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EPIDERMAL GROWTH FACTOR (EGF) AND INSULIN LIKE GROWTH FACTORS (IGF) IN A HUMAN BREAST MILK PROTEIN CONCENTRATE.

A human breast milk protein concentrate (MPC) added to the mother's fresh milk is used in feeding of very low birth weight (VLBW) infants. This procedure preserves the immunologic properties of human milk. We have measured the EGF and IGF levels in the protein concentrate used.
By centrifuge separation of pooled breast milk a fat free milk was obtained and pasteurized (72°C for 15 sec). Lactose and salt were separated by means of ultrafiltration. The retention product was repasteurized and freeze dried. EGF was measured after each step. The MPC was dissolved in acetic acid and separated on a Sephadex G 50 column. EGF was measured by radioimmuno-(RIA) and radioreceptor assay (RRA), IGF by two RRA(IGF I and II). The amount of EGF in the MPC was 68% of that in pooled breast milk (2.0 ng/mg protein versus 2.9). The IGF level(I and II) in the MPC was 70 mU/mg protein and column separation yielded two IGF-RRA peaks - one with MW of 20K(80% of total RRA activity) represented a carrier protein, a second peak with MW 7K consisted of both IGF I and II.
Substantial amounts of growth factors especially EGF is preserved in the concentration process. With the amount of MPC used for VLBW infants the enriched milk contains almost 50% more EGF than fresh non enriched milk. Further studies are necessary to evaluate the clinical significance of such changes in milk composition.

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SOMATOMEDIN C/INSULIN-LIKE GROWTH FACTOR-I (SmC/IGF-I) SERUM LEVELS DURING CHILDHOOD AND ADOLESCENCE.

Using a highly specific RIA we have determined SmC/IGF-I in 160 healthy children and adolescents 0-16 years of age to define the normal range of our assay system. Serum samples were extracted with acid-ethanol. The SmC/IGF-I antiserum was a gift of Drs. UNDERWOOD and VAN WYK, Chapel Hill, NC distributed by the NHPP Baltimore, MD. The intra assay coefficient of variance (CV) was 5.6%, the inter assay CV 9.8% determined at 3 dose levels. There was a slow and constant increase of SmC/IGF-I from very low levels during the first 2 years of life (33 ± 30 ng/ml; x ± SD) to peak levels in the 12-14 years group in girls (460 ± 75 ng/ml) and the 14-16 years group in boys (445 ± 213 ng/ml), both significantly higher than levels in normal adults aged 18-25 years (237 ± 51 ng/ml). From 6-8 years up to 12-14 years mean SmC/IGF-I levels were significantly higher in girls than in boys ($p < 0.01$) SmC/IGF-I in both sexes was highest during TANNER stages III and IV. In conclusion: there is a surprisingly early and marked difference of SmC/IGF-I levels in girls and boys, which only equalize after full puberty is reached. This may be partly due to the earlier onset of puberty in girls and to the stimulatory effect of low concentrations of estrogens on the growth hormone-somatomedin axis even before clinical signs of puberty can be observed.

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DIAGNOSTIC OF IGF-1 INDUCTION IN GROWTH RETARDED CHILDREN: CHANGES OF IGF-1 RECEPTOR NUMBER AND BINDING AFFINITY AFTER 5 DAYS GH ADMINISTRATION.

The acute response of IGF-1 to GH treatment (5 days, 0.1 E/kg per day) has been tested in seven children with growth retardation. All childrens have a normal GH-stimulation . With the change of the IGF-1 level after GH administration we tested the change of the IGF-1 receptor number and -affinity on the isolated lymphocytes of these patients. The IGF-1 level raised from 102 ± 57 ng/ml to 180 ± 94 ng/ml ≙ 186 + 65 %. In 5 patients there was no significant change in receptor affinity (from 0.47 ± 0.33 x 10^9 M^{-1} to 0.45 ± 0.31 x 10^9 M^{-1}). Two subjects had a stimulation of receptor affinity from 0.28 ± 0.1 to 0.48 ± 0.15 · 10^9 M^{-1}.
The receptor number from 6 patients however decreased from 7282 + 3309 to 4926 + 2538. This decrease was strongly correlated to the increase of the IGF-1 level (r= 0.94). One patient had an increase of receptor number from 2500 to 4980.
Our results are corresponding with the suggestion of Rosenfeld et al (1982), that the downregulation of IGF-1 binding is accounted by a decrease in receptor number rather than change in binding affinity. It has to be discussed whether GH itself has an influence of increase of receptor affinity (2 patients) or receptor number (1 patient).

R.G. Rosenfeld et al (1982) Diabetes 31:375

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COMPARISON OF TWO RIA METHODS FOR IGF-I USING EXTRACTED SERA OR WHOLE PLASMA

Parallel measurements of IGF-I (SMC) levels were made in extracted sera by the INCSTAR RIA, and in plasma by the NICHOLS RIA. Four clinical groups were examined: GR 1 - untreated hGH def.; GR 2 - short stature; GR 3 - tall stature, normal and precocious puberty; GR 4 - acromegaly. Five patients in GR 1 were studied before and after 5 days of hGH treatment.

GR	n	mean age y ± SD	INCSTAR IGF-I (nmol/l) m ± SD	NICHOLS IGF-I (nmol/l) m ± SD
1	30	11.2 ± 3	6.2 ± 4.7	10.7 ± 9.2
2	19	7.5 ± 5	11.7 ± 6.7	23.7 ± 18.3
3	22	11.0 ± 4	36.0 ± 13.6	63.9 ± 27.1
4	6	47.3 ± 5	98.3 ± 41.2	145.3 ± 64.3
Analysis of variance F ratio:			60.4	39.3

Using the INCSTAR RIA, 78% of IGF-I values in GR 1 were below normal and a rise in IGF-1 was detected in all 5 pts. treated with hGH. Using the NICHOLS RIA, 33% of basal IGF-I values were below normal and a GH-stimulated rise in IGF-1 was found in 2 of the treated pts. INCSTAR RIA seems more precise and reproducable than the NICHOLS RIA and enables better discrimination of GH deficient pts. from aged matched controls.

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INFLUENCE OF DIETARY NITRATE EXPOSURE ON THYROID HORMONE, SOMATOMEDIN-C/IGF-I CONCENTRATIONS AND GROWTH

Dietary goitrogens are important for the development of endemic goitre, especially in iodine deficiency areas. Due to the increasing nitrate exposure of humans, the influence of dietary nitrate was tested in three groups of 9 six week old piglets.
The thyroid hormones and Sm-C/IGF-I levels of nitrate exposed animals (T4: < 10; T3: 0.8±0.2, rT3:0.3±0.1 nmol/l, Sm-C:0.29±0.09 U/ml) were significantly lower after a five week test period with 412 mg NO3-N/100 g of diet compared to the ad libitum control group (29±6, 1.2±0.3, 0.5±0.1, 0.73±0.27).The mean daily weight gains amounted to 242±76, 274±67 and 393±94 g rsp. T4, T3 and rT3-levels of the nitrate exposed animals normalized after the supplementation with 0.08 mg iodine/100 g diet during 7 days, but the Sm-C/IGF-I concentrations of the nitrate-exposed and pair-fed groups were still diminished.
Chronic nitrate intake inhibits in higher concentrations the thyroid hormone synthesis. Hypothyroidism as well as a probably nitrate induced inhibition of the eating centre lead to diminished Sm-C/IGF-I levels and so to growth retardation.

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SOMATOMEDIN-C/IGF, STEROID AND THYROID HORMONE CONCENTRATIONS DURING PUBERTY

In prepubertal (n=40) and pubertal (n=99) boys (n=60 and girls (n=79) Sm-C/IGF-I was determinated by RIA in different pubertal stages. In most of the children also DHEA-S, Cortisol, 17-OHP, aldosterone, T3, T4 as well testosterone (T) in boys or estradiol (E2) in girls rsp., were measured. Sm-C/IGF-I increased from pubertal stage PH 1 to PH 2, reached a plateau at 12.7-15.6 yrs. of age in girls (PH III-V) and peaked at stage IV in boys (age 14.3±1.1 yrs.). The rise in early and midpuberty was related to increasing levels of gonadal (T or E2 rsp.) and adrenal steroids (DHEA-S,cortisol, aldo), 17-OHP peaked corresponding to the highest sexual hormone concentrations that means during PH IV in girls (E2=546.8±356 pmol/l, 17-OHP=3.4±1.5 nmol/l, n=20) and PH V in boys (T= 25.2±3.2 nmol/l, 17-OHP =5.4±2.7 nmol/l, n=13). No correlation was found between Sm-C/IGF-I and T3 or T4 rsp.,. Conclusions: Sm-C/IGF-I concentrations in children at pubertal stages III-V (according to TANNER) are two- to threefold higher than in adulthood. The Sm-C/IGF-I rise is connected with a corresponding increase of sexual and adrenal steroids.