Growth hormone and IGF-I modulate local cerebral glucose utilization and ATP levels in a model of adult-onset growth hormone deficiency

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Sonntag, William E., Colleen Bennett, Rhonda Ingram, Ashley Donahue, Jeremy Ingraham, Haiying Chen, Tracy Moore, Judy K. Bruno-Bechtold, and David Riddle. Growth hormone and IGF-I modulate local cerebral glucose utilization and ATP levels in a model of adult-onset growth hormone deficiency. Am J Physiol Endocrinol Metab 291: E604–E610, 2006. First published April 25, 2006; doi:10.1152/ajpendo.00012.2006.—Decreases in plasma IGF-I levels that occur with age have been hypothesized to contribute to the genesis of brain aging. However, support for this hypothesis would be strengthened by evidence that growth hormone (GH)/IGF-I deficiency in young animals produces a phenotype similar to that found in aged animals. As a result, we developed a unique model of adult-onset GH/IGF-I deficiency by using dwarf rats specifically deficient in GH and IGF-I. The deficiency in plasma IGF-I is similar to that observed with age (e.g., 50% decrease), and replacement of GH restores levels of IGF-I to that found in young animals with normal GH levels. The present study employs this model to investigate the effects of circulating GH and IGF-I on local cerebral glucose utilization (LCGU). Analysis of LCGU indicated that GH/IGF-I-deficient animals exhibit a 29% decrease in glucose metabolism in many brain regions, especially those involved in hippocampally dependent processes of learning and memory. Similarly, a high correlation between plasma IGF-I levels and glucose metabolism was found in these areas. The deficiency in LCGU was not associated with alterations in GLUT1, GLUT3, or hexokinase activity. A 15% decrease in ATP levels was also found in hippocampus of GH-deficient animals, providing compelling data that circulating GH and IGF-I have significant effects on the regulation of glucose utilization and energy metabolism in the brain. Furthermore, our results provide important data to support the conclusion that deficiencies in circulating GH/IGF-I contribute to the genesis of brain aging.

insulin-like growth factor I; glucose utilization; brain; adenosine triphosphate; aging

INSULIN-LIKE GROWTH FACTOR I (IGF-I), a small peptide structurally related to proinsulin, has an important role in the regulation of cellular and tissue function. Under normal conditions, IGF-I is released from hepatic tissue in response to growth hormone stimulation, circulates in the blood at high concentrations, binds to the IGF-I receptor, and stimulates cellular DNA, RNA, and protein synthesis (8). In addition to its effects on peripheral tissues/organs, there is strong evidence to suggest that both growth hormone and IGF-I are transported across the blood-brain barrier (28, 29, 32, 36), raise brain concentrations of IGF-I, and stimulate IGF receptors found on both neurons and glia. These studies and others provide indirect evidence that alterations in circulating growth factors in general, and growth hormone and IGF-I in particular, have the potential to regulate brain function.

Several aspects of brain function of rodents, nonhuman primates, and man are known to decrease with age. These impairments include deficits in learning and memory, neurogenesis, synaptic density, and alterations in dendritic architecture (20, 21, 34, 37, 43, 45). Furthermore, indexes of brain function, including neurotransmitter synthesis and release, receptor concentrations, and signal transduction, are altered in the aging brain. Although the specific mechanisms responsible for these changes remain elusive, the results of hormone replacement studies suggest that the decreases in plasma IGF-I levels that occur with age contribute to the genesis of brain aging. For example, Markowska et al. (25) demonstrated that chronic infusion of IGF-I into the lateral ventricle of aged rodents increases IGF-I levels in brain tissue and reverses age-related memory deficits. Similar improvements in learning and memory in older animals have been shown after peripheral administration of growth hormone or growth hormone-releasing hormone (19, 34, 35, 48). In addition to its effects on cognitive function, IGF-I increases neurogenesis (20), stimulates acetylcholine release from hippocampal neurons (1) and cortical slices (16), reverses the age-related decline in levels of the N-methyl-D-aspartate (NMDA) receptor subtypes NMDAR2a and NMDAR2b (19), and increases D2 receptor function and vascular density (44). In addition, Lynch et al. (23) reported that age-related decreases in local cerebral glucose utilization (LCGU) are attenuated in specific regions of hippocampus, cortex, and hypothalamus by a 4-wk intracerebroventricular infusion of IGF-I. Because LCGU is highly correlated with neuronal activity (31) and a number of other markers of neuronal function, we have proposed that the decrease in circulating IGF-I with age may be a contributing factor in the decline in neuronal function and specific aspects of learning and memory routinely identified in aged animals. Although the studies of growth hormone/IGF-I replacement to aging animals have provided seminal data suggesting that circulating hormones participate in the genesis of brain aging, further support for this hypothesis would be strengthened by evidence that growth hormone/IGF-I deficiency in young animals produces a phenotype similar to that found in aged animals. As a result, specific models of growth hormone/IGF-I dysfunction in aged animals are needed to test this hypothesis.

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deficiency are likely to provide important insight into the role of these hormones in normal brain function and, by inference, their role in the genesis of learning and memory deficits that occur with age. Paradoxically, previous studies using transgenic GHRKO or mutant animals suggest that severe growth hormone deficiency maintains cognitive function in aging animals (2). Although the basis for this effect is not clear, we have proposed that deficiency in growth hormone and IGF-I early during development may impair maturation of specific organ systems, resulting in a complex array of developmental changes that mask the specific effects of growth hormone and IGF-I deficiency (4, 43). For this reason, we have developed a unique model of adult-onset growth hormone/IGF-I deficiency by using dwarf rats specifically deficient in growth hormone and IGF-I. The deficiency in plasma IGF-I in these animals is similar to that observed with age (e.g., 50% decrease), and replacement of growth hormone restores levels of IGF-I to those found in normal (young) animals. Using this model, we reported that peripubertal administration of growth hormone to growth hormone/IGF-I-deficient dwarf animals is necessary to ensure adequate development of both the pancreatic islet and normal glucose tolerance (4, 43), thus permitting a specific assessment of the effects of growth hormone and IGF-I deficiency. The present study employs this model to investigate the effects of circulating growth hormone and IGF-I on local cerebral glucose utilization (LCGU). Our results provide compelling data that circulating growth hormone and IGF-I have significant effects on the regulation of glucose utilization and energy metabolism in the brain and provide important data to support the conclusion that deficiencies in growth hormone/IGF-I contribute to the genesis of brain aging.

METHODS AND MATERIALS

Animals. Homozygous dw/dw rats originally derived from the Lewis strain were purchased from Harlan Industries (Indianapolis, IN). Previous studies suggest that these animals have a recessive mutation in the transcription factor necessary for development of the somatotroph and, hence, pituitary growth hormone synthesis and plasma growth hormone levels are reduced without changes in other anterior pituitary hormones (5, 27, 48). Homozygous dwarf male rats were bred with females of the Lewis strain to produce heterozygous offspring of normal size. Thereafter, normal-size females heterozygous for the dwarf trait (dw/+) were mated with dwarf males to produce heterozygous and homozygous (dw/dw) littermates; the latter were used in the present study. At 4 wk of age, dwarf animals were identified by reduced body weight and plasma IGF-I levels compared with heterozygous animals and were divided into two treatment groups (Fig. 1): growth hormone-deficient dwarf animals administered growth hormone (200 μg of recombinant porcine growth hormone; Alpharma, Victoria, Australia) from 4 to 14 wk of age and then administered vehicle until they were killed (AO-GHD) or those that continuously received GH injections until they were killed (GH Replete). At time of death (26 wk of age), plasma was collected and analyzed for IGF-I concentrations to independently validate group assignments.

Animals were maintained on a 12:12-h light-dark cycle (lights off at 1800) in a climate-controlled room with food (Purina Mills, Richmond, IN) and water available ad libitum. Body weights and health were monitored biweekly and daily, respectively. All protocols were approved by the Wake Forest University Institutional Animal Care and Use Committee.

Radioimmunoassay of plasma IGF-I. IGF-I (Bachem, Torrance, CA) was radioiodinated using the lactoperoxidase, glucose oxidase method and purified on a Sep-Pac silica cartridge (Waters, Milford, MA). Plasma IGF-I was extracted in acid-ethanol and measured by radioimmunoassay as previously described (46). The intra- and inter-assay coefficients of variance were 8 and 13%, respectively. Materials for analysis of rat IGF-I were generously provided by Dr. A. Parlow and the National Hormone and Pituitary Program.

Local cerebral glucose utilization. Twenty-four hours before testing, GH Replete and AO-GHD animals (n = 9 and 5 animals/group, respectively) were anesthetized with a mixture of halothane and nitrous oxide. Polyethylene catheters (Clay-Adams PE 50) were inserted in the femoral artery and vein and run subcutaneously to exit at the neck. LCGU was measured according to the procedure of Sokoloff et al. (41), as adapted for use in freely moving animals (9).

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appropriate constants according to the operational equation of the method.

GLUT1 and GLUT3 analysis. Analyses of GLUT1 and GLUT3 transporter protein levels in hippocampus were performed by Western blot in a second cohort of animals consisting of eight animals per group. Animals were killed by rapid decapitation, the hippocampus was dissected, and protein was extracted (total protein extraction kit; Sigma-Aldrich, St. Louis, MO). Briefly, tissues were sonicated in 1.5 ml of Chaotropic Membrane Extraction Reagent 3 and tributylphosphate for 1 min in an ice bath. The samples were centrifuged at 14,000 g for 30 min at room temperature, and supernatant was retained. Iodoacetamide (15 mM) was added to alkylate proteins and incubated for 1.5 h at room temperature. The samples were centrifuged at 20,000 g for 5 min to pellet insoluble material. Aliquots were removed and diluted 10-fold, and protein concentration was determined by the Bradford assay (Bio-Rad, Hercules, CA). The resulting aliquots were frozen at −80°C. Protein (30 μg) was electrophoresed on denaturing 4–20% SDS-polyacrylamide gels (SDS-PAGE; Invitrogen, Carlsbad, CA) as described by Laemmli (17). The protein was transferred to a polyvinyldiene difluoride membrane (Millipore, Bedford, MA) with a Nova Trans transfer apparatus (Invitrogen) at 25 V for 90 min. After the transfer, GLUT1 and GLUT3 were detected with rabbit anti-mouse polyclonal antibodies (Abcam, Cambridge, MA) in T20 blocking buffer (Pierce Chemical, Rockford, IL). Signals were visualized using a donkey anti-rabbit IgG coupled with horseradish peroxidase (Amersham Pharmacia Biotech, Piscataway, NJ) diluted 1:2,000 and SuperSignal West Pico Chemiluminescent Substrate (Pierce Chemical). Independent samples were analyzed on 3 blots, and the immunoreactive signals were quantified by transmission densitometry (Quantity One; Bio-Rad). Gels were normalized to control samples within each blot.

Hexokinase activity. Hexokinase (EC 2.7.1.1) activity was determined in both hippocampus and cortex by use of the glucose-6-phosphate dehydrogenase-coupled assay as described by Lai and Blass (18). Briefly, tissues were collected on cold Petri dishes and homogenized in 0.32 M sucrose, 1 mM EDTA, and 5 mM HEPES-Tris at pH 7.4. The homogenate was then centrifuged at 1,300 g for 3 min to pellet nuclei. The supernatant was then centrifuged at 17,000 g to pellet mitochondria. Enzyme activity in the supernatant was assayed in a mixture containing 0.1 M MOPS-KOH, pH 6.8 to pH 7.2, 0.1% Triton X-100, 8 mM MgCl₂, 0.4 mM NADP, 5 mM d-glucose, and 5 U of yeast glucose-6-phosphate dehydrogenase. The reaction was initiated with the addition of ATP (1 mM) and a small volume of tissue extract diluted to a final volume of 1 ml. The rate of reaction was measured after an initial delay of ~1 min followed by a continuous read at 340 nm.

ATP analysis. ATP levels were determined in a separate cohort of animals (5/group) using the ATPlite assay (PerkinElmer, Boston, MA). After rapid decapitation, the right hippocampus was dissected and sonicated for 10 s in 10% trichloroacetic acid followed by centrifugation at 14,000 g for 15 min. The sample was diluted in PBS and analyzed according to the manufacturer’s specifications. The luminescence was measured using the PerkinElmer Victor. The supernatant was analyzed for protein content by the Bradford protein assay, and these data were used to normalize the measured luminescence to protein content.

Data analysis. For these studies, nonparametric statistical methods were used, as analyses using ANOVA and Pearson correlations require a greater sample size to maintain asymptotic normality of the estimates. Therefore, results from the LCGU and ATP studies, glucose transporters and IGF-I levels, and hexokinase activity were analyzed using the Wilcoxon rank sum test. Relationships between plasma IGF-I levels and LCGU were further assessed using the nonparametric Spearman correlation.

RESULTS

Plasma IGF-I, glucose levels, and body weight. Body weights and mean plasma IGF-I levels for each group are shown in Table 1. As expected, AO-GHD animals had significantly lower plasma IGF-I levels (36.8%) compared with the GH Replete animals (P = 0.001). AO-GHD animals also exhibited a reduced body weight compared with GH Replete animals (13.7%), although this difference did not reach statistical significance (P = 0.09). Previous studies indicate that there are no differences in basal glucose and insulin levels between AO-GH-GHD and GH Replete dwarf animals (4). In the present study, under nonfasting conditions, glucose levels were similar in AO-GHD and GH Replete animals (Table 1).

LCGU. Analysis of LCGU indicated that circulating growth hormone and IGF-I regulate glucose metabolism in selected brain regions, including those involved in learning and memory. Representative autoradiographs are shown in Fig. 2. Rates of LCGU were an average of 29% lower in the AO-GHD group (80°C. Protein (30 μg) was electrophoresed on denaturing 4–20% SDS-polyacrylamide gels (SDS-PAGE; Invitrogen, Carlsbad, CA) as described by Laemmli (17). The protein was transferred to a polyvinyldiene difluoride membrane (Millipore, Bedford, MA) with a Nova Trans transfer apparatus (Invitrogen) at 25 V for 90 min. After the transfer, GLUT1 and GLUT3 were detected with rabbit anti-mouse polyclonal antibodies (Abcam, Cambridge, MA) in T20 blocking buffer (Pierce Chemical, Rockford, IL). Signals were visualized using a donkey anti-rabbit IgG coupled with horseradish peroxidase (Amersham Pharmacia Biotech, Piscataway, NJ) diluted 1:2,000 and SuperSignal West Pico Chemiluminescent Substrate (Pierce Chemical). Independent samples were analyzed on 3 blots, and the immunoreactive signals were quantified by transmission densitometry (Quantity One; Bio-Rad). Gels were normalized to control samples within each blot.

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LCGU. Analysis of LCGU indicated that circulating growth hormone and IGF-I regulate glucose metabolism in selected brain regions, including those involved in learning and memory. Representative autoradiographs are shown in Fig. 2. Rates of LCGU were an average of 29% lower in the AO-GHD group compared with the same area in GH Replete animals (P = 0.028). Trends were evident in other cortical and subcortical regions (anterior cingulate, entorhinal cortex, and sensory-motor cortex), with values ranging from P = 0.075 to 0.129. In the hippocampus (Fig. 3B), both CA1 and CA3 (P = 0.028 each) and subiculum (P = 0.035) exhibited decreased glucose metabolism in response to growth hormone/IGF-I deficiency, and trends were evident in the dentate gyrus (P = 0.055). Finally, in the hypothalamus (Fig. 3C), AO-GHD animals had significantly lower LCGU in the arcuate (P = 0.016) and ventromedial (P = 0.048) nuclei as well as in the lateral hypothalamus (P = 0.033).

Spearman correlational analysis between plasma IGF-I and LCGU in these brain regions indicated a relationship between IGF-I levels and LCGU. A significant correlation between plasma IGF-I and LCGU was found in the sensory-motor cortex (P = 0.004) and CA1 (P = 0.037), CA3 (P = 0.020), dentate gyrus (P = 0.02), and subiculum (P = 0.02) in the hippocampus.

Glucose transporters and hexokinase activity. The operational method of the equation for analysis of LCGU assumes

Table 1. Effects of GH on body weight, IGF-I, glucose, and hexokinase activity

<table>
<thead>
<tr>
<th>Group</th>
<th>Body Weight, g</th>
<th>IGF-I, ng/ml</th>
<th>Glucose, mg/dl</th>
<th>Hexokinase Activity, μmol NADPH produced/min⁻¹/50 mg tissue⁻¹</th>
</tr>
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<tbody>
<tr>
<td>AO-GHD</td>
<td>387±21.2</td>
<td>491±26.5*</td>
<td>138±2.5</td>
<td>Hippocampus: 203±6.6</td>
</tr>
<tr>
<td>GH Replete</td>
<td>449±17.2</td>
<td>779±31.9</td>
<td>131±3.7</td>
<td>Cortex: 195±6.8</td>
</tr>
</tbody>
</table>

Values are means ± SE. AO-GHD, adult-onset growth hormone (GH) deficient. *P < 0.001.
similar levels of glucose uptake and metabolism of 2-[14C]DG to glucose 6-phosphate between treatment groups. Western blot analysis of glucose transporter proteins GLUT1 and GLUT3 revealed that levels of these proteins in the hippocampus were similar in AO-GHD and GH Replete animals. Representative blots for GLUT1 and GLUT3 are shown in Fig. 4. Analysis of optical density revealed no statistical differences between experimental groups.

The phosphorylation of glucose by hexokinase is necessary for sequestering glucose inside the cell after uptake via hexose transporters in plasma membranes. The activity of hexokinase was determined by measuring glucose-6-phosphate dehydrogenase-coupled reduction of NADP⁺. No differences in the activity of hexokinase were evident between GH Replete and AO-GHD animals (P = 0.560; Table 1).

**ATP analysis.** The product of glucose metabolism is the generation of ATP from oxidative phosphorylation. In an independent cohort of AO-GHD and GH Replete animals (n = 5/group), a 15% reduction in ATP levels was evident in growth hormone-deficient animals (P = 0.048; Fig. 5).

**DISCUSSION**

Although there is an evolving literature suggesting that circulating growth hormone and IGF-I regulate several aspects of brain function in aged animals, the role of these hormones in the regulation of glucose metabolism in young adult animals has not been investigated. Previous studies demonstrate that IGF-I augments brain glucose utilization during brain development (6). By use of IGF-I-deficient mice, glucose utilization was found to be significantly reduced throughout the brain, and exogenous IGF-I increased glucose utilization. These changes

![Fig. 2. Coronal section though the brain of GH Replete (A) and AO-GHD animals (B) at the level of the hippocampus, demonstrating relative glucose metabolism. Red areas of pseudocolor image indicated enhanced glucose metabolism. Hippocampal subregions CA1, CA3, and dentate regions (DG) are indicated. Note that local cerebral glucose utilization (LCGU) is decreased in most structures of the brain, including cortical and thalamic regions.](image)

![Fig. 3. LCGU in specific brain regions of GH Replete and AO-GHD animals. A: results from 5 cortical subregions and GH Replete animals generally exhibit higher LCGU compared with AO-GHD animals (anterior cingulate, P = 0.046; retrosplenial, P = 0.013; entorhinal, P = 0.072; motor, P = 0.112; sensory, P = 0.059). B: similar findings are evident in hippocampal regions (CA1, P = 0.034; CA3, P = 0.0688; dentate, P = 0.1189; subiculum, P = 0.019). C: hypothalamic regions. Two of the 4 regions studied reached statistical significance. As with the cortical and hippocampal regions, LCGU was greater in GH Replete compared with AO-GHD animals (dorsal, P = 0.0586; ventromedial, P = 0.0286; accute, P = 0.0305; lateral, P = 0.2733). Data represent means ± SE. *P < 0.05.](image)
were associated with decreased hexokinase activity and GLUT4 levels. Because IGF-I expression is low in adults, those authors suggested that IGF-I may not have an important role in glucose metabolism at older ages. The present experiment was designed to assess whether alterations in circulating growth hormone and IGF-I regulate local cerebral glucose utilization and subsequently cellular ATP levels in mature animals. Using a unique model of adult-onset growth hormone/IGF-I deficiency, we evaluated glucose utilization in various brain regions, including cortical, hippocampal, and hypothalamic subregions. In all cases, local cerebral glucose utilization was reduced in growth hormone/IGF-I-deficient animals compared with animals with normal growth hormone and IGF-I levels. Subsequent analysis of ATP levels in hippocampus supported this finding, as those animals with increased glucose utilization demonstrated higher levels of cellular ATP. The reduction in local cerebral glucose utilization in response to modest growth hormone/IGF-I deficiency provides clear evidence that the levels of these circulating hormones regulate brain energy metabolism through components of the glycolytic pathway.

The operational method of the equation for analysis of glucose utilization requires that glucose uptake and metabolism do not alter basal glucose levels or levels of either of these two transporter molecules suggests that glucose flux into the brain is most likely not a contributing factor in the decreased LCGU after growth hormone/IGF-I deficiency. After transport, glucose is phosphorylated at the C-6 hydroxyl position to produce glucose 6-phosphate, a reaction catalyzed by the enzyme hexokinase. This reaction requires ATP and magnesium and maintains the product, glucose 6-phosphate, in the cell, since the negative charge associated with the phosphate precludes crossing the plasma membrane. We considered the possibility that growth hormone/IGF-I deficiency may lead to reduced hexokinase activity, decreased production of glucose 6-phosphate, and reduced ability to retain glucose in the brain and may potentially bias calculation of rates of glucose utilization between the treatment groups. However, no differences in hexokinase activity were found between growth hormone/IGF-I-deficient and replete animals; therefore, the reduced rate of 2-[14C]DG uptake in the brains of growth hormone/IGF-I-deficient animals must reflect a reduction in glucose metabolism. This conclusion was supported by a corresponding reduction in cellular ATP levels in growth hormone/IGF-I-deficient animals.

Circulating growth hormone and IGF-I decrease with age, and correlational and replacement studies over the past decade have supported the conclusion that a reduction in these potent anabolic hormones contributes to the development of the aged phenotype, including the loss of skeletal muscle mass, immune function, bone mass, and cellular protein synthesis in many organs and tissues. Several studies have now provided convincing evidence that both growth hormone and IGF-I cross the blood-brain barrier, and we and others have proposed that decreases in circulating levels of these hormones contribute to alterations in brain function with age. Certainly, a substantial decline in IGF-I levels occurs in hippocampus and cortex of aged animals, and intracerebroventricular administration of IGF-I or peripheral administration of growth hormone-releasing hormone or growth hormone to raise plasma IGF-I levels ameliorates the age-related decline in reference and working memory. Although the specific mechanism(s) of IGF-I-induced cognitive improve-
ment remains unknown, IGF-I is reported to increase paired pulse facilitation, AMPA currents, long-term potentiation, neurotransmitter release and receptor expression, neurogenesis, and synaptic complexity. Furthermore, Lynch et al. (23) reported that intracerebroventricular administration of IGF-I reverses the age-related decrease in glucose utilization in the hippocampus, arcuate nucleus of the hypothalamus, and anterior cingulate cortex of aged rodents. Similar decreases in glucose utilization have been documented in humans and nonhuman primates with increasing age (12, 13). Because both growth hormone and IGF-I levels decrease substantially with age, deficiency in circulating levels of these hormones appears to be an important contributing factor in impairments in brain energetics, and subsequently cognitive function, in aged animals.

Although IGF-I replacement in aged animals consistently has beneficial effects on brain function, the contribution of age-related decreases in IGF-I to mechanisms of aging are difficult to determine from studies of aged animals alone. Decreases in IGF-I receptors occur with age, and alterations in signaling properties of the hormone (10, 11) have the potential to mask (or modify) actions of hormones within specific brain regions. In the present study, we have taken an alternative approach through the use of a novel model of adult-onset growth hormone/IGF-I deficiency that is specific to growth hormone and IGF-I. Similar to our findings in aged animals (23), growth hormone/IGF-I deficiency in adults results in reduced LCUG not only in hippocampal regions involved in working and reference memory, but also in thalamic, cortical, and hypothalamic regions. Our results provide convincing data that the levels of circulating growth hormone and IGF-I have an important role in modulating energy metabolism throughout the brain of young and aged animals and that the age-related declines in growth hormone and IGF-I are likely primary factors in loss of energy metabolism with age.

Measurements of brain glucose utilization are often used as an indication of neuronal activity. For example, Sibson and colleagues (39, 40) used in vivo 13C-NMR spectroscopy methods to conclude that a 1:1 stoichiometric relationship exists between glutamate neurotransmitter cycling and oxidative glucose metabolism. The same investigators proposed that, in cortex, greater than 80% of glucose oxidation drives glutamatergic neuronal activity. We have studied elements of glutamatergic neurotransmission in the context of the decline of growth hormone and IGF-I with age, and our findings indicate that IGF-I administration reverses age-related decreases in NMDA receptor subtypes 2A and 2B in hippocampus (42). Hippocampal NMDA receptor function is believed to be crucial for long-term memory consolidation (38). Furthermore, mice with a specific deletion of the NMDAR1 gene in hippocampal CA1 pyramidal cells exhibit a lack of NMDA receptor-mediated synaptic currents, impaired long-term potentiation at CA1 synapses, and deficits in spatial memory (50), object recognition, olfactory discrimination, and contextual fear memory (33). Although the effects of adult-onset growth hormone/IGF-I deficiency on NMDA receptor subunit expression or receptor function have not yet been determined, we have reported that dwarf rats demonstrate an accelerated rate of cognitive impairment with increasing age (43). Whether these deficiencies are directly related to alterations in glutamate release or glutamate receptor subunit expression, or result from a more complex process involving synaptic complexity and/or neurogenesis, remains to be determined.

The dwarf model of adult-onset growth hormone/IGF-I deficiency used in this study provides unique advantages in assessing the effects of circulating growth hormone and IGF-I. Importantly, the dwarf rat exhibits a specific deficiency in growth hormone and IGF-I, without alterations in other endocrine parameters that have compromised other models. The deficiency in circulating IGF-I is appropriately 50%, which compares favorably with the reduction in IGF-I that is observed in aged rodents, nonhuman primates, and humans. Analysis of lifespan and end-of-life pathology in this model suggests that growth hormone and IGF-I, in addition to their roles in glucose metabolism, have an important role in the maintenance of vasculature integrity, as GH/IGF-I-deficient animals exhibited significant increases in intracerebral hemorrhage and cardiac thrombus that contributed to their deaths. Interestingly, this pathology was delayed in direct proportion to the length of time they were treated with GH during adolescence. Whether these findings are related to alterations in glucose metabolism remains to be determined. In summary, the unique model of adult-onset growth hormone deficiency presented here allows cause-and-effect relationships to be established between hormonal changes that occur with age and elements of brain aging without the confounding influences of multiple hormone deficiencies or hormone deficiencies that occur throughout development and compromise maturation of other organ systems.

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REFERENCES


