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DIFFERENTIAL EFFECTS OF HYPO- & HYPERGLYCEMIA ON COGNITIVE FUNCTION & PANCREATIC POLYPEPTIDE (PP) RESPONSES. S. Gschwend, C. Ryan, T. Williams, S. Arslanian, J. Atchison, D. Becker, Children's Hospital of Pittsburgh, Pittsburgh, PA 15213, USA.

We have documented a detrimental effect of mild hypoglycemia (HYPO) on cognitive function in children with IDDM. A similar effect has been postulated, but not verified, for hyperglycemia (HYPER) or its recovery to euglycemia (EU). We compared cognitive performance, measured by Choice Reaction Time (CRT) & Trailmaking-B (TMB), during HYPO, HYPER & EU, under hyperinsulinemic (90μU/ml) clamp conditions in 44 children aged (9-19) yrs with IDDM duration 8(2.6-15) yrs. Tests for CRT, TMB & PP were performed at baseline (PG 5.5mM, period I) in all 3 groups & repeated at the same intervals: periods II & III at 5 & 45 min of HYPO (PG 3.3mM, n=20) HYPER (PG 20mM, n=13) or EU (PG 5.5mM, n=11) & period IV on return to PG 5.5 mM. RESULTS: CRT in period II & III of HYPO deteriorated by 12 & 15% ($p<.06$ & $<.01$ resp.) compared to EU; TMB deteriorated by 25 & 40% (p.05 & ns resp). During HYPER there was no significant change compared to EU at any period. Neither hyperglycemia nor the 14.5 mM drop had an effect on cognitive tests, PP or symptomatology. PP levels correlated with change of CRT & TMB in period III irrespective of PG levels (CRT vs PP r=-.61, p.001; TMB vs PP r=-.35, p<.02). Thus, acute HYPER & its rapid return to EU are not associated with cognitive impairments or PP changes while hypoglycemia is.

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TRANSIENT NEONATAL DIABETES MELLITUS (TNDM) AND SUBSEQUENT (10 yr later) PERMANENT IDDM UNRELATED TO AUTOIMMUNITY.

We describe the sixth case reported until now of permanent diabetes not associated with serological evidence of autoimmunity in a child who developed TNDM 10 yr earlier. A small for gestational age infant developed hyperglycemia at 25 days of age and required insulin therapy for the first 9 mo of life. During a 10 yr longitudinal follow-up, ICA, IAA and organ specific and non-specific autoantibodies were negative, but sequential IVGTT showed a first phase insulin response (FPIR)<1st centile (15-28 uU/ml) and mean HbA1c value was 6.1 ± 0.8%. Transient hyperglycemia and glucosuria were recorded at age 4 and 6.3 yr during an intercurrent illness. HLA type was DR2. At age 10 yr & 1 mo (Tanner stage 1-2)a progressive blood glucose increase was observed from 4 to 7 a.m. with a spontaneous normalisation before noon. FPIR was 12 uU/ml. Six isophane insulin units injected at 10 p.m. prevented glycemia increase. Six mo later (FPIR = 21 uU/ml), insulin therapy was discontinued because of hypoglycemia. At age 11.6 yr (Tanner stage 2), overt diabetes appeared after an intercurrent illness (FPIR = 18 uU/ml; ICA & IAA negative) & permanent insulin treatment was started. During 3 yr period preceding insulin therapy, a progressive decrease in growth velocity was observed with high stimulated GH and low IGF1 levels. With insulin therapy (0.51 ± 0.15 U/Kg/day) a catch-up growth and a normalization of IGF1 were obtained. The physiological increase in insulin resistance during puberty could be at the origin of (definitive?) insulin dependence in this subject.

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A cytokine link between the environment and the immune system in Type I diabetes.

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Type I diabetes is caused by an auto immune mediated destruction of the insulin producing pancreatic beta cells. Although particular alleles at the MHC locus can markedly increase the risk of developing diabetes, the discordance rate in identical siblings is greater than 50%. Thus, the disease process appears to involve an interaction between the environment (possibly a viral infection), the pancreatic beta cells and the immune system in a genetically susceptible host. We have tested several hypotheses that could explain this interaction by generating transgenic mice in which the beta cells express specific proteins. Several lines of transgenic mice were generated in which the beta cells express a cytokine that is induced by environmental stresses and that is expressed by the beta cells of patients with recent onset Type I diabetes. These transgenic mice develop a pathology that closely resembles Type I diabetes. We have also successfully prevented the diabetes in these mice using a monoclonal antibody directed against the cytokine.

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HIGH PREVALENCE OF LOW PLASMA IGF-1 LEVELS IN CHILDREN AND ADOLESCENTS WITH INSULIN DEPENDENT DIABETES MELLITUS. T. Quattrin[1], N. Gesundheit[2] and M. Trevisan[3]; [1]Dept of Pediatrics, SUNYAB; [2] Dept. of Clin. Research, Genentech, Inc.; [3]Dept of Preventive Medicine, SUNYAB

Plasma IGF-I levels have been shown to be low in selected patients with poorly controlled IDDM. The aim of this study was to determine the prevalence of depressed IGF-I levels and to correlate these values to metabolic control in a larger cohort of IDDM patients. Data were collected from 65 randomly selected patients on conventional insulin Rx, followed in a university-based diabetes clinic, age 6-21 years, duration 68±6 months, The data are expressed as mean ± SEM and Mann-Whitney U was used for statistical analysis. The patients were divided on the basis of their glycated Hemoglobin (HbA1) ≥ 11% and ≤ 10.9% (nl HbA1 6.6-8.8%). IGF-I was determined by RIA (Endocrine Science) after acid/ethanol extraction; reference values were adjusted for age and Tanner stage. "Low" IGF-I level was defined as a value lower than -1SD from the mean.

RESULTS:

	N	Age (yrs)	Insulin Dose (u/kg)	Cholesterol (mg/dl)	IGF-1 (ng/ml)	% of low IGF-1
HbA1 ≤ 10.9	40	13.2 ± .6	.9 ± .04	180 ± 6	332 ± 20	23%
HbA1 ≥ 11.0	25	13.7 ± .9	.9 ± .05	192 ± 9	298 ± 28	48%

The prevalence of low IGF-I levels is significantly higher in patients with HbA1 ≥11% ($p<0.05$). In addition there was a correlation between HbA1 and cholesterol levels ($r=0.25$), but no correlation between the latter and IGF-I was observed

Conclusions: These data suggest that a decrease in plasma IGF-I levels is a common finding in poorly controlled IDDM. It is yet to be shown in a controlled, prospective trial whether improved metabolic control can increase circulating IGF-I or, conversely, whether administration of recombinant IGF-I can improve metabolic control.

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IGF-1 AND TYPE I DIABETES. L.F.Simoes de Moura, Pediatric Endocrinology and Growth, Children's Hospital of Coimbra, Coimbra University, 3000 Coimbra, Portugal.

To study the effect of Ketoacidosis(KA) and chronic loss of calories(glycose) on IGF-1 synthesis, ß-hydroxybutyrate(ß-HB) and HbA1C were compared in 3 groups of children with identical mean chronologic age(10.4Y±3.6Y/10Y±2.5Y): normal children, children with "controled" type I diabetes, and children with diabetic KA. Each group was composed by 19 children. In normal controls, IGF-1 was significantly higher than in "controled" diabetics($t=2.23;p=0.04$) and in KA($t=-5.22;p=0.0001$). ß-HB concentration was similar in normal controls and in "controled" diabetics, but significantly higher in KA($t=-5;p=0.0002$). No correlation between ß-HB and IGF-1, in KA, was observed. Growth hormone (GH) was significantly more elevated in KA than in normal controls ($t=-1.9;p=0.03$). HbA1C values were significantly higher in "controled" diabetics than in normal children(4.3%±0.7% / 7.2%±1.5% - $t=-7.4$; $p=0.0001$). The samples are relatively small, but its analysis suggests that IGF-1 synthesis, in type I diabetes, is mainly affected by the "invisible chronic malnutrition"; despite high GH concentration in KA, IGF-1 synthesis seems to be inhibited by the cellular malnutrition; IGF-1, probabily, is also an efficient parameter for metabolic control in this disease. KA seems not to affect IGF-1 synthesis.

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THE ROLE OF SOMATOLACTOGENIC HORMONES AND RECEPTORS IN THE GROWTH AND FUNCTION OF THE ENDOCRINE PANCREAS. J.H. Nielsen, A. Møldrup, N. Billestrup and E.D. Petersen, Hagedorn Research Institute, DK-2820 Gentofte, Denmark.

Growth hormone (GH) and prolactin (PRL) are diabetogenic in humans, but not in rats. We have previously demonstrated that GH, PRL and placental lactogen (PL) stimulates both proliferation and insulin production in isolated rat islets in culture. The aim of the present study was to test whether GH influences the function of isolated human islets in culture. Islets were obtained by collagenase digestion of pancreatic tissue obtained from eight necrokidney donors aged 12 to 58. Groups of 50 islets were cultured in RPMI 1640 supplemented with 0.5% normal human serum with or without 1 μg/ml hGH. Insulin was measured in the medium during a culture period of 7 or 14 days. The accumulated insulin release varied between 5.4 and 71.1 ng per islet per week. Islets from two donors showed no increase in response to GH, five showed a modest increase (3.1-7.7 ng) and only one, a 12-year old girl, showed a marked increase (29.9 ng). As the human insulin gene promoter contains a putative GH-responsive element similar to that of the rat genes the variation in responsiveness may be due to an age- and sex-dependent variation in the number of GH and PRL receptors. We are at present measuring the expression of the receptor genes in human islets. In conclusion the results support the hypothesis that the diabetogenic effect of the somatolactogenic hormones in adult man is due to an age-dependent decrease in the responsiveness of the pancreatic β cells to the trophic effect of these hormones.