to isolate the effects of GH overexpression on longevity, but it appears as though GH excess is associated with reduced lifespan.

Likewise, animals that are GH deficient also have alterations in several systems such as metabolic, reproductive and stress response systems, but these animals also have increased lifespan. Several different mouse models of GH deficiency or resistance live longer than their normal siblings (Brown-Borg et al. 1996; Coschigano et al. 2000; Flurkey et al. 2001). Taken together, it appears as though the absence of GH delays physical aging while increasing longevity.

While the specific mechanism for increased longevity in GH-IGF-1 deficient Ames dwarf mice and GH resistant GH receptor knockout (GHRKO) animals is unclear, the findings that longevity is capable of increasing in a given species are interesting. However, the quality of life for these long-lived animals remains in question. One aspect of importance is cognitive function. Studies assessing psychological profiles of GH-IGF-1 deficient/resistant humans and rodents have reported levels of intellectual capability varying from mental retardation to exceptional performance (Laron 1999; Meyer-Bahlburg et al. 1978; Sartorio et al. 1986; Frankel and Laron 1968; Galatzer et al. 1993; Kinney et al. 2001a,b; Kinney-Forshee et al. 2004). Drotar et al. (1980) reported that GH deficient children were ineffective at problem-solving, while other studies have reported deficits in spatial orientation and visual motor integration (Steinhausen and Stahnke 1976, 1977; Steinhausen and Wefers 1976; Abbot et al. 1982). Interestingly, many studies have reported normal intelligence and normal-to-good scholastic achievement for GH deficient/resistant children (Frisch et al. 1990; Holmes et al. 1984; Dean et al. 1985; Sartorio et al. 1986; Ranke 1987; Galatzer et al. 1987; Kranzler et al. 1998). In addition, Rosenbloom et al. (1996) reported exceptional school performance for GH receptor deficient children. Few studies have reported decreased intelligence quotient (IQ) in children with GH deficiency/resistance, but several studies have reported lower than normal academic achievement and more frequent grade retention in GH deficient/resistant children, indicating a disparity between IQ and academic achievement (Stabler 1991; Steinhausen and Stahnke 1976; Holmes et al. 1984; Money et al. 1967; Stabler 1991; Takano et al. 1994; Vicens-Calvert et al. 1993). These results suggest that the poor academic achievement frequently reported for these children could be the result of social factors instead of reduced intellectual capacity.

Studies assessing cognitive ability in adults with GH deficiency/resistance have produced more controversy regarding the effects of GH and IGF-1 on brain function. Kranzler et al. (1998) reported that in a population of Equadorian GH resistant (Laron) patients, intelligence was similar to normal relatives. Moreover, the

GH resistant females in this population were characterized as "exceptional school performers" (Guevara-Aquirre and Rosenbloom 1993). Several studies have also reported that cognition is impaired in patients with either childhood- or adult-onset GH deficiency, and that their impairments were improved with GH treatment (Sartorio et al. 1996; Deijen et al. 1996; Burman et al. 1995; Deijen et al. 1998). Other studies report that GH treatment can improve feelings of vitality, mental alertness, and feelings of well-being in GH deficient adults (Degerblad et al. 1990; Jorgensen et al. 1991; Almkvist et al. 1986; McGauley et al. 1990, Binnerts et al. 1992). Sartorio et al. (1995) reported that improvements in feelings of well-being are reversed when GH treatment is discontinued after 6 months. However, Baum et al. (1998) failed to find changes in cognitive function or quality of life following 18 months of GH replacement in 40 men with adult-onset GH deficiency. It is unclear whether replacing GH results in improvement in cognition and/or behavior in GH deficient patients. Moreover, the presence of cognitive and behavioral deficits in these patients has not yet been fully accepted and continues to be challenged.

Animal studies looking at the role of GH and/or IGF-1 in behavior, learning and memory have generally found GH to be beneficial to cognitive function in normal animals (Schneider-Rivas et al. 1995; Thornton et al. 2000). The Schneider-Rivas study found that injections of either GH or GHRH facilitated learning and memory in an inhibitory avoidance task. However, enhanced performance was found in only the young (3-month-old) rats, while old (24-month-old) rats showed no improvement following injection. Thornton et al. (2000) administered GHRH to rats for 21 months followed by testing in the Morris water maze, a test of spatial learning and memory. When results from these animals were compared with 6-month-old age-matched control rats, those rats that had received GHRH injections were found to perform better than age-matched controls. The authors concluded that the administration of GHRH attenuated the typical age-dependent decrease in learning and memory capability, although it is difficult to isolate the specific cause of these improvements without further studies.

The various dwarf mice, including the growth hormone receptor knockout (GHRKO) and Ames dwarfs, provide a valuable resource for studying the effects of GH and IGF-1 on brain function. The Ames dwarf mice have a primary pituitary deficiency resulting in the failure of adenohypophyseal somatotroph, lactotroph and thyrotroph development (Bartke 1964). These mice have a homozygous mutation in the Prop-1 locus on chromosome 11, resulting in deficiencies in GH, prolactin (PRL), and thyroid stimulating hormone (TSH) (Sornson et al. 1996; Bartke et al. 2001). The GHRKO mice have a mutation in the GH receptor, making them GH resistant (Zhou et al. 1997). Both models of GH deficiency have a dwarf phenotype and increased longevity. The increased longevity makes these mice valuable models in which to study the aging brain.

Tests of locomotor activity in the GH-R-KO mice failed to find an age-related reduction in activity levels compared to their younger counterparts, whereas old normal animals showed a reduction in activity compared to their younger counterparts (B.A. Kinney-Forshee, unpublished data). Results for the open field test revealed a similar preservation of locomotor activity in GHRKO mice when compared to normal siblings (Kinney-Forshee et al. 2004). These findings are in contrast to the gradual decline in locomotor activity previously reported in rhesus monkeys and in several strains of rodents (Moscrip et al. 2000; Weinert and Waterhouse 1999).

Results for locomotor activity testing in the stocks segregating for Ames dwarfism indicate that neither normal nor dwarf mice experience an age-related reduction in locomotor activity. While the old normal animals were more active than the old dwarf animals, the old dwarf animals were more active than the young dwarfs (Kinney et al. 2001b).

While more locomotor tests must be completed in these animals to determine whether GH deficiency/resistance alters age-related changes in locomotor activity, there is a trend suggesting that the GH resistant animals do not experience the same age-related decline in locomotor activity as normal animals of this strain. Also, the tests of the Ames dwarf mice and the GH-R-KO mice were completed at different chronological ages,

which may suggest that the delay in age-related changes is apparent at middle age and becomes minimal as the animals reach elderly status.

Study of elevated plus maze activity in Ames dwarf mice and their normal siblings support results obtained in previous studies with the Senescence-Accelerated mouse (SAM) performed by Miyamoto et al. (1992), in that the old groups appeared to experience a decline in anxious behavior compared to the young groups (Kinney et al. 2001b). Both young normal and young Ames dwarf mice exhibited much more anxious behavior compared to the old groups, whereas the old normal and Ames dwarf mice did not differ from each other. Taken together, it appears that both the old normal and dwarf animals were less anxious than their younger counterparts, and that the dwarf animals showed no clear delay in age-related reduction in anxious-like behavior. Perhaps this finding suggests that GH/IGF-1 deficiency does not positively influence the primary areas of the brain responsible for emotionality.

An open-field test for the Ames dwarf strain contradicted the elevated plus maze results (Kinney-Forshee et al. 2004). In this test there were clear differences in exploratory behavior between young and old normal animals but no differences between young and old Ames dwarf mice. Further, young normal animals spent less time exploring open areas when compared to their older counterparts, implying anxious behavior. Such differences in emotionality were not found in the young and old Ames dwarf mice. In fact, the young and old Ames dwarf mice did not differ on any measure of this test, implying that the old Ames dwarf mice may not experience a reduction in anxious-like behavior at the same rate as their normal siblings.

The apparent differences in findings between the elevated plus maze and the open field test could be due to differences in the ages of animals used in each test. The animals used in the open field test were younger than those used in the elevated plus maze. In fact, those used in the elevated plus maze were near the end of their lifespan. Perhaps these results indicate that the Ames dwarf mice do experience an increase in anxiety-like behavior with age, but they do not experience this increase at the same rate as their normal siblings. Very different results were obtained when the GHRKO mice were tested in the elevated plus maze. Results for these tests failed to find genotype-related differences in emotionality between old normal and old GHRKO mice in this strain (Kinney et al. 2001a).

Cognitive testing revealed the most striking differences between old mutants and their normal siblings. In inhibitory avoidance studies, both the Ames dwarf and the GHRKO mice did not show cognitive decline at the rate of their normal siblings. While the old normal animals in the Ames dwarf strain performed poorly on the 15-day retention test, the old Ames dwarf animals had a much smaller decline in retention. Although the old dwarf animals did not differ from the old normals in retention performance, they also did not differ from the young groups (Kinney et al. 2001b). Further, the age of the old dwarf group was 22–29 months, whereas the old normal group was 20–23 months. At these ages, both of these groups were equivalent to about late middle-age and nearly the same biological age. While further studies need to be done with older dwarf animals, the findings presented here suggest that dwarfs may not experience the expected cognitive decline as quickly as normal animals.

Similar findings were obtained in two separate avoidance learning tests with GHRKO mice (Kinney et al. 2001a). The inhibitory avoidance studies using GHRKO looked at learning and memory in two separate paradigms. The first utilized a repeated-measures design, in which the same animals were tested in three separate retention tests. Results from this study showed that over time, memory in old normal animals declined whereas old GHRKO mice showed no significant decline. The second study subjected the animals to independent retention tests. There were no differences between GHRKO and normal mice in the 24 h retention test, but by the 7-day retention test, the old normal animals had poorer retention than their young counterparts. The 28-day test also revealed a greater decline in long-term memory for the normal animals compared to their younger counterparts, whereas the memory of GHRKO mice did not change significantly or differ from their younger counterparts.

Taken together, these results suggest that GH deficient/resistant animals are not learning impaired and that the delay in physiological aging seen in these mice is paralleled by a delay in cognitive aging.

Water maze learning tests revealed findings similar to the inhibitory avoidance test for the GHRKO strain but very different results for the young and old Ames dwarf mice. Like the inhibitory avoidance test, the old normal animals of the GHRKO strain performed poorly compared to the old GHRKO and the young normal and GHRKO mice, while the latter three groups did not differ from each other (Kinney-Forshee et al. 2004). In the Ames dwarf strain, old normal animals also did not perform as well as their younger counterparts but fared better than the old dwarf animals. Additionally, old dwarf animals performed more poorly than their younger counterparts (B. A. Kinney, unpublished data). These findings are in contrast to those for the inhibitory avoidance task, in which old normal animals showed deficits in retention but old Ames dwarf animals performed no different than young normal and Ames dwarf groups. Perhaps the discrepancies in test results were due to the decline in locomotor activity seen in young and old dwarf animals.

There are several possible physiological factors that may contribute to the apparent delay in cognitive aging seen in GHRKO mice. Perhaps GH deficiency/resistance indirectly delays brain aging by altering the activity of other hormones and/or neurotransmitters. In addition, GH deficiency/resistance induces a reduction in basal glucose levels and enhancement of insulin sensitivity (Borg et al. 1995). Also, the Ames dwarf mice exhibit elevated catalase activity in liver and kidney, elevated catalase and superoxide dismutase activity in the hypothalamus and some indications of reduced oxidative damage compared to controls (Brown-Borg et al. 1999; Brown-Borg and Rakoczy 2000; Hauck and Bartke 2000; Sanz et al. 2002). Previous studies have suggested that the age-induced increase in oxidative damage may be an important factor in cognitive deficits seen during aging (Forster et al. 1996).

Recently, it was suggested that IGFs, brain-derived neurotrophic factor (BDNF) and serotonin may stimulate proteins involved in learning and memory, cellular stress adaptation, growth and repair, cell survival and neurogenesis (Mattson et al. 2004). Several studies have revealed the importance of GH/IGF-1 for cognitive function. Shi et al. (2005) found that 28-day IGF-1 treatments appeared to enhance synaptic efficacy. Although the Ames dwarf mice are GH and IGF-1 deficient, hippocampal GH and IGF-1 and neurogenesis in the dentate gyrus are increased in adult Ames dwarf mice compared to normal siblings (Sun et al. 2005a,b). These results may explain the delayed cognitive aging seen in these mice as well as in the GHRKO mice.

Much work is still needed to determine the role of GH/IGF-1 on learning and memory and whether the key to delayed cognitive aging is maintenance of hippocampal IGF-1 levels. To date it is undetermined whether GH deficiency leads to mental impairment and whether treatments in GH deficient patients improve brain function. Animal studies have revealed that GH/IGF-1 treatments appear to be beneficial to cognitive function and may reduce age-related cognitive decline. Work with mutant GH deficient/resistant animals shows that, in addition to delayed physical aging and longer lifespans, the Ames dwarf and GHRKO mice maintain their cognitive abilities longer than their normal siblings. Further studies looking at hippocampal gene expression revealed that GH and IGF-1 were expressed at higher levels in the hippocampus of Ames dwarf mice compared to their normal siblings. Taken together, these studies suggest that GH/IGF-1 deficiency/resistance does not result in impaired brain function and that these conditions may provide neural protection that delays the normal age-related decline in cognitive function.

References

Abbot D, Rotnem D, Genel M et al (1982) Cognitive and emotional functioning in hypopituitary short statured children. Schizophr Bull 8:310–319

Almkvist O, Thoren M, Saaf M et al (1986) Effects of growth hormone substitution on mental performance in adults with growth hormone deficiency: a pilot study. Psychoneuroendocrinology 11:347–352

Balbis A, Dellacha JM, Calandra RS et al (1992) Down

regulation of masked and unmasked insulin receptors in the liver of transgenic mice expressing bovine growth hormone gene. Life Sci 51:771–778

Bartke A (1964) Histology of the anterior hypophysis, thyroid and gonads of two types of dwarf mice. Anat Rec 149:225–235

Bartke A, Cecim M, Tang K et al (1994) Neuroendocrine and reproductive consequences of overexpression of growth hormone in transgenic mice. Proc Soc Exp Biol Med 206:345–359

Bartke A, Coschigano K, Kopchick J et al (2001) Genes that prolong life: relationships of growth hormone and growth to aging and life span. J Gerontol 56A: B340–B349

Baum HBA, Katznelson L, Sherman JC et al (1998) Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult-onset GH deficiency. J Clin Endocrinol Metab 83:3184–3189

Binnerts A, Swart GR, Wilson JHP et al (1992) The effect of growth hormone administration in growth hormone deficient adults on bone, protein, carbohydrate and lipid homeostasis as well as on body composition. Clin Endocrinol 37:79–87

Borg KE, Brown-Borg HM, Bartke A (1995) Assessment of the primary adrenal cortical and pancreatic hormone basal levels in relation to plasma glucose and age in the unstressed Ames dwarf mice. Proc Soc Exp Biol Med 210:126–133

Brown-Borg HM, Rakoczy SG (2000) Catalase expression in delayed and premature aging mouse models. Exp Gerontol 35:199–212

Brown-Borg HM, Borg KE, Meliska CJ et al (1996) Dwarf mice and the aging process. Nature 384:33

Brown-Borg HM, Bode AM, Bartke A (1999) Antioxidative mechanisms and plasma growth hormone levels. Endocrine 11:41–48

Burman P, Broman JE, Hetta J et al (1995) Quality of life in adults with growth hormone (GH) deficiency: response to treatment with recombinant human GH in a placebo-controlled 21-month trial. J Clin Endocrinol Metab 80:3585–3590

Cecim M, Alvarez-Sanz M, Van De Kar L et al (1996) Increased plasma corticosterone levels in bovine growth hormone (bGH) transgenic mice: effect of ACTH, GH and IGF-1 on in vitro adrenal corticosterone production. Trans Res 5:187–192

Coschigano KT, Clemmons D, Bellush LL et al (2000) Assessment of growth parameters and life span of GHR/BP gene-disrupted mice. Endocrinology 14: 2608–2613

Cullen KJ, Yee D, Sly WS et al (1990) Insulin-like growth factor receptor expression and function in human breast cancer. Cancer Res 50:48–50

Dean HJ, McTaggart TL, Fish DG et al (1985) The educational, vocational, and marital status of growth hormone-deficient adults treated with growth hormone during childhood. Am J Dis Child 139:1105–1110

Degerblad M, Almkvist O, Grunditz R et al (1990) Physical and psychological capabilities during substitution therapy with recombinant growth hormone in adults with growth hormone deficiency. Acta Endocrinol 123:185–193

Deijen JB, de Boer H, Blok GJ et al (1996) Cognitive impairments and mood disturbances in growth hormone deficient men. Psychoneuroendocrinology 21: 313–322

Deijen JB, de Boer H, van der Veen EA (1998) Cognitive changes during growth hormone replacement in adult men. Psychoneuroendocrinology 23:45–55

Drotar D, Owens R, Gotthold J (1980) Personality adjustment of children and adolescents with hypopituitarism. Child Psychiatry Hum Dev 11:59–66

Flurkey K, Papaconstantinou J, Miller RA et al (2001) Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. Proc Natl Acad Sci USA 98:6736–6741

Forster MJ, Dubey A, Dawson KM et al (1996) Age-related losses of cognitive function and motor skills in mice are associated with oxidative protein damage in the brain. Proc Natl Acad Sci USA 93:4765–4769

Frankel JJ, Laron Z (1968) Psychological aspects of pituitary insufficiency in children and adolescents with special reference to growth hormone. Isr J Med Sci 4:953–961

French RA, Broussard SR, Meier WA et al (2002) Age-associated loss of bone marrow hematopoietic cells is reversed by GH and accompanies thymic reconstitution. Endocrinology 143:690–699

Frisch H, Hausler G, Lindenbauer S et al (1990) Psychological aspects in children and adolescents with hypopituitarism. Acta Paediatr Scand 79:644–651

Galatzer A, Aran O, Beit-Halachmi N et al (1987) Rehabilitation status of young adults with hGH deficiency after termination of therapy. Pediatr Adolesc Endocrinol 16:257–267

Galatzer A, Aran O, Nagelberg J et al (1993) Cognitive and psychosocial functioning of young adults with Laron syndrome. In: Laron Z, Parks JS (eds) Lessons from Laron syndrome (LS) 1996–1992. Karger, Basel, pp 53–60

Guevara-Aguirre J, Rosenbloom AL (1993) Psychosocial adaptation of Ecuadorian patients with growth hormone receptor deficiency/Laron syndrome. Pediatr Adolesc Endocrinol 24:61–64

Hauck S, Bartke A (2000) Effects of growth hormone on hypothalamic catalase and Cu/Zn superoxide dismutase. Free Radic Biol Med 28:970–978

Holmes CS, Thompson RG, Hayford JT (1984) Factors related to grade retention in children with short stature. Child Care Health Dev 10:199–210

Jorgensen JOL, Pedersen SA, Thuesen L et al (1991) Long-term growth hormone treatment in growth hormone deficient adults. Acta Endocrinol 125:449–453

Kalu DN, Orhii PB, Chen C et al (1998) Aged-rodent models of long-term growth hormone therapy-lack of deleterious effect on longevity. J Biol Sci 53:B452–B463

Khansari DN, Gustad T (1991) Effects of long-term, low-dose growth hormone therapy on immune function and life expectancy of mice. Mech Ageing Dev 57:87–100

Kinney BA, Coschigano KT, Kopchick JJ et al (2001a) Evidence that age-induced decline in memory retention is delayed in growth hormone resistant GH-R-KO (Laron) mice. Physiol Behav 72:653–660

Kinney BA, Meliska CJ, Steger RW et al (2001b) Evidence that Ames Dwarf mice age differently from their normal siblings in behavioral and learning and memory parameters. Horm Behav 39:277–284

Kinney-Forshee BA, Kinney NE, Steger RW et al (2004) Could a deficiency in growth hormone signaling be beneficial to the aging brain? Physiol Behav 80:589–594

Kranzler JH, Rosenbloom AL, Martinez V et al (1998) Normal intelligence with severe insulin-like growth factor I deficiency due to growth hormone receptor deficiency: a controlled study in a genetically homogeneous population. J Clin Endocrinol Metab 83: 1953–1958

Laron Z (1999) The essential role of IGF-1: lessons from the long-term study and treatment of children and adults with Laron syndrome. J Clin Endocrinol Metab 84:4397–4404

Laron Z (2005) Do deficiencies in growth hormone and insulin-like growth factor-1 (IGF-1) shorten or prolong longevity? Mech Ageing Dev 126:305–307

Marcus R, Butterfield G, Holloway L et al (1990) Effects of short-term administration of recombinant human growth hormone to elderly people. J Endocrinol Metab 70:519–527

Mattson MP, Maudsley S, Martin B (2004) A neural signaling triumvirate that influences ageing and age-related disease: insulin/IGF-1, BDNF and serotonin. Age Res Rev 3:445–464

McGauley GA, Cuneo RC, Salomon F et al (1990) Psychological well-being before and after growth hormone treatment in adults with growth hormone deficiency. Horm Res 33:52–54

Meites J (1988) Neuroendocrine biomarkers of aging in the rat. Exp Gerontol 23:349–358

Meyer-Bahlburg HFL, Feinman JA, MacGillivray MH et al (1978) Growth hormone deficiency, brain development, and intelligence. Am J Dis Child 132:565–572

Money J, Drash PW, Lewis V (1967) Dwarfism and hypopituitarism: statural retardation without mental retardation. Am J Ment Defic 72:122–126

Moon HD, Simpson ME, Li CH et al (1950) Neoplasm in rats treated with pituitary growth hormone. I. Pulmonary and lymphatic tissues. Cancer Res 10: 297–308

Moscrip TD, Ingram DK, Lane MA et al (2000) Locomotor activity in female rhesus monkeys: assessment of age and calorie restriction effects. J Gerontol 55: B373–B380

Muller EE, Cella SG, De Gennaro Colonna V et al (1993) Aspects of the neuroendocrine control of growth hormone secretion in ageing mammals. J Reprod Fertil 46:99–114

Miyamoto M, Kryota Y, Nishiyama M, Nagaoka A (1992) Senescence-acceleratedmouse (SAM): age-related reduced anxiety-like behavior in the SAM-P/8strain. Physiol Behav 51:979–985

Pendergast WR, Li Y, Jiang D et al (1993) Decrease in cellular replicative potential in "giant" mice transfected with the bovine growth hormone gene correlates to shortened life span. J Cell Physiol 156:96–103

Ranke MB (1987) A note on adults with growth hormone deficiency. Acta Paediatr Scand 331:80–82

Rosenbloom AL, Guevara-Aguirre J, Rosenfeld RG et al (1996) The little women of Loja—growth hormone-receptor deficiency in an inbred population of southern Ecuador. N Engl J Med 323:1367–1374

Rudman D (1985) Growth hormone, body composition and aging. J Am Geriatr Soc 33:800–807

Rudman D, Feller G, Nagraj HS et al (1990) Effects of human growth hormone in men over 60 years old. N Engl J Med 323:1–6

Sanz A, Bartke A, Barja G (2002) Long-lived Ames dwarf mice: oxidative damage to mitochondrial DNA in heart and brain. J Am Aging 25:119–122

Sartorio A, Peri G, Molinari E et al (1986) The psychosocial outcome of adults with growth hormone deficiency. Acta Med Auxol 18:123–128

Sartorio A, Molinari E, Riva G et al (1995) Growth hormone treatment in adults with childhood onset growth hormone deficiency: effects on psychological capabilities. Horm Res 44:6–11

Sartorio A, Conti A, Molinari E et al (1996) Growth, growth hormone and cognitive functions. Horm Res 45:23–29

Schneider-Rivas S, Rivas-Arancibia S, Vazquez-Pereyra F et al (1995) Modulation of long-term memory and extinction responses induced by growth hormone (GH) and growth hormone releasing hormone (GHRH) in rats. Life Sci 56:PL433–PL441

Shi L, Linville MC, Tucker EW et al (2005) Differential effects of aging and insulin-like growth factor-1 on synapses in CA1 of rat hippocampus. Cereb Cortex 15:571–577

Sonntag WE, Lynch C, Thornton P et al (2000) The effects of growth hormone and IGF-1 deficiency on cerebrovascular and brain ageing. J Anat 4:575–585

Sornson MW, Wu W, Dasen JS et al (1996) Pituitary lineage determination by the prophet of pit-1 homeodomain factor defective in Ames dwarfism. Nature 384:327–333

Stabler B (1991) Growth hormone insufficiency during childhood has implications for later life. Acta Paediatr Scand 377:9–13

Steger RW, Bartke A, Cecim M (1993a) Premature ageing in transgenic mice expressing different growth hormone genes. J Reprod Fertil 46:61–75

Steger RW, Bartke A, Yun JS et al (1993b) Neuroendocrine function in transgenic mice with phosphoenolpyruvate carboxykinase/human growth hormone (PEPCK/hGH) hybrid gene and very high peripheral levels of hGH. Transgene 1:19–26

Steinhausen H, Stahnke N (1976) Psychoendocrinological studies in dwarfed children and adolescents. Arch Dis Child 51:778–783

Steinhausen HC, Stahnke N (1977) Negative impact of growth-hormone deficiency on psychological functioning in dwarfed children and adolescents. Euro J Pediatr 126:263–270

Steinhausen HC, Wefers D (1976) Intelligence structure and

personality in various types of physical handicap in childhood and adolescence. Neuropaediatrie 7:313–321

Sun LY, Al-Regaiey K, Masternak MM et al (2005a) Local expression of GH and IGF-1 in the hippocampus of GH-deficient long-lived mice. Neurobiol Aging 26:929–937

Sun LY, Evans MS, Hsieh J et al (2005b) Increased neurogenesis in dentate gyrus of long-lived Ames dwarf mice. Endocrinology 146:1138–1144

Takano K, Tanaka T, Saito T, Committee for the Study Group of Adult GH Deficiency (1994) Psychosocial adjustment in a large cohort of adults with growth hormone deficiency treated with growth hormone in childhood: summary of a questionnaire survey. Acta Paediatr Scand Suppl 399:16–19

Thornton PL, Ingram RL, Sonntag WE (2000) Chronic [D-Ala2]-growth hormone-releasing hormone administration attenuates age-related deficits in spatial memory. J Gerontol 55:B106–B112

Vance ML (1990) Growth hormone for the elderly? N Engl J Med 323:52–54

Vicens-Calvert E, Bargada M, Potau N et al (1993) Psychosocial status of adults with growth hormone deficiency. Acta Endocrinol 128:71

Weinert D, Waterhouse J (1999) Daily activity and body temperature rhythms do not change simultaneously with age in laboratory mice. Physiol Behav 66:605–612

Zhou Y, Xu BC, Maheshwari HG et al (1997) A mammalian model for Laron syndrome produced by targeted disruption of the mouse growth hormone receptor/binding protein gene (The Laron mouse). Proc Natl Acad Sci USA 94:13215–13220