Induction of a metabolic syndrome relies on timing of high fat feeding and brain melanocortin system blockade.
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Differential role of insulin in the Nitric Oxide (NO) production and Plasminogen Activator Inhibitor-1 (PAI-1) release in fibroblasts from insulin resistant individuals. Insights into the signaling pathway.
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Background and Aims: Insulin resistance is associated to both increased plasma PAI-1 and decreased NO availability. This might contribute to accelerated atherosclerosis in insulin resistant states. Insulin can stimulate both NO and PAI-1 release in a variety of cell types. However, in order for PAI-1 to be increased in insulin resistant states, one has to postulate that, in these conditions, pathways leading to the stimulated PAI-1 synthesis are still insulin sensitive while pathways leading to NO production are impaired. We determined insulin effect on both NO and PAI-1 release in fibroblasts from individuals with different degrees of insulin resistance.

Materials and Methods: Six fibroblast strains were cultured from skin biopsies obtained from 3 insulin sensitive (IS, clamp M>7mg/Kg/min) and 3 insulin resistant (IR, clamp M<5mg/Kg/min) volunteers matched for age and BMI. On each strain, we measured, in separate experiments, insulin stimulation of NO synthesis (conversion of 1H-arginine into 1H-citrulline) and PAI-1 release (ELISA).

Results: Insulin stimulated PAI-1 release was not different in fibroblasts from IS and IR individuals (54±6 vs 43±5 ng/ml and 100±11 vs 88±9 ng/ml, at 10 and 100 nM insulin respectively, p= n.s.). Conversely, the effect of insulin (100nM) on NO release was significantly less in fibroblast from IR as compared to IS individuals (respectively 0.85±0.09 vs 1.25±0.14 nmol/min/mg protein, p<0.05). To gain insight into the signaling pathways leading to insulin stimulated PAI-1 release, we repeated the experiments in the presence and in the absence of Ly2940029 (an inhibitor of phosphatidylinositol 3-kinase [PI3-K]) or of PD98059 (an inhibitor of mitogen-activated protein kinases [MAPK]). After exposure to Ly2940029, insulin (100nM) induced PAI-1 secretion was decreased in both fibroblasts from IS and IR individuals, by 70% ± 6 and 65% ± 5, respectively (both p<0.05 vs control). Exposure to PD98059 was also followed by decreased insulin induced PAI-1 release in both cell strains (both p > 65% as compared to control, p< 0.05). This shows that insulin stimulated PAI-1 synthesis in both cell strains is due to PI3-K activation followed by MAPK activation.

Conclusion: We conclude that insulin ability to stimulate PAI-1 release is preserved in cells from IR individuals in which NO release is resistant to insulin stimulation and that MAPK activation plays a central role in insulin stimulation of PAI-1 release in cells from both IR and IS individuals. Thus, in the insulin resistance syndrome, hyperinsulinemia might be one the culprit for the observed increase in PAI-1 levels while insulin resistance can account for impaired insulin induced vasodilation.

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Diverse regulation of delta-6 desaturase in dietary-induced and/or genetically fixed insulin resistance.
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Background and Aims: Our previous studies have shown that insulin resistance is associated with different fatty acid (FA) profile in insulin target tissues, possibly due to an impairment of the desaturation pathway. Thus, the aim of our study was to measure enzyme activity of and gene expression based on fatty acid composition in total phospholipid fraction in liver.

Materials and Methods: Delta-6 desaturase was determined radiometrically in a microsomal fraction in liver of control Wistar (C) and the hereditary hypertriglyceridemia/insulin resistance associates with a lower activity of gene expression for the delta-6 desaturase. In contrast, a reduced activity of delta-6 desaturase in liver of rats fed a high carbohydrate diet. In harmony with a raised index of delta-6 desaturase (as calculated from liver fatty acid profile as a ratio of n-6 polyunsaturated fatty acids metabolites to the linoleic acid), a higher activity of the delta-6 desaturase was found in liver of rats fed the high sucrose diet (HS: 89.7±1.5; C: 62±0.7 pmol/mg/min; p<0.01). However, these changes were not accompanied by appropriate changes in the hepatic mRNA levels for delta-6 desaturase.

Conclusions: Our results have shown that 1) the high sucrose-induced insulin resistance goes with a higher activity of, and the 2) hereditary hypertriglyceridemia/insulin resistance associates with a lower activity of and gene expression for the delta-6 desaturase. Thus, a diverse regulation of the aforementioned key desaturation enzyme seems to participate in the abnormal fatty acid profile of both, the diet-induced and the genetically fixed insulin resistance.

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Induction of a metabolic syndrome relies on timing of high fat feeding and brain melanocortin system blockade.

Background and Aims: Obesity is associated with the development of a metabolic syndrome characterized firstly by an insulin and leptin resistance.

In a rat model for diet induced obesity (blockade of the brain melanocortin system by a 14-day icv infusion of SHU9119 combined with a high fat diet), we previously observed that, despite exaggerated hyperleptinemia in SHU9119-treated HF rats relative to rats fed a high carbohydrate diet (HC, CHO = 60% of energy), plasma insulin and adiponectin levels were comparable among diet groups. The present study investigated whether these secretion profiles of adipose and skeletal hormones are influenced by the duration of adaptation to HF feeding before SHU9119 treatment.

Materials and Methods: Male Wistar rats (n=64) were either adapted to HF feeding for 2 months prior to the onset of SHU9119-infusion (LT), or were switched from the HC to the HF diet at the onset of SHU9119 infusion (ST).

Results: Following 14-day SHU9119 treatment, early light phase plasma leptin levels were not different among groups (44.4 ± 7.7 ng/ml in LT and 36.5 ± 5.3 ng/ml in ST rats). Baseline plasma adiponectin levels were significantly higher in LT (7.9 ± 0.9 ng/ml) than in ST rats (5.0 ± 0.4). Interestingly, plasma insulin levels were markedly higher in ST (33.0 ± 7.4 ng/ml) than in LT (8.3 ± 1.1 ng/ml). Thus, despite comparable increases in food intake, plasma adiponectin was 36 % lower, whereas plasma insulin was 400% higher in ST relative to LT rats.

Conclusion: This dramatic increase in plasma insulin concentration in ST rats might indicate severe insulin resistance as a consequence of acute HF exposure and low brain melanocortin activity.

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Prevention of obesity and insulin resistance by glucokinase expression in skeletal muscle of transgenic mice.

Background and Aims: In type 2 diabetes, glucose phosphorylation, a regulatory step in glucose utilization by skeletal muscle, is impaired. Since glucokinase expression in skeletal muscle of transgenic mice increases glucose phosphorylation, we examined whether these mice can counteract the obesity and insulin resistance induced by a high-fat diet. Since glucose phosphorylation is the first regulatory step in glucose utilization by skeletal muscle, is impaired. Since glucose phosphorylation is the first regulatory step in glucose utilization by skeletal muscle, is impaired. Since glucose phosphorylation is the first regulatory step in glucose utilization by skeletal muscle, is impaired.

Materials and Methods: Transgenic mice expressing glucokinase in skeletal muscle were fed a high-fat diet for 12 weeks. Effects on body weight, food intake, glucose tolerance and insulin sensitivity were analysed.

Results: When fed this diet, control mice became obese while transgenic mice remained lean. Furthermore, high-fat fed control mice developed hyperglycemia and hyperinsulinemia (a 3-fold increase), indicating that they were insulin resistant. In contrast, transgenic mice were normoglycemic and showed only a mild increase in insulinemia (1.5-fold).

Conclusion: These results suggest that the rise in glucose phosphorylation by glucokinase expression in skeletal muscle leads to increased glucose utilization and energy expenditure that counteracts weight gain and maintains insulin sensitivity.