Long-Term Administration of Acipimox Potentiates Growth Hormone Response to Growth Hormone–Releasing Hormone by Decreasing Serum Free Fatty Acid in Obesity

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Obesity is associated with an impairment of normal growth hormone (GH) secretion and blunted responses to all stimuli. A high plasma free fatty acid (FFA) level is frequently observed in obesity. FFA participates in the regulation of pituitary GH secretion. To determine whether the derangement of GH secretion in obesity is associated with high plasma FFA levels, tests with GH-releasing hormone (GHRH) and acipimox (ACX), an antilipolytic agent able to decrease FFA, were undertaken in six obese subjects and seven normal control subjects. In addition, the effect of prolonged suppression of FFA level on GH response to GHRH after administration of ACX for 1 month was also examined in each of the obese subjects. The GH response in obese subjects (median, 9.1 μg/L) to GHRH (1-29) (1 μg/kg intravenously [IV]) was significantly blunted as compared with normal control subjects (23.5 μg/L, $P < .05$). Basal FFA levels were higher in obese subjects (855.2 μEq/L) than in normal control subjects (514.6 μEq/L, $P < .05$). One-dose ACX (500 mg) decreased FFA levels in both obese and normal subjects: the lowest FFA levels in obese subjects (158.3 μEq/L) 2 to 2.5 hours after ACX were similar to those of normal control subjects (108.7 μEq/L). One-dose ACX potentiated GHRH-stimulated GH response in both obese and normal subjects. GH responses potentiated by ACX in obese subjects (27.1 μg/L) were similar to GH responses to GHRH in normal control subjects, but lower than in normal subjects treated with ACX plus GHRH (58.5 μg/L, $P < .05$). Thereafter, all of the obese subjects were treated with ACX for 1 month, after which the ACX plus GHRH tests were repeated. After 1 month of acipimox administration in the obese subjects, GH responses (38.8 μg/L) were significantly higher than those of obese subjects treated with GHRH and one-dose ACX plus GHRH ($P < .05$). They were similar to GH responses of normal control subjects receiving the one-dose ACX plus GHRH test. In conclusion, in obesity the prolonged suppression of FFA levels induced by long-term administration of ACX potentiated somatotrope responsiveness, likely acting at the pituitary level, suggesting that the duration of FFA suppression had an important relation to the magnitude of GH response.

OBESITY is associated with the impairment of normal growth hormone (GH) secretion and blunted responses to all stimuli such as hypoglycemia, GH-releasing hormone (GHRH), L-dopa, arginine, glucagon, physical exercise, and sleep.[1-4] GH secretory dysfunction in obesity can be explained by three possible mechanisms: impairment in GHRH release from the hypothalamus, high somatostatin activity of the hypothalamus, or decreased responsiveness of the pituitary somatotrope cells.

The hyperinsulinemia and insulin resistance frequently observed in obesity are associated with increased levels of plasma free fatty acid (FFA).[5] FFA participates in the regulation of pituitary GH secretion. Decreased plasma FFA levels stimulate GH secretion, and increased levels block GH secretion elicited by all stimuli.[6,7] Therefore, the high FFA levels of obesity might be responsible for the GH secretory dysfunction. Also, it was previously reported that the GH increase was significantly greater during longer FFA suppression versus shorter FFA suppression in normal subjects.[8]

In this study, we evaluated the effect of acipimox (ACX), an antilipolytic agent able to decrease FFA, on the GH response to GHRH in normal and obese subjects. We also evaluated the effect of chronic suppression of FFA levels on the GH response to GHRH after administration of ACX for 1 month in the obese subjects.

SUBJECTS AND METHODS

Subjects

Six obese Korean men aged 20 to 30 years (mean ± SE, 24.3 ± 2.1) and seven normal men aged 24 to 28 years (26.1 ± 3.2) were studied. The normal control subjects were within 10% of their ideal body weight, and the obese subjects weighed more than 130% of their ideal body weight as determined by the Fogarty Center Conference on Obesity. Their body mass index was 31.8 ± 1.2 kg/m^2, and the waist to hip ratio (0.98) showed that all were upper-body obese. An oral glucose tolerance test was performed on each to screen for impaired glucose tolerance or diabetes mellitus: none tested positive for either. None had other medical problems or had used any hormonal preparations within the 60 days before the study. All subjects were matched in lifestyle, without any special diet or exercise. Their routines before and during the 1-month ACX administration were similar.

Study Protocol

The study was approved by the Hospital Ethics Committee, and informed consent was obtained from each subject. All subjects were asked to arrive at the hospital at 8 AM on the day of the study after fasting overnight. Intravenous (IV) cannulas were placed in the antecubital vein of each subject, and the subjects were administered a slow infusion of 0.9% NaCl. After a 1-hour rest period to minimize the effects of physical activity and nonspecific stress on GH levels, the tests were started. Subjects remained supine during the entire study. The following two tests were performed in random order 7 days apart.

GHRH test. At 9 AM (time −120 minutes), a placebo was administered orally. Two hours later (time 0), 1 μg/kg GHRH

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(1-29)NH_2 (BACHEM Feinchemikalien, Bubendorf, Switzerland) was injected as an IV bolus. Blood samples were collected at −150, −120, −90, −60, −30, 0, 15, 30, 60, and 120 minutes.

One-dose ACX plus GHRH test. At 9 AM (time −120 minutes), 500 mg ACX (Olbetam; Farmitalia Carlo Erba, Milan, Italy) was administered orally. Two hours later (time 0), 1 μg/kg GHRH was injected as an IV bolus. Blood samples were collected at −150, −120, −90, −60, −30, 0, 15, 30, 60, and 120 minutes.

ACX plus GHRH test after 1-month administration of ACX. ACX 500 mg (250 mg every 12 hours, 8 AM and 8 PM) was administered orally for 1 month to the same obese subjects. Normal subjects were excluded from this test, because it was unnecessary to administer ACX to normal control subjects who had a normal range of serum FFA. At the end of the 30 days, a one-dose ACX plus GHRH test was performed as described earlier. There were no changes in diet, exercise, or body weight during the 1-month ACX administration.

Each specimen was centrifuged immediately, and the plasma was stored at −70°C until assayed.

Hormonal Assays

GH level was measured by an immunoradiometric assay from Daiichi (Tokyo, Japan); the sensitivity was 0.1 μg/L, and intraassay and interassay coefficients of variation were 1.3% and 1.4%, respectively. All samples from each subject were analyzed in duplicate at the same time. FFA concentrations were determined by calorimetry.

Statistical Analysis

The results are expressed as the median. Statistical comparisons were made using the Mann-Whitney *U* test between different groups and the Wilcoxon rank test and Friedman two-way ANOVA between related groups. These tests were used because the assays yielded non–normally distributed results. The area under the GH secretory curve was calculated by a trapezoidal method. *P* less than .05 was considered statistically significant.

RESULTS

In normal control subjects, GHRH administration induced a clear-cut increase in plasma GH levels. The median peak GH level was 23.5 μg/L 30 minutes after GHRH (Fig 1). ACX decreased FFA levels. The lowest level (108.7 μEq/L) occurred 2 to 2.5 hours after ACX, and levels continued to be suppressed throughout the test. ACX pretreatment also potentiated the plasma GH response. The median peak plasma GH level was 58.5 μg/L ($P < .05$), and the area under the GH response curve (67.3 μg/L · h) also increased nearly twofold ($P < .05$; Fig 2).

In obese subjects, the response to GHRH administration was lower (Fig 1). The median peak GH level was 9.1 μg/L, significantly lower than the response in normal control subjects. Basal FFA levels (855.2 μEq/L) were higher in obese subjects than in normal controls (514.6 μEq/L,

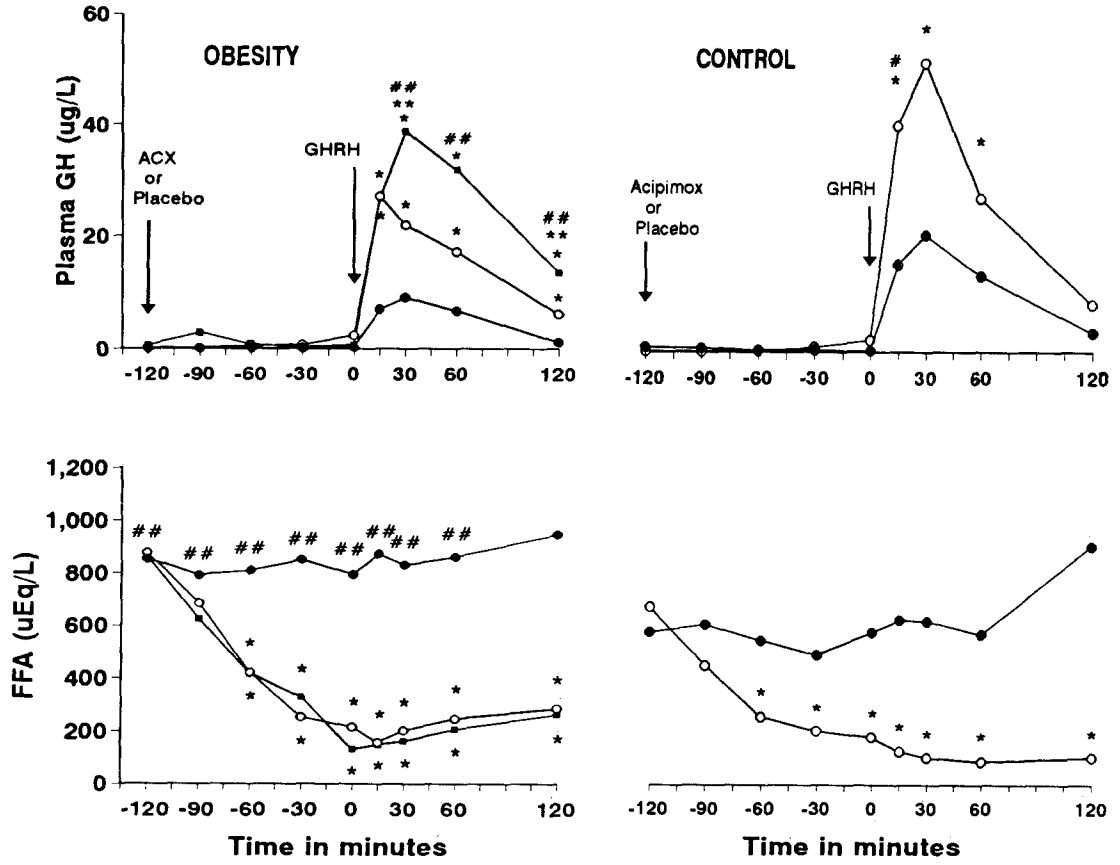

Fig 1. Median plasma GH and FFA concentrations after administration of GHRH 1 μg/kg IV (●) or one-dose ACX, 500 mg plus GHRH (○) in 6 obese subjects and 7 normal controls, and ACX plus GHRH test after administration of ACX 500 mg/d for 1 month (■) in the obese subjects. *$P < .05$ *v* GHRH; **$P < .05$ *v* ACX plus GHRH; #$P < .05$ *v* ACX plus GHRH after long-term ACX; ##$P < .05$ *v* GHRH in controls.

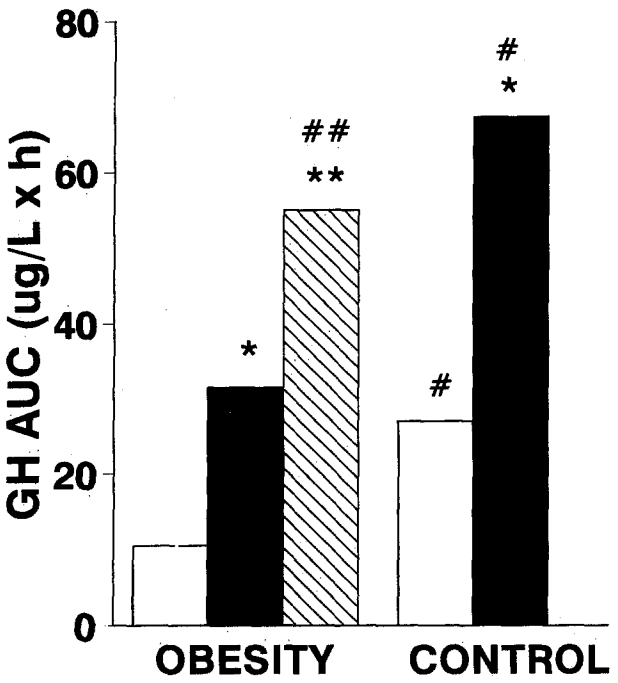

Fig 2. GH response area under the curve (AUC) after administration of (□) GHRH and (■) ACX + GHRH in 6 obese subjects and 7 normal controls, and (▨) LACX + GHRH (ACX plus GHRH test after administration of ACX 500 mg/d for 1 month) in the same obese subjects. *$P < .05$ v GHRH; **$P < .05$ v GHRH and ACX + GHRH in obesity; #$P < .05$ v GHRH in obesity; ##$P < .05$ v GHRH in controls.

$P < .05$). ACX decreased FFA levels in both obese and normal control subjects. In obese subjects, the lowest FFA levels (158.3 μEq/L) 2 to 2.5 hours after ACX were similar to those in normal control subjects receiving ACX. However, FFA levels increased gradually thereafter in obese subjects. Pretreatment with ACX also potentiated the plasma GH response. The median peak plasma GH level (27.1 μg/L) and the area under the GH response curve (31.5 μg/L · h) were similar to GH responses to GHRH in normal control subjects without pretreatment of ACX.

Administration of ACX for 1 month resulted in a further enhancement of plasma GH response. The median peak plasma GH level (38.8 μg/L) and the area under the GH response curve (55.7 μg/L · h) were higher than those obtained with the GHRH test and the one-dose ACX plus GHRH test ($P < .05$) in obese subjects, and were similar to the GH responses of the one-dose ACX plus GHRH test in normal control subjects.

DISCUSSION

The results of this study confirm that obese subjects show a markedly blunted GH response to GHRH, and the restoration of GH response by ACX pretreatment suggests that the FFA level plays an important role in GH secretion in obesity, as previously reported by others.[9-11] In addition, we also demonstrated that the prolonged decreased FFA levels induced by long-term administration of ACX potentiated the somatotrope responsiveness, likely acting at the pituitary level.

Consistent with our previous study,[5] we found that GH secretory dysfunction might be associated with the high plasma FFA levels frequently observed in obesity. In 1995, we also reported[12] that ACX potentiated the GH response to GHRH with pyridostigmine pretreatment in obesity. The combined action of ACX and pyridostigmine should have a potentiating effect on GH release from the pituitary gland, assuming a partial reduction of somatostatin release by pyridostigmine plus increased somatotrope responsiveness by decreasing the FFA level with ACX. These findings suggest that ACX may not be significantly involved in somatostatin secretion at the level of the hypothalamus.

ACX was used to decrease plasma FFA levels in this study. The pharmacologic action of ACX is to block FFA release from adipose tissue,[13] leading to a decrease in plasma FFA levels. In a previous report,[14] ACX was shown to enhance the GH response to GHRH in normal control subjects. We found that ACX potentiated the GH response to GHRH in both normal and obese subjects. The enhanced GH responses induced by one-dose ACX in obese subjects were similar to GH responses to GHRH alone in normal control subjects, but not to responses potentiated by ACX in normal control subjects. These results indicated that high plasma FFA levels may result in the reversible defect of the somatotropes in obesity, and that the GH response is significantly greater during the longer duration of FFA suppression induced by long-term administration of ACX. These results suggested that in obesity, chronic increased FFA levels may lead to a reduced responsiveness of the somatotrope. We could support the hypothesis that endogenous GHRH release is well preserved and the somatotropes are intact and functioning in obesity. In our study, ACX decreased FFA levels in both obese and normal control subjects. FFA levels of obese subjects increased gradually thereafter, whereas FFA levels of normal control subjects continued to be suppressed throughout the test after ACX administration. The basal FFA level did not decrease after long-term administration of ACX in obese subjects. This is in agreement with the report by Saloranta et al,[15] who also showed that the basal FFA level was not suppressed after long-term treatment with ACX. Since FFA is the major energy source of the body, it can be speculated that the body attempts to maintain energy production constant by allowing FFA levels to increase to compensate for being suppressed. Since GH levels are important for the maintenance of lipolysis while fasting, if the secretion of GH was elevated during ACX treatment, it could be responsible for the finding that FFA levels rebounded with long-term treatment with the drugs.

A decrease in GH stores consequent to a decrease in GHRH secretion cannot be excluded but seems improbable, since it has been reported that pituitary GH content is similar in genetically obese rats and lean control rats.[16] Other reports state that FFA may influence GH secretion by acting at the hypothalamus or pituitary level.[17-20] Casanueva et al[6] demonstrated that FFA-induced blockade

of GH secretion was exerted at the pituitary level. The studies showed that the FFA (caprylic and oleic acid) inhibited GH release to GHRH but did not alter prolactin release in rat anterior pituitary cells. In contrast, Imaki et al[18] found that in rats immunized with antisomatostatin serum, the inhibitory effects of FFA on GH secretion could be mediated, at least in part, by an increase in somatostatin secretion.

In conclusion, our results strongly suggest that in obesity the prolonged suppression of FFA level induced by long-term administration of ACX potentiated somatotrope responsiveness, likely acting at the pituitary level, suggesting that the duration of FFA suppression is important for the magnitude of GH secretion in obesity, although other factors might also be involved in GH derangement.

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