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Growth Hormone Response to Arginine in Normal Subjects and in Patients with Chemical Diabetes and Effect of Clofibrate and of Metergoline (39765)

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Growth hormone (GH) has been implicated in the pathogenesis of diabetes mellitus and of diabetic microangiopathy (1-3). However, studies concerning GH secretion in diabetes have yielded variable results. GH has been found low in maturity-onset diabetes (4) and high in juvenile (5) or in poorly controlled diabetes (6). In chemical diabetes (CD), GH response to oral glucose has been found either decreased (7) or elevated (8).

The aim of our work was to evaluate the release of GH in response to arginine in patients with chemical diabetes (CD), that is in patients with normal fasting blood glucose levels, but with abnormal glucose tolerance. Since GH is involved in lipid metabolism (1, 9, 10) we have attempted to correlate the arginine-induced GH release with the serum triglyceride and cholesterol levels and to evaluate the effect of clofibrate, a known hypolipemic agent, on GH secretion.

In recent years, several studies have suggested the existence of a monoaminergic control of GH secretion. Thus, catecholamines (11), and particularly dopamine (12), have been shown to stimulate GH release, while serotonin has been found to stimulate (13), to inhibit (14), or to have no effect (15, 16). Recently, we have found that metergoline, a specific antiserotonin agent (17, 18), increases GH response to arginine in normal subjects (19). For this reason we have studied also the effect of this drug in patients with CD.

Materials and methods. We studied 86 volunteers, 20 to 80 years old. Twenty-six of them suffered various degrees of obesity. None of them had a family history of diabetes. All of them were given an oral glucose tolerance test (OGTT) after an overnight fast and were divided into CD and controls, according to the criteria of Fajans and Conn (20), with no correction for advancing age. On different days, all subjects underwent an arginine infusion test (AIT) (25 g of l-arginine monochloride infused as a 10% solution over a 30-min period). On the morning of the AIT, serum triglycerides and cholesterol levels were also determined. All tests were performed at 9 AM.

In seven subjects with normal OGTTs (two of them were obese) and eight patients with CD (three obese), the AIT was repeated after treatment with clofibrate (3 g/day for 10 consecutive days). Seven normal subjects and eight CD patients, of normal body weight and properly matched for age and sex, were treated with metergoline (2 mg every 4 h) for 3 days and, on the fourth morning, a second AIT was performed.

Serum GH levels were measured by radioimmunoassay (21). The GH response was expressed as the area under the curve describing the increment above the fasting level (ng/ml/120 min). Serum triglycerides and cholesterol levels were determined according to the methods of Eggstein (22) and Watson (23), respectively.

The statistical significance of the results was calculated by means of the Student's *t* test. Whenever a normal distribution of the data was not obtained the Wilcoxon nonparametric test was also applied.

Results. The GH response to arginine in the seven groups of subjects studied is shown in Fig. 1. A significant difference was found between males and females and between obese and nonobese females with normal glucose tolerance, but not between the three groups of patients with CD. When males and females with normal glucose tolerance were considered together, GH secretion was found impaired when the serum triglyceride levels were higher than 172

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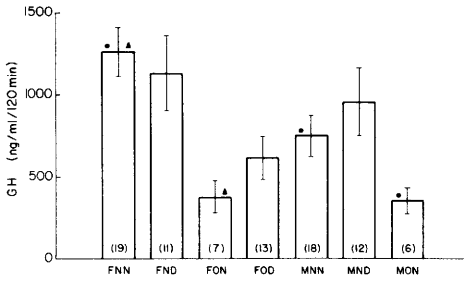

FIG. 1. Serum growth hormone (GH) response to intravenous arginine in patients with normal glucose tolerance and in patients with chemical diabetes. Average ± SEM. Number of cases in parentheses. F, females; M, males; NN, nonobese, nondiabetic; ND, nonobese, diabetic; ON, obese, nondiabetic; OD, obese, diabetic; ●, $P < 0.02$; ▲, $P < 0.01$.

mg% and when the patients were obese, although GH-triglyceride and GH-body weight regression lines could not be obtained. In CD patients these differences were smaller and were not statistically significant (Figs. 2 and 3). No relationship between serum cholesterol levels and GH secretion was found either in normal subjects or in patients with CD. When the subjects were classified according to sex, obesity, and serum triglyceride levels, no statistically significant differences in GH release were found between normal subjects and patients with CD (Figs. 1-3). Clofibrate treatment reduced triglyceride levels in control subjects (173.3 ± 19.56 to 106.6 ± 18.61 mg/100 ml; $P < 0.005$), but not in patients with CD (149.2 ± 19.62 to 133.7 ± 11.12 mg/100 ml; N.S.), and significantly enhanced the GH response to arginine (Fig. 4A) in the controls, but not in the CD patients. Metergoline treatment enhanced GH release in normal subjects, but not in the CD patients (Fig. 4B).

Discussion. Our data indicate that chemical diabetes does not significantly alter the serum GH concentration or its response to arginine although it seems to reduce the differences between males and females, and between obese and nonobese females, findings observed also by other investigators (13, 24).

In subjects with normal OGTT, but not in those with CD, obesity and elevated serum triglyceride levels were associated with a blunted GH release. Reduction of hypertriglyceridemia by clofibrate, without changes in body weight, resulted in a significant enhancement of arginine-induced GH release in the controls, but not in the CD patients. Thus, our data suggest the existence of an inverse relationship between GH release and serum triglyceride levels in normal subjects. Other known effects of clofibrate are not likely to explain our results. For example, clofibrate increases tryptophan concentration in the plasma and in the brain (25), but tryptophan inhibits hypoglycemia-induced GH release (14) and, therefore, an increased plasma concentration of this amino acid by clofibrate could only lead to a reduction in GH secretion, not to an enhancement. Similarly, tryptophan is a biosynthetic precursor of serotonin and, although serotonin may stimulate GH release (26), our data indicate that the GH re-

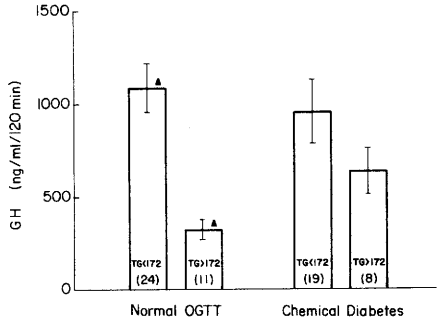

FIG. 2. Serum growth hormone response to intravenous arginine in patients with normal oral glucose tolerance (OGTT) and with chemical diabetes divided according to their serum triglyceride levels (TG). Average ± SEM. Number of cases in parentheses. ▲, $P < 0.01$.

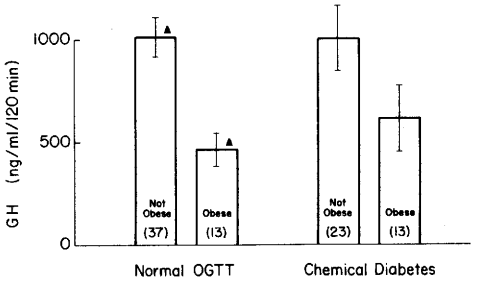

FIG. 3. Serum growth hormone response to arginine infusion in patients with normal oral glucose tolerance (OGTT) and with chemical diabetes, obese and not obese. Average ± SEM. Number of cases in parentheses. ▲, $P < 0.01$.

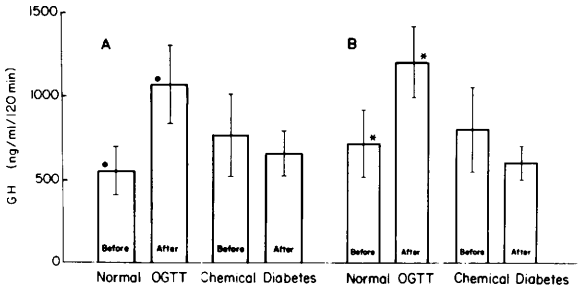

FIG. 4. Serum growth hormone response to intravenous arginine in patients with normal oral glucose tolerance (OGTT) and with chemical diabetes. (A) Before and after clofibrate treatment. (B) Before and after metergoline treatment. Average ± SEM. ●, $P < 0.02$; *, $P < 0.05$.

sponse to arginine was enhanced by metergoline, a specific antiserotonin agent. Therefore, it would appear that, in normal subjects, the effect of clofibrate on serum triglyceride levels is of greater importance than its effect on serum tryptophan concentration. Our results with metergoline are in contrast with the observation that cyproheptadine, another antiserotonin agent, administered in a single intravenous infusion or repeatedly, by the oral route, reduces the GH response to arginine (27) and to insulin hypoglycemia (32). Thus, it would appear that different treatment schedules are not responsible for the different effects of metergoline and cyproheptadine on GH release. On the other hand, it should be noted that cyproheptadine is also an antihistaminic agent and that dexchlorpheniramine and meclastine, two other antihistaminic drugs (28), inhibit arginine-induced GH release (29).

We have no satisfactory explanation for the failure of metergoline and clofibrate to reduce the GH response to arginine in patients with CD. An insulin-mediated effect of arginine on GH release seems to be ruled out by the fact that both clofibrate (30) and metergoline (31) reduce the insulinogenic effect of arginine in normal subjects as well as in patients with CD. On the other hand, a proposal of a minor/different sensitivity of the hypothalamus and/or the pituitary to metergoline and clofibrate in CD patients, is at present tempting, but deserves further investigation.

In our study all the tests were always performed at the same time in the morning. In addition, basal GH levels in CD patients and in controls were not different. These two factors, taken together, indicate that our results were not due to oscillations in GH release similar to those observed in patients with overt diabetes mellitus.

In conclusion, our results suggest that, in CD patients, GH release is not overtly abnormal, although it is not as well-regulated as it is in normal subjects. Other studies will determine whether the deterioration of GH release will precede or follow the deterioration in glucose tolerance as CD progresses to overt diabetes mellitus.

Summary. The growth hormone response to arginine infusion was greater in normal females than in normal males and was impaired in patients with obesity and/or elevated serum triglyceride levels, but with normal glucose tolerance. In patients with chemical diabetes these differences were smaller and were not statistically significant. Both clofibrate, a hypolipemic agent, and metergoline, an antiserotonin drug, enhanced GH response to arginine in normal subjects, but not in patients with CD.

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