

Testing With GRF (1-29) NH₂ and Somatomedin-C Measurement for the Evaluation of GH Deficiency

A large number of provocation tests are available for evaluating the somatotrophic function of the adenohypophysis. The tests are performed with substances and doses that exhibit pharmacologic, but not physiologic, effects. With most tests, it remains unclear whether they directly stimulate the pituitary or the hypothalamus. The detection and synthetic production of growth-hormone-releasing factor (GRF) (1-40) and GRF (1-44) have enabled us to estimate the secretion of growth hormone (GH) in a physiologic and specific way.

Recently, Ranke et al performed similar GRF tests in a large series of patients with growth disorders, administering the fragment (1-29) NH₂ as an intravenous bolus in a dose of one μ g/kg. In addition, serum somatomedin-C (Sm-C) levels were determined by radio-

immunoassay (RIA). Thirty-eight children with familial short stature, familial tall stature, early normal puberty, or premature thelarche and pubarche served as controls. The usual arginine and insulin tests were normal in an additional 48 children with intrauterine growth retardation (IUGR), constitutional delay of growth and adolescence, dysmorphic dwarfism, or Turner's syndrome. These children were compared to 45 children with growth hormone deficiency (GHD) and abnormal insulin and arginine tests. Prior to these investigations, comparative measurements with GRF (1-40) and GRF (1-29) NH₂ were performed in 11 healthy volunteers. The results of both studies were indistinguishable from each other.

In the control group, the median maximal concentration that was

reached was 45.3 ng/ml. The values were distributed logarithmically: $\ln x \pm \ln SD$ was 3.81 ± 0.67 . The lowest normal GH value was 10.0 ng/ml. The median maximal values for the other groups were: IUGR, 67.2; constitutional delay, 28.0; dysmorphic short stature, 85.9; and Turner's syndrome, 25.8. Statistically, no difference could be established between and among the various groups. Correlations with age, sex, relative height, and pubertal development were not statistically significant.

In the pituitary dwarfs, the median maximal value was 5.1 ng/ml, but the individual levels varied considerably. In 11 patients, maximal GH levels exceeded 10 ng/ml, but all levels fell below 40 ng/ml. There was no significant correlation between the maximal GH levels after GRF and the peak values after arginine and insulin. However, the correlation between the peaks after GRF and the max-

imal levels reached during deep sleep was positive.

Sm-C levels above 0.4 U/ml in healthy prepubertal children and above 0.6 U/ml in pubertal children were considered normal. Sixteen of 22 prepubertal patients with GHD had both subnormal GH peaks after GRF and low Sm-C levels.

In 12 of 38 controls, the Sm-C concentration was <0.4 U/ml, with normal peak values seen after GRF administration. In 19 of 23 pubertal patients with GHD, Sm-C and GH determinations were subnormal. One of the remaining four patients had a low Sm-C level with a normal peak of GH after GRF; the other three had normal Sm-C and GH levels. In these latter children, the previously established diagnosis of hypopituitarism certainly should be questioned. Nevertheless, 11 (25%) of 45 GH-deficient patients had GH increases in response to GRF that were within the normal range. Consequently, one has to assume a normal adenohypophysis in these patients and hypothalamic GRF deficiency as the primary cause of the dwarfism in this group. This is in accordance with earlier findings.

Ranke MB, Gruhler M, et al: *Eur J Pediatr* 1986;146.

Editor's comment—This is one of the largest published series evaluating the GRF test. The authors, among others, confirm the usefulness of the GRF (1-29) NH₂, which appears equally as potent as GRF (1-40) and GRF (1-44). With regard to the pathogenesis of pituitary dwarfism, it appears that a large number (25%) of patients have GHD due to a primary hypothalamic defect. However, it is probable that many more patients might actually have primarily impaired GRF production if the GRF test were to be repeated after several days of priming with GRF. One would not necessarily expect a pituitary gland that has been at rest

for many years to respond fully to one dose of GRF. With regard to the diagnostic value of the GRF test, investigation with GRF alone may produce a rather high incidence of false-negative results in patients with GHD. Thus, the combination of GRF and arginine and/or another test, along with the determination of Sm-C concentration, appears helpful. On the other

hand, the use of Sm-C values alone entails the danger of obtaining too many false-positive results in patients who may have GHD. Thus, the Sm-C level can be complemented by the GRF test; these tests plus another test for GH sufficiency using a pharmacologic agent, such as insulin or L-dopa, are important in evaluating patients with suspected GHD.

Role of GH-Releasing Factor and Somatostatin on Somatic Growth in Rats

The investigator studied the role of growth-hormone-releasing hormone (GHRH) and somatostatin (somatotropin-release-inhibiting factor [SRIF]) in affecting growth hormone (GH) secretion and long-term growth in the rat by passively immunizing animals with antisera raised against GHRH and SRIF. GHRH antiserum administration significantly inhibited the normal increase in body weight observed in both young male and female rats as well as in newborn rats. The effects of GHRH and somatostatin antisera administration on serum GH concentrations were studied in neonatal rats. In animals between 1 and 20 days old, GHRH-antiserum administration significantly decreased serum GH concentrations compared with levels in control animals. In animals between 1 and 10 days of age, SRIF-antiserum treatment had no effect on GH concentrations, whereas SRIF-antiserum treatment significantly increased GH concentration in 15-day-old and 20-day-old animals.

Wehrenberg WB: *Endocrinology* 1986;118:489-495.

Editor's comment—These results confirm that the control of pulsatile GH secretion is through the episodic release of GHRH. Thus, it is not unexpected that those rats treated with GHRH antiserum would grow at a reduced rate; however, no data were pres-

ented to determine what organ systems were affected. Both male and female rats showed similar 25% to 30% decrements in weight gain, implying that GHRH is not involved in regulating the sexually dimorphic growth rates. In addition, the antiserum to GHRH was effective from birth, suggesting that neonatal, as well as later, growth is dependent on GHRH secretion.

In contrast, the passive immunization of neonatal rats with an antiserum to SRIF indicated that it is not until sometime after the tenth day of age that endogenous SRIF can actively regulate GH secretion. Previous investigators have not been able to show biologic effects of SRIF in animals under 5 days of age, so this finding in the present study is not unexpected. Thus, the results suggest that the elevated GH concentrations in neonatal rats are due to hypothalamic GHRH release.

That the rats treated with GHRH antiserum grew at all implies that the pituitary may release GH by a non-GHRH-dependent mechanism, or that some other growth factor(s) is (are) responsible for part of the complex process called growth.

One cannot necessarily transfer results obtained in rats to humans. It would be interesting to ask, however, if the human neonate has the same mechanism for GH release since human neonates have elevated GH determinations during the first few days of life.