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Nutritional regulation of incretin secretion in controls, impaired glucose tolerance and type 2 diabetes

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Background and aims: While studies suggest that excessive sugar intake is associated with the development of type 2 diabetes (T2DM) and non-alcoholic fatty liver, it is unclear whether this is primarily related to sugar metabolites such as glucose and fructose or to the postprandial hormonal responses, particularly incretins, glucose-dependent insulinotropic peptide (GIP) and glucagon like pepetide-1 (GLP-1). We investigated the effects of sucrose and its isomer Palatinose ingestion on endogenous GIP and GLP-1 release and their relation to hepatic insulin clearance (HIC) in normal (NGT), impaired glucose tolerant (IGT) and T2DM participants.
Materials and methods: In a randomized, within-subject crossover study 15 NGT (control), 10 IGT and 10 T2DM subjects were studied for 180 min consuming 50 g either Palatinose or sucrose solutions which are dimers of glucose and fructose but resorbed either distally or proximally due to different 1,6 vs 1,2 linkage to evaluate glucose and insulin responses. Postprandial GIP and GLP-1 levels were assessed and related to HIC.
Results: Following oral sucrose, blood glucose levels peaked significantly ~2 fold after 30 min which were 38% ($p<0.001$) and 26% ($p<0.05$) higher than Palatinose intake in NGT and IGT subjects, respectively. In T2DM, maximal postprandial glucose excursions after sucrose and Palatinose intake were at 60 min and were ~20% significantly lower with Palatinose ingestion ($p<0.01$). Palatinose intake resulted in similar insuliniAUC levels in NGT, IGT and T2M (10.44±2.2, 10.9±2.3 and 11.5±3.3 nmol/l x180 min, respectively). InsuliniAUC levels after sucrose ingestion were 88%, 32% and 55% higher than Palatinose intake in NGT, IGT and T2DM ($p<0.01$, $p<0.05$ and $p=0.1$, respectively). Following sucrose intake, plasma concentrations of GIP increased significantly with 4.1, 3.1 and 2.8 fold in NGT, IGT and T2DM subjects, respectively. It reached its peak after 15 min sucrose load, while by Palatinose intake GIP levels peaked at 60 min with 2 fold increase in NGT and IGT and 1.5 fold increase in T2DM subjects compared to baseline. Palatinose intake compared with sucrose increased secretion of active GLP-1 (GLP-1iAUC) ~77% ($p<0.01$), 85% ($p<0.01$) and 84% ($p<0.05$) in NGT, IGT and T2DM groups, respectively. Sucrose caused only minor increases. Compared with sucrose, Palatinose intake improved HIC rate ~32% ($p<0.001$), 30% ($p<0.05$) and 37% ($p<0.05$) in NGT, IGT and T2DM, respectively. Across all groups, there was an inverse association between GIPiAUC and HIC ($r=-0.44$, $p<0.001$). In contrast, GLP-1iAUC was positively associated with the increased HIC ($r=0.4$, $p=0.001$).
Conclusion: Palatinose possesses a favorable profile for diabetes nutrition by lowering postprandial endogenous GIP levels, increasing GLP-1 concentrations and saving insulin secretion which ultimately results in improved management of blood glucose. Palatinose improves HIC in IGT and T2DM subjects. An inverse relationship between HIC and postprandial GIP concentrations and positive association between GLP-1 nad HIC suggest that the pattern of incretin secretions determines the rate of HIC. In particular, modulation of GIP secretion can be considered as a potential therapeutic target for improving hepatic glucose metabolism and the treatment of fatty liver.
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Altered mitochondrial metabolism is involved with increased amplifying pathways modulation of insulin secretion in protein malnourished obese mice

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Background and aims: Glucose-induced insulin secretion (GIIS) stimulates dependent and independent mechanisms of KATP channels. Low protein and high-fat diets, during important stages of development favor obesity progress inducing several changes in pancreatic islets. The changes on the independent mechanisms of KATP channels, also called amplifying pathways, induced by the combination of these two treatments are unknown. Our aim was investigating the role of these pathways on GIIS modulation of malnourished obese mice.
Materials and methods: After weaning, 21 days old male C57BL-6 mice were randomly assigned into the control group (C) which received a normo-protein diet (14% protein) during 105 days; the control-high fat diet (HFD) (CH) received normo-protein diet for 45 days and after that was treated with a HFD (60% fat) for 60 days. The protein restricted R and RH groups were fed with a low protein diet (LPD) (6% protein), receiving the same HFD treatment. Insulin tolerance was assessed by euglycemic-hyperinsulinemic clamp. In order to investigate amplifying pathways control of insulin secretion, we incubated islets with glucose (G2.8; 11.1; 22.2 mM) in the presence of K+ (30 mM) and diazoxide (250 μm). Insulin content was measured by radioimmunoassay. Protein kinases A and C and mitochondrial metabolism were also assessed.
Results: HFD decreased glucose uptake (C=25.6±2.1/CH=15.9±2.36; R=50.0±5.1/RH=18.18±3.9 mg/kg/min). GIIS was higher in animals fed with HFD (G22.2 C=1.58±0.18/CH=3.0±0.3; R=1.08±0.12/RH=1.8±0.3 ng/mL/hour/islet). The influence of amplifying pathways in insulin secretion was lower in R animals (G22.2 C=0.757±0.1; R=0.33±0.09 ng/mL/hour/islet). There were no differences among C and CH in all glucose concentrations. Additionally, the role of amplifying pathways was higher in RH (G22.2 R=0.33±0.09; RH=1.67±0.22). Whereas PKA and PKC content were not altered, ATP production displayed a trend to be reduced in RH. Basal mitochondrial membrane potential and glutamate dehydrogenase (GDH) protein content were nearly 40 and 50% higher, respectively.
Conclusion: Higher amplifying pathway modulation of insulin secretion of obese protein malnourished mice is associated with impaired mitochondrial function and GDH content. This could be one of the mechanisms reprogrammed by early protein malnutrition, since this effect does not appear in animals fed with a normal protein plus HFD.
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