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 states, pathways leading to 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 H-arginine into H-citrulline) and PAI-1 release (ELISA).

Results: Insulin stimulated PAI-1 release was not different in fibroblasts from IS and IR individuals (5±4 vs 43±5 pmol/ml/ng/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 L-arginine (an inhibitor of phosphatidylinositol 3-kinase [PI3-K]) or of PD98059 (an inhibitor of mitogen-activated protein kinases [MAPK]). After exposure to L-arginine (1000 nM) 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 by >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 stimulated PAI-1 synthesis in both cell strains.

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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 for the key desaturation enzyme, i.e. the delta-6 desaturase in liver of rats with either a high sucrose diet-induced or hereditary fixed hypertriglyceridemia and insulin resistance.

Materials and Methods: The control Wistar (C) and the hereditary hypertriglyceridemic (hHTg) rats were fed for 21 days a standard rat chow. In addition, another group of normal rats was fed for the same time interval the high sucrose diet [65 cal % of sucrose (HS)]. The enzyme activity of delta-6 desaturase was determined radiometrically in a microsomal fraction using the 1-14C-linoleic acid as substrate. The relative abundance of mRNA for the delta-6 desaturase was measured by the Northern blot technique using a specific cDNA probe. Fatty acid composition of total phospholipid fraction in liver was determined by capillary gas chromatography after TLC separation.

Results: 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. In contrast, a reduced activity of delta-6 desaturase in liver of hHTg rats (hHTg: 13.07±0.7; C: 62±0.7 pmol/mg/min; p<0.01) was associated with a similar decrease in the abundance of delta-6 desaturase mRNA (hHTg: 0.05+0.007; C: 0.21+0.047; arbitrary units; p<0.001).

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 hyperlipemiaemia 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 hepatic 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 mg/ml) than in ST rats (5.0 ± 0.4). Interestingly, plasma insulin levels were markedly higher in ST (33.0 ± 7.4 mg/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.

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). They also showed improved whole-body glucose tolerance and insulin sensitivity and increased intramuscular concentrations of glucose 6-phosphate and glycogen. A parallel increase in uncoupling-protein 3 mRNA levels in skeletal muscle of GK-expressing transgenic mice was also observed.

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.