Suppression of the Hypothalamus-Pituitary Somatotrope Axis in Men With Spinal Cord Injuries

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Thirty-two men with spinal cord injury (SCI) were studied for evaluation of the hypothalamus-pituitary somatotrope axis, using growth hormone-(GH)-releasing hormone (GHRH) and insulin-induced hypoglycemia. Twenty-six age-matched normal male volunteers served as controls. Six SCI subjects (18.7%) had elevated basal follicle-stimulating hormone (FSH) levels, eight (25.0%) had hyperprolactinemia, and 11 (34.4%) had reduced serum insulin-like growth factor-1 (IGF-1) levels. Twenty SCI subjects (62.5%) had reduced and/or delayed GH responses to GHRH, and eight (25.8%) had reduced GH response to insulin-induced hypoglycemia. Seven of eight hyperprolactinemic SCI subjects showed reduced GH response to GHRH and/or insulin-induced hypoglycemia. These findings are consistent with the notion that SCI subjects have a reduced central dopaminergic tone.

SPINAL CORD INJURY (SCI) in adult males may result in various hormonal changes.[1-12] Low 3,5,3′-triiodothyronine (T_3) and/or thyroxine (T_4),[4] normal, low, or high testosterone,[3,6-9] normal or high follicle-stimulating hormone (FSH) and luteinizing hormone (LH),[3,6-12] and normal or high prolactin[3,8,10,11] levels have been reported. Low T_3 and/or T_4 serum levels were related to euthyroid sick syndrome.[4] The hypothalamus-pituitary-gonad axis of SCI subjects has been extensively investigated,[3,6-12] but no common pathogenetic mechanism was found. In a previous study at our institution of the hypothalamus-pituitary-gonad axis and the hypothalamus-pituitary-thyroid axis in SCI subjects, a high proportion of SCI males were found to have hyperprolactinemia and enhanced gonadotropin, prolactin, and thyrotropin (TSH) responses to LH-releasing hormone (LHRH) and TSH-releasing hormone, respectively.[8] Thus, it is proposed that there may be a reduced central dopaminergic tone in SCI subjects.[8] However, other central neurotransmitter changes cannot be excluded. Since dopamine is an important regulator of growth hormone (GH) secretion,[13] this study investigated the hypothalamus-pituitary somatotrope axis of SCI subjects.

SUBJECTS AND METHODS

Fully developed male SCI patients who met the following conditions were recruited for this study: traumatic SCI occurring more than 6 months before the study, but present stable medical condition without pressure sores, pneumonia, renal failure, epididymitis, or other febrile diseases. No traumatic brain injury, genitalia injury, or respiratory failure had been associated with their injury, nor was there prior history of an endocrine disorder; however, both before and during the study period magnesium oxide and baclofen were prescribed in several patients. Low-dose baclofen (5 mg twice or three times daily) was used in one quadriplegic and four paraplegic subjects, and high-dose baclofen (20 mg three times daily) was used in another three quadriplegic subjects for spasticity. All subjects had a normal blood chemistry screening including fasting blood glucose, hemoglobin A_{1c}, liver enzymes, and serum total protein and albumin levels (>3.5 g/dL); anemia was not present (hemoglobin level >12 g/dL). Subjects with urinary tract infection were treated with antibiotics before each blood sampling for endocrine studies. The age of the subjects varied from 21.6 to 46.1 years, with a mean of 33.6. Intervals between injury and study varied from 0.9 to 16.2 years, with a mean of 7.0. The level of injury varied from C5 to T12, and all lesions were complete. Eight patients had cervical- and 24 had thoracic-level injury; eight were quadriplegic and 24 paraplegic. All were sexually mature before being paralyzed.

Twenty-six age-matched men were recruited as controls. They ranged in age from 24 to 46 years, with a mean of 33.5. They were taking no medication and did not use tobacco or alcohol.

Endocrinologic Studies

All subjects, including normal controls, were studied between 8 and 9 AM after an overnight fast. After taking two basal blood samples (15 minutes apart), GH-releasing hormone 1 μg/kg body weight ([GHRH] Kabi Pharmacia, Stockholm, Sweden) was administered by intravenous bolus. Subjects remained supine throughout, and blood was sampled for GH at −15, 0, 20, 40, 60, 90, and 120 minutes after injection. The next day, an insulin-induced hypoglycemia test (regular insulin 0.125 U/kg body weight; Nordisk Pharmaceutical, Gentofte, Denmark) was performed in all subjects except one SCI patient who declined to participate. All had a blood glucose nadir less than 40 mg/dL, although some patients did not develop hypoglycemic symptoms. Blood glucose and GH levels were measured.

Two milliliters of serum from three basal samples taken on different dates were pooled to obtain basal hormone levels listed in Table 1.

Radioimmunoassay

All hormones were assayed by commercial radioimmunoassay (RIA) kits: T_4, T_3, TSH, FSH, LH, prolactin, and cortisol by the Amersham RIA kit (Buckinghamshire, England); corticotropin by the Nichols high-sensitivity corticotropin RIA kit (San Juan Capistrano, CA); GH by the Nichols high-sensitivity GH RIA kit; insulin-like growth factor-1 (IGF-1) by the Nichols IGF-1 RIA kit; and testosterone by the Biodata RIA kit (Allentown, PA). All of these commercial kits had been used previously in our laboratory with interassay and intraassay variations of less than 10%.

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Table 1. Basal Serum Hormone Levels of 32 Men With SCI and 26 Age- and Sex-Matched Controls

	SCI Subjects (n = 32)		Normal Controls (n = 26)	
Hormone	Mean ± SD	Range	Mean ± SD	Range
T_3 (nmol/L)	1.69 ± 0.28	1.35-2.34	1.67 ± 0.41	1.40-2.98
T_4 (nmol/L)	105 ± 17	76-143	109 ± 18	75-133
TSH (mU/L)	1.5 ± 1.4	0.4-4.5	1.3 ± 1.0	0.4-4.0
GH (μg/L)	0.5 ± 1.0	0.2-5.0	1.0 ± 0.9	0.2-5.0
Prolactin (pmol/L)	361 ± 289	58-1,385	304 ± 107	102-537
Cortisol (nmol/L)	392 ± 131	179-616	375 ± 125	146-644
FSH (mIU/mL)	10.8 ± 9.5*	1.3-23.2	5.9 ± 2.7	1.7-12.3
LH (mIU/mL)	7.3 ± 5.9	2.3-35.7	5.7 ± 2.9	2.0-12.0
Testosterone (nmol/L)	17.4 ± 5.5	10.9-34.6	16.4 ± 4.8	11.1-22.9
IGF-1 (μg/L)	146 ± 44*	40-238	201 ± 41	163-284

*$P < .01$ *v* control.

Statistical Analysis

GH responses to GHRH of SCI subjects and normal controls were first compared by repeated-measures ANOVA, and then each time point GH response was compared using Student's *t* test. Baseline hormone and peak GH response to insulin-induced hypoglycemia of these two groups were compared by Student's *t* test. Linear regression was used to analyze the correlation between peak and area of GH response to GHRH or insulin-induced hypoglycemia and serum testosterone level or IGF-1 level. Statistical analysis was performed using the computer statistical package SPSS/4.0 (SPSS, Chicago, IL).

RESULTS

Mean basal hormone levels of 32 SCI subjects and 26 normal controls are listed in Table 1. All subjects had normal serum T_4, T_3, TSH, cortisol, GH, LH, and testosterone levels. Six subjects had elevated basal FSH levels, eight had hyperprolactinemia, and 11 had suppressed IGF-1 levels. The mean serum FSH level of SCI subjects was significantly greater than that of normal controls ($P < .01$). The mean serum IGF-1 level of SCI subjects was significantly less than that of normal controls ($P < .01$). There was no significant difference in mean basal serum levels of T_4, T_3, TSH, cortisol, LH, prolactin, and GH between SCI subjects and normal controls. As a group, quadriplegic subjects had lower serum T_4 (94 ± 10 *v* 108 ± 18 mmol/L) and T_3 (1.45 ± 0.11 *v* 1.77 ± 0.26 nmol/L) levels as compared with paraplegic subjects ($P < .01$). Body mass index (BMI) of SCI subjects (paraplegic, 19.9 ± 3.1 kg/m^2; quadriplegic, 19.4 ± 3.7; whole group, 19.8 ± 3.2) was significantly less than that of normal controls (21.9 ± 2.4; $P < .01$).

GH responses to GHRH in SCI patients and 26 age-matched controls are shown in Fig 1. There was a significantly decreased GH response to GHRH in SCI subjects as compared with normal controls. Twelve SCI subjects (37.5%) had peak GH responses less than 7 ng/mL, the lower limit of normal ranges in this laboratory. Ten SCI subjects (31.3%) had a delayed peak GH response. In total, 20 SCI subjects (62.5%) had a GH response to GHRH that was reduced and/or delayed.

The area of GH response to GHRH in SCI subjects (paraplegic, 1,023 ± 920 min · ng/mL; quadriplegic, 574 ± 574; whole group, 911 ± 861) was significantly less than that of normal controls (1,374 ± 804; $P < .05$).

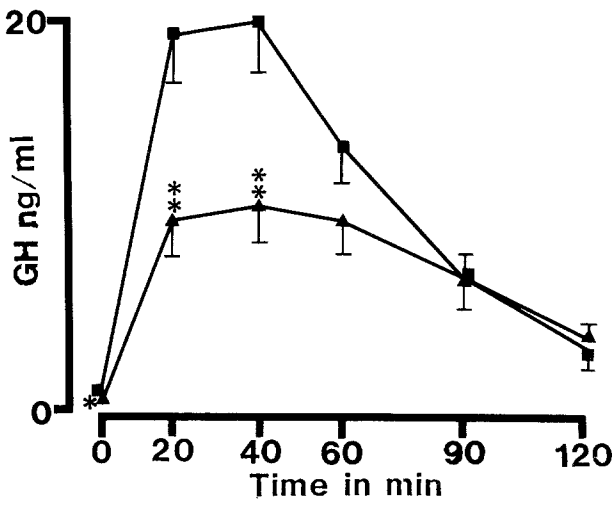

Fig 1. GH response (mean ± SE) to GHRH 1 μg/kg body weight intravenously in 24 paraplegic and 8 quadriplegic men (▲) and 26 age-matched normal controls (■). *$P < .05$, **$P < .01$: SCI *v* normal controls.

The maximal GH response to insulin-induced hypoglycemia is shown in Fig 2. Eight SCI subjects (25.8%) had a peak GH response less than 7 ng/mL, the lower limit of normal response in this laboratory. Eighteen SCI subjects (56.3%) had a reduced GH response to GHRH and/or insulin-induced hypoglycemia. Two SCI subjects had reduced GH responses to both GHRH and insulin-induced hypoglycemia. The mean peak GH response to insulin-induced hypoglycemia in SCI subjects was not significantly different from that in normal controls (21.8 ± 18.2 *v* 17.3 ± 12.9 ng/mL).

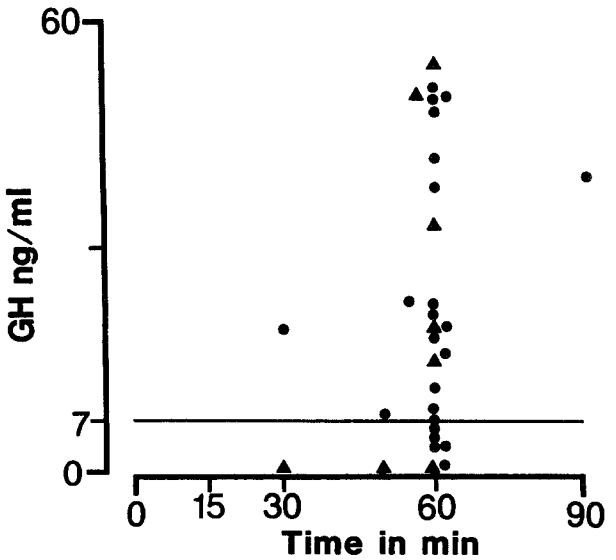

Fig 2. Maximal GH response to insulin hypoglycemia in 31 SCI men. Maximum GH level of 7 ng/mL is considered in this laboratory to be the lower limit of normal response. (▲) Quadriplegic; (●) paraplegic.

There was no significant difference in GH response to GHRH between paraplegic and quadriplegic subjects. Seven of 11 SCI subjects with low serum IGF-1 levels had reduced and/or delayed GH responses to stimuli.

There was no significant correlation between peak and area under the curve of GH response to GHRH or insulin-induced hypoglycemia and serum testesterone level or IGF-1 level.

DISCUSSION

The high incidence of hyperprolactinemia in these SCI subjects is consistent with previous studies.[3,8,10,11] The elevated serum FSH levels were consistent with the impaired spermatogenesis frequently seen in SCI males.[8,9,12] Over one third of the SCI subjects had suppressed serum IGF-1. The mean basal GH level of paraplegic subjects was less than that of controls. Since serum IGF-1 level is dependent on integrated serum GH level,[14] reduced serum IGF-1 levels in SCI subjects suggest that the hypothalamus-pituitary somatotrope axis was suppressed in these subjects.

Previously, Bauman et al[15] reported reduced serum IGF-1 levels and reduced GH response to arginine infusion in SCI subjects. They suggested that physical inactivity is responsible for this phenomenon. In the present study, 18 SCI subjects (56.3%) had a reduced GH response to GHRH and/or insulin-induced hypoglycemia. However, there was no significant difference in GH response to GHRH and insulin-induced hypoglycemia between paraplegic and quadriplegic subjects here. Most of these paraplegic subjects are employed and active in their daily lives. Therefore, to what extent physical inactivity may have contributed to reduced GH secretion in this study is uncertain.

Many factors such as age, sex, hormone milieu, physical activity, nutritional state, stress, and adiposity, as well as other conditions, have been described to influence GH secretion.[16] Some criteria herein were carefully controlled: subjects were healthy, young, active, and under little stress, and had good nutritional status. These patients experienced recurrent lower urinary tract infections, which in each subject occurred on average once per year. Although they were treated before the study and, whenever infections were detected, during follow-up visits to our clinic, it is still not known how much the urinary tract infection suppressed GH secretion, but this factor seemed unimportant. SCI subjects had normal fasting blood glucose and hemoglobin A_{1c} levels, although a high prevalence of carbohydrate intolerance was reported in SCI subjects. Androgens have been shown to enhance basal and stimulated GH secretion in peripubertal and adult males.[17-19] Various degrees of hypogonadism have been reported in SCI subjects. Although free testosterone level was not measured here, serum testosterone levels were within normal limits and subjects still had normal-sized testes. Thus, hypogonadism is not likely an important factor affecting GH secretion in the SCI subjects. Furthermore, there was no correlation between serum testosterone levels and GH responses to GHRH or insulin-induced hypoglycemia in these subjects.

SCI may result in progressive loss of percent and total lean body mass and an increase of percent fat mass.[20-23] Denervation atrophy and reduced energy expenditure are implicated.[21] Reduced lean body mass and increased adiposity can decrease GH secretion and serum IGF levels; in reverse, reduced IGF levels can further decrease lean body mass. Thus, a suppressed hypothalamus-pituitary somatotrope axis in SCI may set up a vicious cycle. Since SCI causes denervation atrophy below the level of injury, there is uneven distribution of lean body mass and fat mass in comparison to able-bodied men. It is not known whether uneven distribution of lean body mass affects GH secretion to the same degree as when the mass is evenly distributed. Recently, peripheral muscular sensory input, impaired in SCI, has been demonstrated to affect secretion of GH.[24] However, there was no correlation between serum IGF-1 level and peak GH response to insulin-induced hypoglycemia or area under the curve of GH response to GHRH in SCI subjects. This suggests that the reduced serum IGF-1 level in SCI was multifactorial.

In this study, mean BMI of SCI subjects was significantly less than that of normal controls. BMI is a surrogate measure of fat mass, but it is a relatively poor measure of adiposity in SCI subjects. SCI subjects were found to have greater adiposity even in the presence of lower BMI as compared with normal controls.[22] This study did not measure fat mass. Subjects with SCI may have greater fat mass, and this possible increase in adiposity may have contributed to suppression of GH release to provocative stimulation. Whether increased adiposity in SCI subjects is the cause or the consequence of suppressed GH secretion is unknown.

The mechanism of suppression of the hypothalamus-pituitary somatotrope axis in SCI subjects is unclear at present. GH secretion is mainly controlled by the stimulatory influence of GHRH and the inhibitory influence of somatostatin, both of which are modulated by hypothalamic neurotransmitters,[13] of which dopamine is a major factor. Thus, dopamine antagonist was shown to inhibit GH response to various stimuli.[25,26] In this study, 20 subjects (62.5%) had an impaired GH response to GHRH stimulation. It has been suggested that insulin-induced hypoglycemia stimulates GH secretion through a reduction in somatostatin secretion.[27] Eight subjects (25.8%) had an impaired GH response to insulin-induced hypoglycemia. Furthermore, eight subjects (25%) had hyperprolactinemia, and seven of them also had an impaired GH response to GHRH and/or insulin-induced hypoglycemia. Since prolactin is under dopamine tonic suppression, hyperprolactinemia suggests reduced dopaminergic tone in these subjects. Nearly one third of the SCI subjects exhibited a delayed GH response to GHRH. Delayed hypophyseal hormone response is commonly seen in patients with hypothalamic dysfunction.[28-30] In a previous study, an elevated gonadotropin response to LHRH, elevated TSH, elevated prolactin response to TSH-releasing hormone, and hyperprolactinemia were found in a group of SCI subjects.[8] It was proposed then that central dopaminergic tone may be reduced in SCI subjects.[8] Ten subjects in this study had also participated in the previous study. Three of them had hyperprolactinemia, five had an elevated LH response to

LHRH, and five had an impaired GH response to GHRH and insulin-induced hypoglycemia. This evidence leads to the conclusion that there is a reduced central dopaminergic tone in SCI subjects. However, findings here do not exclude the possibility of alteration of other neurotransmitters involved in regulation of GH secretion.[16] Further studies are needed to clarify neurotransmitter changes after SCI.

Recently, Bauman et al[31] reported that long-term use of baclofen, a gamma-aminobutyric acid derivative, in SCI subjects improved the blunted GH response to arginine infusion. In this study, there were no significant differences in GH responses to GHRH and insulin-induced hypoglycemia between SCI subjects with or without baclofen. The discrepancy may be explained by the smaller doses of baclofen used here in comparison to those of Bauman et al. Baclofen and other gamma-aminobutyric acid agonists were shown to induce GH secretion acutely, but inhibited the GH response to insulin-induced hypoglycemia or arginine infusion after prolonged use in normal subjects.[32-34]

In conclusion, this study demonstrated that GH response to GHRH and insulin-induced hypoglycemia was reduced in SCI subjects, and that serum IGF-1 level was also decreased. Although the mechanism is not clear, this finding is consistent with hypothesis that central dopaminergic tone is reduced after chronic SCI.

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