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1 SEXUAL DIMORPHISM OF GROWTH HORMONE (GH) SECRETION BY CULTURED PITUICYTES OF YOUNG GONADECTOMIZED RATS.

To study the sexual dimorphism of GH secretion, 22-day-old rats, 8 female (F) and 8 male (M), were gonadectomized and their pituitaries dispersed 10 days later. Plated at 5 x 10^4 cells in 1-ml wells, the cultured monolayers were incubated for 4 h with 1-40 human GH-releasing factor (hGRF, 0.2-60 nM), and rat GH (rGH) was measured. F cells were more sensitive to hGRF than M cells, and rGH increased with 0.2 nM hGRF by 110±30 (SD)%, and with 20 nM hGRF to a peak of 500±40% of controls. M cells responded more vigorously than F cells, with a threshold increase at 1 nM hGRF by 105±33% and a peak of 780±60% at 60 nM hGRF. Thus, dimorphism of GH secretion persisted in pituicytes of prepubertal rats deprived of sex steroids (SS). To determine the role of SS, cultured pituicytes of gonadectomized rats were incubated with 5 nM estradiol (E_2) or testosterone (T) for 9 days. In the F cells, T augmented basal secretion by 53±12% and dedecreased its sensitivity to hGRF; while in the M cells, basal secretion, sensitivity and potency of hGRF were unaffected by T. E_2 augmented basal secretion by 62±12% in F cells and by 28±7% in M cells. It decreased hGRF sensitivity and potency in F cells, while in M cells it increased potency but not sensitivity. We conclude that the sexual dimorphism of rGH secretion at the pituitary is partly inherent in the respective sex before pubertal hormone changes and is partly induced by SS through their effect on GRF sensitivity and potency.

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2 NO EVIDENCE FOR A DEFECT IN GROWTH HORMONE BINDING TO LIVER MEMBRANES OF THALASSEMIC CHILDREN.

The hypothesis of a defect in growth hormone (GH) binding has been suggested to explain the growth failure of thalassemic children. We have measured GH binding sites in membrane fractions prepared from liver biopsies. 6 girls and 11 boys with thalassemia major, aged 3 to 15, all prepubertal, were studied at the time of splenectomy. A liver biopsy was performed for histological studies. Part of it (about 500 mg wet weight) was used to prepare a microsomal membrane fraction. Specific binding of ^{125}I-hGH (human GH) expressed in percentage of total radioactivity per mg membrane protein ranged from 4 to 51%. Activities of 2 other membrane markers varied much less than hGH binding: the range of insulin binding was 98-179% of total radioactivity per mg membrane protein and the ratio hGH binding/5'nucleotidase activity varies in the same proportion (10 fold) as does the binding of hGH. Histological hepatic changes were assessed with respect to siderosis, fibrosis, inflammation and necrosis. No correlation was found between these parameters and hGH binding. All patients had retarded growth (mean SDS of -2.6) and no relationship was found between the growth failure and the level of hGH binding. Maximum plasma GH peak during 2 pharmacological tests was normal in 13 children, low in 2, not obtained in 2. Plasma IGF-I levels were low (mean 170±36 mU/ml). In conclusion: 1) Specific hGH binding to liver microsomal membranes was observed and showed great variations; 2) Insulin and hGH binding to liver membranes do not show parallel changes, which suggests that possible membrane alterations are not the only reason for the variations in hGH binding; 3) Plasma IGF-I levels were not related to GH binding. Thus, a defect in GH binding to liver membranes is probably not the main cause for the growth retardation of thalassemic children.

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3 CONTRIBUTION OF GROWTH HORMONE PULSE AMPLITUDE AND PERIODICITY TO MID CHILDHOOD GROWTH - AN ASSESSMENT BY TIME SEQUENCE ANALYSIS

Mid childhood growth has been studied in 21 short children (14M,7F) aged 5.2-11.9 years growing with height velocity (HV) SDS between 0 and -0.8 (Group A) and 29 short children (21M,7F) growing with HV SDS < -0.8 (Group B). 24 hr GH profiles were analysed by an iterative method of pulse detection and subjected to time sequence analysis to determine dominant periodicities within the data array.

Children aged <7 years from Group A had a dominant periodicity of 5 hours but after this age there was a shift to a 3 hour periodicity. In the whole sample (Groups A and B), differences between growth rate could be explained entirely by pulse amplitude. The modulation of childhood growth by GH pulse amplitude persisted into puberty in 14 tall pubertal girls in whom the periodicity of GH secretion remained unchanged.

6 children from Group B had a similar sum of GH pulse amplitudes to the Group A children but a faster pulse frequency (11-14 pulses/24 hours) with a dominant periodicity of 2.3 hours. This led to a HV SDS -1.1- -3.0. We define this codition as neurosecretory dysfunction. To grow at a normal velocity a child needs 6 - 9 GH pulses/24 hours.

We conclude that mid childhood and pubertal growth is GH pulse amplitude modulated with a periodicity of 3 hours. The major cause of poor growth velocity is low GH pulse amplitude but a sub group exists in which disturbance of pulse frequency is the major contributor.

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4 CORRELATIONS OF THE PARAMETERS OF 24-HOUR GH SECRETION WITH GROWTH VELOCITY IN 93 CHILDREN OF VARYING HEIGHT.

Several parameters of 24-hour GH secretion : maximum peak, integrated concentration (IC) and number of peaks (above 5 ng/ml) were studied in 93 children of varying height : 55 children with growth retardation, 22 of normal height (± 2 SD), and 16 tall children, and correlated with their growth velocity (cm/yr). Sampling for GH measurement was carried out over a 24-hour period, every 30 minutes during the day and every 20 minutes during the night. Growth velocity was calculated in cm/yr for the two preceding years and height in SDS.

The group was composed of 74 boys and 19 girls. Mean chronological age was 10 yrs 6 months. Growth velocity was 4.7 cm/yr for the group as a whole, 3.9 cm/yr for the children with growth retardation, 4.6 cm/yr for the normal children and 7.4 cm/yr for the tall children. Study of 24-hour GH secretion for the group as a whole gave the following results : maximum peak 22.4 ± 13.4 ng/ml, number of peaks 4.6 ± 1.9 and IC 3.5 ± 2 ng/ml. The multiple regression test showed a significant correlation (p 0,001) between growth velocity and the number of peaks during the night and over the 24-hour period. This correlation also existed in all three groups but was stronger in the normal children than in the other two groups. However, no correlation was found between growth velocity, value of the maximum peak and integrated concentration in the group as a whole nor in three groups.

In conclusion, the pulsatile nature of GH secretion is the factor with the closest correlation with growth velocity, in children with growth retardation as well as in children of normal height and tall children; on the other hand, there is no significant correlation with maximum peak and 24-hour integrated concentration.