Diabetes and Fuel Metabolism

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AUTOANTIBODIES TO BRAIN GLUTAMIC ACID DECARBOXYLASE IN CHILDREN WITH NEWLY DIAGNOSED IDDM.

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Glutamic asid decarboxylase (GAD) is considered as target antigen in pancreatic beta cell autoimmunity. Two isoforms of GAD (islet and brain GAD) were found recently. Surprisingly, in circulation of app. 80% of recently diagnosed IDDM patients autoantibodies to brain GAD(bGAD) have been demonstrated by others. To define autoantibodies to the bGAD in sera of 37 children (1-14 years old) with newly diagnosed IDDM an indirect immunofluorescent staining of rat cerebellum criosections was performed. Patients sera were examined 1-12 days after from the beginning of the insulin treatment. Autoantibodies to the bGAD were found in 83,3% of these patients. Moreover, bGAD-positivity in different age groups was analysed: 1st group - 1-4 years old; 2nd group - 5-9 years old and 3d group - 10-14 years old and the prevalence of bGAD reactivity in sera of the 3d group of patients was found. Since our data confirmed the high frequency of autoantibodies to bGAD in circulation of children with newly diagnosed IDDM, this immunological marker is rather common for patients of 10-14 years age. The information thus acquiared will then be used for better understanding of the epidemiology of IDDM in children. Futher we intend to study the possible correlation between the character of the onset of the desease and bGAD-positivity.

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IDENTIFICATION OF A MARKER TO ENRICH POPULATIONS OF ENDOCRINE CELL PRECURSORS FROM THE HUMAN FETAL PANCREAS. A. Hayek, G.M. Beattie, M.I. Mally, T. Otonkoski, J.S. O'Brien, and F. Levine. Lucy Thorne Whittier Children's Center, The Whittier Institute, La Jolla, CA 92037, and Department of Pediatrics, University of California, San Diego, La Jolla, CA 92093-0634, USA

Isolation of the endocrine cell precursors from the human fetal pancreas is important for the understanding of islet cytodifferentiation. The progenitor cells, from which all four islet endocrine cell types arise, are present within the epithelium of the fetal pancreatic duct. Following enzymatic digestion and culture of the fetal pancreas we obtained cell clusters resembling islets but with a high content of undifferentiated cells. Histochemical staining revealed very high acid β-galactosidase activity in most cells within the clusters. After transplantation into athymic nude mice, the clusters gave rise to tissue rich in differentiated endocrine cells. The histochemical finding of high acid β-galactosidase activity was confirmed by direct measurement of lysosomal enzyme activities. In addition, we found that the expression of acid β-galactosidase was developmentally regulated, peaking at 18-24 weeks gestation and declining to low levels in adult islets. Using a fluorogenic β-galactosidase substrate, we were able to enrich for a subpopulation of cells high in acid β-galactosidase activity with flow cytometry. Evidence identifying these cells as potential islet cell precursors included, besides the transplantation experiments, the colocalization in vitro of tyrosine hydroxylase, a known marker of embryonic islet cells. Thus, our results indicate that high acid β-galactosidase activity serves as a marker to enrich populations of endocrine cell precursors.

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NICOTINAMIDE AND INTERLEUKIN-1 (IL-1) EFFECTS ON HUMAN PANCREATIC ISLET FUNCTION. **U. Zumsteg, M. Brendel, R. Alejandro and J. Nerup, Steno Diabetes Center, 2820 Gentofte, Denmark and Diabetes Research Institute, University of Miami, Miami, FL 33101, USA**

The cytokine IL-1ß inhibits rodent ß-cell function in a time- and dose-dependent manner and has been implicated as effector molecule in the IDDM pathogenesis. In isolated rat islets IL-1 toxicity to ß-cells is dependent on generation of free nitric oxide radicals. Nicotinamide (NA), a free radical scavenger and inhibitor of poly-ADP-ribose synthetase prevents macrophage mediated islet cell destruction and autoimmune diabetes in the NOD mouse, and NA shows promising preventive effects in prediabetic humans. Here we studied IL-1 sensitivity and NA protection of isolated human islets using a completely intra-species in vitro system: A 24 hr human islet exposure to authentic recombinant human IL-1ß (150pg/ml) reduces 16.7 mM glucose-challenged islet insulin release to 0.19±0.08ng/islet/2hrs vs 0.41±0.14 in controls ($p<0.05$). Coincubation with 10 mM NA counteracts the IL-1 effect to 0.38±0.13ng/islet/2hrs (ns vs controls) without showing any intrinsic effect on ß-cell function by itself. A 6 hr human islet IL-1 exposure already leads to a 30% decrease of insulin accumulation while in rat islets functional inhibition is seen only after 24 hrs of IL-1 exposure . In conclusion isolated human islets are most sensitive to IL-1 induced ß-cell suppression and NA protects human islet function against the IL-1 attack.

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GENETIC INFLUENCES ON HEIGHT AND WEIGHT IN CHILDREN / ADOLESCENTS WITH TYPE-I DIABETES MELLITUS (IDDM). **R.W.Holl, M.Seifert, A.Thon, M.Grabert and E.Heinze. Department of Pediatrics I, University of Ulm, D-7900 Ulm, Germany.**

The development of overweight has recently been recognized as a common finding especially in adolecents with IDDM. However, both normal longitudinal growth and the prevention of overweight are major goals in pediatric diabetology. We therefore investigated, how genetic factors contribute to this undesirable event. At the time of diagnosis, children with type-I diabetes are lean and slightly taller than average (SD-scores: height: +0.51±0.07; weight: +0.33±0.06; BMI: +0.08±0.05; n=251, mean±SE). However, after >10 years, a significant portion of the patients loose height and become overweight: (height: -0.16±0.08; weight: +0.77±0.09, BMI: +1.10± 0.1; n=87). In a subgroup of 156 patients (74 boys, 82 girls, mean age 13.5 years), height and weight of both parents was measured at our institution. Height-SDS was +0.21±0.09 for fathers and +0.22±0.08 for mothers. The correlation between midparental height and height-SDS in the patients (+0.19±0.08) was highly significant ($r=0.41$, $p<0.0001$). In contrast, patients with IDDM were considerably more overweight (SD-score: +0.83±0.01) compared to their parents (+0.28±0.1 for fathers and +0.41±0.1 for mothers), and weight correlated only weakly between parents and IDDM children ($r=0.20$, $p<0.05$). This correlation was significantly stronger in boys ($r=0.31$, $p<0.001$) compared to girls ($r=0.10$, n.s.). Interestingly, in IDDM girls, the SD-score for weight increased significantly with age ($r=0.28$, $p<0.01$), but not in boys ($r=0.18$, n.s.). The age of menarche in the mothers (13.3 ± 0.1 years) was not different from their daughters (13.4 ± 0.3 years). Conclusion: In IDDM girls, obesity is primarily due to factors related to the disease, while genetic predisposition plays a minor role. In contrast, with modern therapeutic regimen, stunted growth or delayed puberty is no longer a major problem, as height in IDDM children strongly reflects their genetic potential.

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RELATIONSHIP BETWEEN BLOOD PRESSURE AND MICROALBUMINURIA IN ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS

The aim of this study was to determine the role of increased blood pressure (BP) in the development of incipient diabetic nephropathy in the young. In 1985 we started a comprehensive program for early detection of kidney disease in diabetic children and adolescents. This program consisted of regular measurement of urinary albumin excretion (UAE) by RIA method (every 6 months) and BP (every 3 months). Unsterile urine were excluded; BP was measured following the criteria of the American Academy of Pediatrics. Glycemic and metabolic control was assessed every 3 months by measuring HbA1c, serum cholesterol and triglycerides. During the follow-up 11 adolescents and young adults (age 14-22 yr, duration of diabetes 9.3-19.7 yr) developed persistent microalbuminuria, defined as UAE greater than 30 ug/min/1.73 m^2 in at least two out of three consecutive measurements; at the beginning of the study these patients had UAE and BP in the normal range (UAE: 5-12 ug/min/1.73 m^2; systolic BP: 108-123 mmHg; diastolic BP: 70-82 mmHg). Diabetics with microalbuminuria had normal systolic and diastolic BP during the first year of UAE persistingly in the microalbuminuric range. A significant increase of both systolic and diastolic BP became evident during the fourth year of persistent microalbuminuria. Microalbuminuric diabetics had poorer long-term glycemic control than normoalbuminuric patients (matched for sex, age and duration of diabetes)(7-year HbA1c 9.2 ± 1.3 vs. 8.3 ± 1.2; $p<0.03$); serum cholesterol was higher in diabetics with microalbuminuria. Increase of BP seems to develop after that persistent microalbuminuria becomes evident; thereafter, elevated BP can contribute to the development of clinical diabetic nephropathy and end-stage renal failure.

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PRORENIN (PR) AND DIABETIC NEPHROPATHY (DN): A STUDY OF ADOLESCENTS WITH IDDM AND THEIR SIBLINGS. D Dangman, JW Balfe, C Crompton, E Sochett, A Chatzilias, B Cotter, D Osmond, Depts of Pediatrics and Physiology, Univ of Toronto, Hosp for Sick Children, Toronto, Canada M5G 1X8.

We wished to study (i) in IDDM adolescents, the relationship of plasma PR concentrations, measured by direct monoclonal antibody assay, to the presence of microalbuminuria (MA), BP and metabolic control (HbA1c); and (ii) whether PR levels differ in siblings of IDDMs with and without MA. To do this, we measured PR concentrations in (a) IDDM adolescents with MA (n=25); (b) an IDDM group without MA (nonMA, n=25) matched for age, sex, disease duration, and BMI; and (c) the nondiabetic siblings of these 2 groups (n=38). Of the BP measures, only diastolic BP was significantly higher in the MA group (59±6 vs 55±6 mm Hg, $p<0.03$). PRs were significantly greater in the MA compared to nonMA group (226±68 vs 168±50 pg/ml, $p<0.0001$), being higher in 23 (92%) of the 25 MA members of the matched pairs. In the MA group, PR showed an inverse correlation with current HbA1c ($r=-0.50$, $p<0.01$), but no relationship to IDDM duration, disease mean HbA1c or BP in either IDDM group. PR concentrations in the IDDMs were significantly greater than in their nondiabetic siblings (197±67 vs 135±50 pg/ml, $p<0.0001$). Also, siblings of MA IDDMs had significantly higher PRs than those of nonMA IDDMs (158±56 vs 115±32 pg/ml, $p<0.001$). In summary, PR concentrations (i) were greater in most IDDM adolescents with MA compared to matched nonMA IDDMs and may serve as an indicator of incipient DN; (ii) were significantly higher in IDDMs compared to their siblings; and (iii) were higher in the siblings of those IDDMs with than those without MA. These data suggest that plasma PR concentrations may be affected by factors related both to diabetes itself (metabolic control) as well as to the presence of DN. Further there may be an important genetic component to PR concentrations, and thus to DN.