Alcoholism Abolishes the Growth Hormone Response to Sumatriptan Administration in Man

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To assess the possible influence of alcoholism on serotonergic control of growth hormone (GH) secretion, 6 mg of the 5-HT1D serotonergic receptor agonist, sumatriptan, was injected subcutaneously in a group of nine normal controls (aged 32 to 49 years) and in nine age-matched nondepressed male alcoholic subjects after 10 to 25 days of abstinence from alcohol. During the same period, subjects were also tested with GH-releasing hormone ([GHRH] 1 μg/kg body weight in an intravenous [IV] bolus) and L-arginine, which releases GH from somatostatin inhibition (50 g in 50 mL normal saline over 30 minutes) to determine whether GH secretion in response to alternate secretagogues is preserved in alcoholics. A control test with administration of normal saline instead of drug treatments was also performed. Plasma GH levels were recorded over 2 hours in all tests. Administration of placebo did not change plasma GH levels in any subject. Similar GH responses were observed in normal controls and alcoholic subjects when GHRH or arginine were administered. A significant GH increase was observed in normal controls after sumatriptan injection; in contrast, GH secretion was not modified by sumatriptan administration in alcoholic patients. These data show that alcoholism is associated with an impairment in the serotonergic-stimulatory regulation of GH secretion, whereas GH responses to direct pituitary stimulation with GHRH or to release from somatostatinergic inhibition with arginine appear to be preserved in alcoholics.

THE CENTRAL ADRENERGIC system is thought to have a dominant stimulatory role in the control of growth hormone (GH) secretion.[1,2] Particularly, stimulation of α_2-adrenergic receptors has been found to induce activation of GH-releasing hormone (GHRH).[3-6] However, studies reported by Conway et al[7] in the rat have shown that α_2-adrenergic receptor–stimulated GH release is mediated by serotonergic neurotransmission. Recently, a blunted GH response to the α_2-adrenoceptor agonist, clonidine, has been described in alcoholics[8] and has been attributed to alterations in central adrenergic mechanisms.

In view of the well-known serotonergic disorder affecting alcoholic patients, we wondered whether alterations in the control of GH release unmasked by clonidine could be attributed to an underlying serotonergic defect. The availability of the specific 5-HT1D receptor agonist, sumatriptan, which selectively stimulates GH secretion,[9,10] provided the possibility to test serotonergic control of GH secretion in alcoholics. Furthermore, to establish possible alterations in alcoholics in the activity of the major regulators of GH secretion, ie, GHRH and somatostatin, the same subjects were tested on different occasions with GHRH and with arginine, an amino acid that likely stimulates GH secretion by inhibiting hypothalamic somatostatin release.[11]

SUBJECTS AND METHODS

Nine male chronic alcoholics aged 32 to 48 years with a history of continuous ethanol consumption of 11.7 ± 3.4 years (mean ± SEM) were informed of the purpose of the study and gave their informed consent. The study was in accordance with the Helsinki II Declaration.

The patients were recruited when they came to the center for alcoholism of the Institute of Internal Medicine, University of Parma, and asked to participate in a rehabilitation program. All patients were assessed with the Hamilton Rating Scale for Anxiety[12] and the Hamilton Rating Scale for Depression[13] with negative results. All subjects had normal body weight (body mass index [mean ± SE], 22.7 ± 0.9).

Two physicians performed clinical examinations of the patients. Only subjects with normal or slightly altered liver function were included in the study. Particularly, the presence of hepatic abnormalities was assessed with laboratory tests (plasma levels of aspartate transaminase, 48 ± 13 [mean ± SD of nine patients] UIK; alanine transaminase, 31 ± 15 UIK; gamma-glutamyl transpeptidase, 115 ± 40 U/L) and with liver, spleen, and portal vessel echography. Ultrasound examination and, in dubious cases, biopsy excluded the presence of cirrhosis.

Nine normal men (aged 32 to 50 years; body mass index, 23.0 ± 1.1) participated in the study as controls. Control and alcoholic subjects showed normal plasma levels of free fatty acids (controls, 0.7 ± 0.08 mmol/L; alcoholics, 0.67 ± 0.07), measured with a colorimetric method using kits provided by Boehringer (Mannheim, Germany).

From the time of admission to the rehabilitation program (10 days before the first test), alcoholics were on a standard normocaloric diet. Controls were required to follow a similar diet for 10 days before and during the period of study.

Each subject was tested four times within 2 weeks (sumatriptan, GHRH, arginine, and placebo tests). Tests started 10 days after alcohol withdrawal and were performed in random order separated by 5-day intervals.

The experimental procedure was similar for all tests.

At 9 AM on the day of experiment, intravenous (IV) indwelling needles were inserted into antecubital veins of subjects in the recumbent position and fasting from the previous evening. The needles were kept patent with a slow infusion of normal saline (NaCl 0.9%); one needle was used for blood sampling and the other for GHRH, arginine, or saline administration. Sumatriptan was given subcutaneously. In all tests, a basal blood sample was withdrawn 30 minutes after needle insertions, just before drug administration (time 0). Further blood sampling was performed at 15, 30, 45, 60, 90, and 120 minutes.

The tests were performed as follows: sumatriptan test, 6 mg sumatriptan (Imigran; Glaxo, Verona, Italy) diluted in 0.5 mL

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Submitted November 22, 1994; accepted March 28, 1995.

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0026-0495/95/4412-0012$03.00/0

distilled water was injected subcutaneously at time 0; GHRH test, 1 μg/kg body weight GHRH (1-29; Geref, Serono, Rome, Italy) diluted in 1 mL normal saline was injected as an IV bolus at time 0; arginine test, 30 g arginine monohydrochloride diluted in 50 mL normal saline was infused IV over a 30-minute period from time 0; and placebo test, an IV injection of 2 mL normal saline at time 0 was followed by infusion of 50 mL normal saline over 30 minutes. In addition, 0.5 mL distilled water was injected subcutaneously at time 0.

Blood pressure and heart rate were monitored at each sampling time.

Assays

Blood samples were collected and centrifuged cold; plasma was stored at −20°C until assayed. Plasma GH levels were determined by radioimmunoassay (RIA)[14] using commercial kits. All samples were analyzed in the same assay and in duplicate. Sensitivity and intraassay and interassay coefficients of variation were 0.5 ng/mL, 3.6%, and 8%, respectively.

Plasma insulin-like growth factor-I (IGF-I) and 24-hour urinary cortisol levels were also measured, because both hormones are known to influence GH secretion.[15] Plasma levels of IGF-I were measured in samples taken at time 0 of sumatriptan, GHRH, arginine, and placebo tests. They were evaluated by RIA using kits obtained from Nichols Institute (San Juan Capistrano, CA). Urinary cortisol level was measured after extraction with dichloroethane in a sample collected over the 24 hours preceding each test.

Cortisol was determined by RIA with commercial kits (Amlec, Westbrook, ME). In our laboratory, the normal range of urinary cortisol values is 80 to 250 nmol/24 h. Sensitivity of the assay was 2.8 nmol/L. Intraassay and interassay coefficients of variation were 3.7% and 7.5%, respectively. The four values for plasma IGF-I and 24-hour urinary cortisol obtained in each subject (before the four tests) were averaged. Each mean was considered the individual value for each subject and used for statistical analysis within each group.

Statistical analysis was performed with Wilcoxon's matched-pair rank-sum test, the Kruskall-Wallis test, and ANOVA, as appropriate. Data are reported as the mean ± SE.

RESULTS

Basal GH levels were similar in control and alcoholic subjects (Figs 1 and 2). In both groups, GHRH (Fig 1A) and arginine (Fig 1B) induced significant increments in plasma GH concentrations. GH responses in the two groups were similar ($P > .01$ at times 15, 30, and 45 minutes and $P > .05$ at time 60 minutes *v* baseline for GHRH test; $P > .01$ at times 45 and 60 minutes and $P > .05$ at times 30, 90, and 120 minutes *v* baseline for arginine).

Administration of placebo was without effects on GH secretion in all subjects (Fig 2). Sumatriptan administration induced a striking increase in plasma GH levels ($P < .01$ at times 30, 45, and 60 minutes and $P < .05$ at time 90 minutes *v* baseline) in the control group (Fig 2). In contrast, sumatriptan injection did not change plasma GH concentrations in alcoholic patients (NS *v* baseline at any time point, $F = 27.80$, $P < .01$ *v* normal controls) (Fig 2).

Plasma IGF-1 levels were significantly higher in controls (225 ± 17 ng/mL) than in alcoholic subjects (145 ± 15 ng/mL, $P < .01$). Free urinary cortisol levels were similar in controls (168.0 ± 21.0 nmol/24 h) and alcoholic subjects (165.3 ± 18.2).

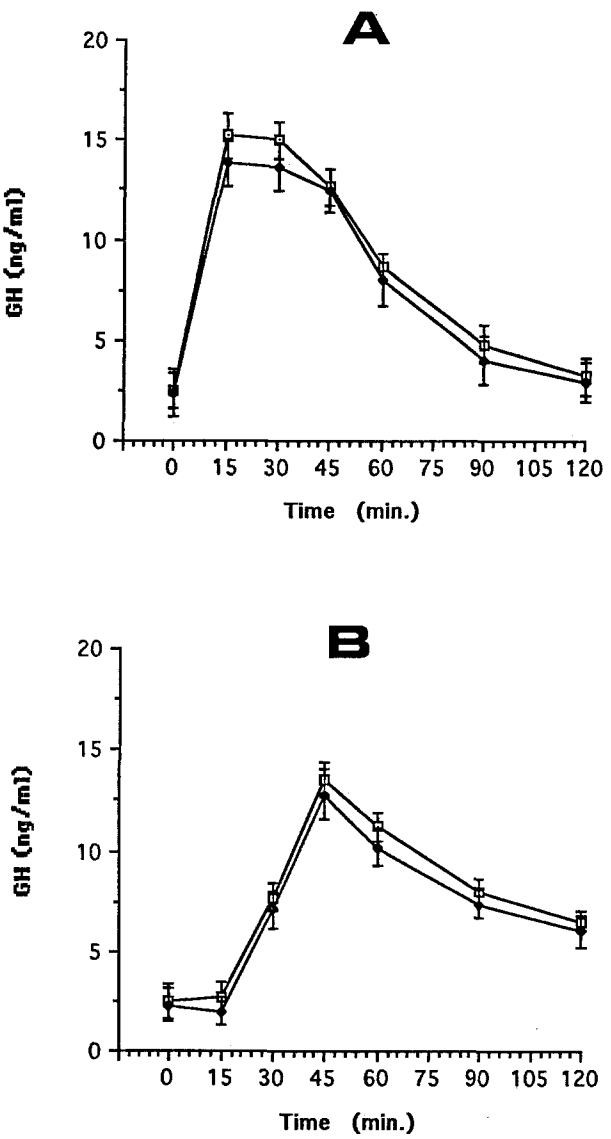

Fig 1. Effect of IV administration of GHRH 1 μg/kg body weight as a bolus at time 0 (A) or of arginine 30 g infused over 30 minutes from time 0 (B) on plasma GH concentrations in 9 normal controls (□) and 9 alcoholics (◆). Each point represents the mean ± SE.

No blood pressure alterations or side effects were observed after drug administration in any subject.

DISCUSSION

In agreement with previous findings,[8] our alcoholics did not show significant alterations in GH response to GHRH. This observation and the normal GH response to arginine argue against defects at the pituitary level of GHRH- or somatostatin-mediated mechanisms in alcoholics. On the other hand, the absent GH response to sumatriptan in the same subjects suggests the existence of a serotonergic dysfunction in alcoholics.

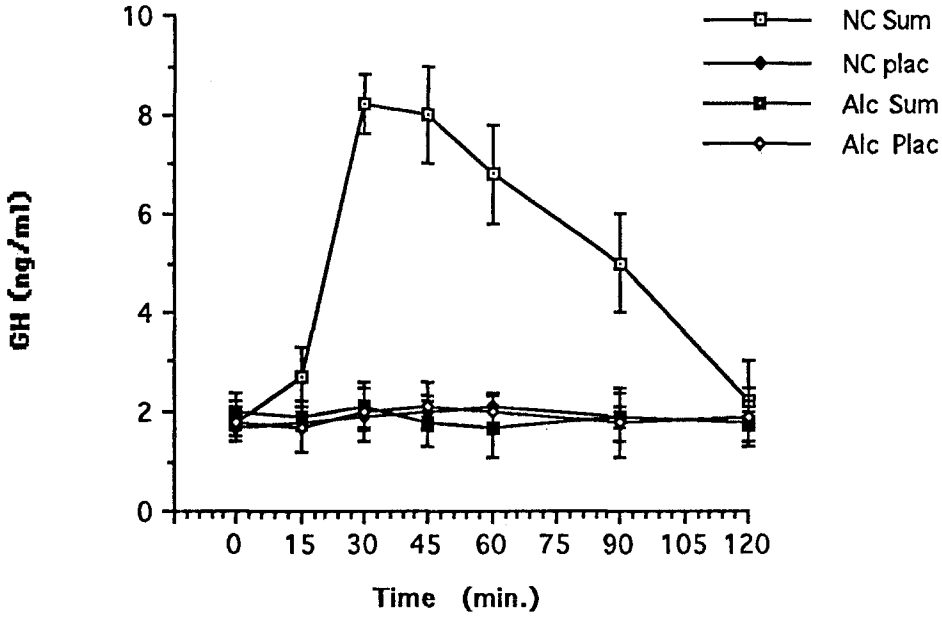

Fig 2. Effect of subcutaneous administration at time 0 of 6 mg sumatriptan (Sum) or placebo (Plac) on plasma GH concentrations in 9 normal controls (NC) and 9 alcoholics (Alc). Each point represents the mean ± SE.

A variety of studies based on manipulation of serotonin activity and/or content in the brain have shown that alterations in serotonergic neurotransmission are involved in modulation of alcohol intake,[16,17] tolerance,[18] and dependence.[19] At present, it is unknown whether serotonergic alterations are the cause or the result of alcohol ingestion. In fact, alcohol dependence and anxiety disorders frequently coexist, and a central serotonergic dysfunction has been proposed as a common neurochemical etiology for both disorders.[20] On the other hand, alcohol is known to modify serotonergic transmission at various levels in the central nervous system.[21]

Even though a number of serotonergic receptor subtypes (eg, 5-HT1A, 5-HT1B, 5-HT1C, 5-HT1D, and 5-HT2) have been described, information regarding selective receptor alterations in alcoholism is scant. In fact, a different involvement of serotonergic receptor subtypes in alcoholism might explain selective changes in the control of different pituitary hormones. For example, corticotropin (ACTH) release is stimulated by activation of serotonin 5-HT2 and 5-HT1C receptors. Using 6-chloro-2-(1-piperazinyl)pyrazine (MK 212), a specific serotonin 5-HT2 and 5-HT1C receptor agonist, Lee and Meltzer[22] have found that ACTH stimulation via these receptors is not altered in alcoholics studied at least 2 weeks after alcohol withdrawal. In contrast, in the present study the sumatriptan test has demonstrated that alcoholics have a specific defect in 5-HT1D receptor–mediated neurotransmission in the control of GH secretion.

The finding of a deficient activity of α_2-adrenergic[8] and serotonergic 5-HT1D neurotransmission in the control of GH secretion in alcoholic patients suggests that the central regulation of GH secretion may be impaired in alcoholism. In fact, studies in rats demonstrated an important role of these neurotransmitters in the control of 24-hour spontaneous episodic GH surges.[1,2,23,24] Since GH has an important role in the control of IGF-I levels,[25] finding low IGF-I levels in alcoholic patients lends further support to the hypothesis that GH secretion is altered in alcoholics. Low circulating IGF-I levels in our alcoholics cannot be attributed to liver failure,[26] because none of our patients was affected by significant alterations in hepatic function.

Previous studies showed normal[27-29] or increased[30] circulating levels of ACTH/cortisol in alcoholics; however, 24-hour free urinary cortisol levels were normal in our alcoholics. Taken together, these observations on GH and ACTH/cortisol secretory systems in alcoholics are similar to those found in senescence. In fact, senescence is characterized by decreased GH and normal ACTH/cortisol secretions. However, it is still unknown to what extent a GH decline in the presence of a preserved ACTH function contributes to the decrements in protein synthesis, bone loss, and impaired immunologic, liver, and renal function that characterize alcoholism.

In conclusion, we observed altered serotonin regulation of GH secretion in alcoholic patients. Specifically, stimulation of 5-HT serotonin receptors with sumatriptan does not evoke the increase in GH normally found in nonalcoholic controls.

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