POSTER 40

BETA CELL DYSFUNCTION, OXIDATIVE STRESS AND S6K1 ACTIVATION IN PANCREAS IN THE ZUCKER OBESE RAT MODEL

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Introduction: Insulin resistance and beta cell dysfunction are leading components in the pathogenesis of type 2 diabetes mellitus. Over-nutrition leads to activation of the mTOR/S6K1. S6K1 activation leads to serine phosphorylation of IRS1, triggering its proteosomal degradation and interfering with insulin metabolic signaling.

Aim of Study: We investigated the role of over-nutrition on S6K1 pathway, oxidative stress and insulin signaling in the Zucker Obese (ZO) rat, which displays severe obesity, systemic insulin resistance, glucose intolerance, and hypertension.

Methods: 9 week old male ZO and Zucker Lean (ZL) had Intravenous Glucose Tolerance Test (IVGTT)s. In pancreatic tissue we assessed NADPH oxidase activity by spectrophotometry. Expression of NADPH oxidase subunit Rac1, IRS1, Ser Phosphorlated IRS1, Akt, Phosphorylated Akt, and Tyrosine-389 Phosphorylated S6K1 were examined by Western Blot analysis. Student t testing was used.

Results: Systolic blood pressure and pancreatic NADPH oxidase activity was increased in ZO animals relative to ZL controls ($p>0.05$). During IVGTT analysis, the area under the curve (AUC) for glucose was significantly increased in ZO rats compared to ZL ($p<0.05$).The Insulin Resistance Index was calculated as $AUC_{Gluc} \times AUC_{Ins}$ $AUC_{Gluc} \times AUC_{Ins}$ and was also significantly increased in ZO compared to ZL($p<0.05$). NADPH oxidase activity and Rac-1 expression was increased in ZO. Furthermore, serine (S^{473}) phosphorylation/activation of Akt was decreased in ZO.

Conclusions: Our findings indicate that ZO animals display impaired systemic and pancreatic insulin signaling as well as elevated BP. These abnormalities occur in concert with increased oxidative stress due to enhanced activation of tissue NADPH oxidase activity.