Obesity and Cardiac Microvascular Function

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Roux-en-y gastric bypass surgery reverses obesity-induced vascular dysfunction by blunting jnk2-endothelial activation
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Introduction: Roux-en-Y gastric bypass (RYGB) reduces weight and long-term cardiovascular risk in obese patients. We showed that endothelial-mediated vasorelaxation improves rapidly in diet-induced obese (DIO) rats within 8 days after RYGB and is associated with reduced activation of JNK independently from weight loss.

Purpose: We investigated whether in vivo inhibition of JNK with two different JNK inhibitors in sham-operated rats mimics the beneficial endothelial effects of RYGB.

Methods: DIO rats underwent RYGB or sham surgery, and sham-operated ad libitum-fed rats received either vehicle (AL) or the unspecific JNK inhibitor SP600125 40mg/kg/day s.c. (SP) for 8 days post-surgery. In a second experiment, sham-operated rats received either control peptide TAT (TAT) or the highly specific JNK peptide inhibitor DJNK-1 20mg/kg/day s.c. (DJNK) for 8 days post-surgery. Thereafter, thoracic aortic rings were isolated and subjected to ex vivo isometric tension recordings. After submaximal contraction with norepinephrine (10^-6mol/L), cumulative relaxation responses were performed to GLP-1 (7–36) amide (10^-10 to 10^-6mol/L) or insulin (10^-10 to 10^-6mol/L). In TAT and DJNK rats, some aortic rings were isolated as before and pre-incubated ex vivo with 5 uM DJNK for 30 min before vasodilation experiments. Western blot analyses of JNK, the inhibitory phosphorylation of insulin receptor substrate-1 (IRS-1) on ser307, and downstream cellular insulin signaling including Akt, eNOS-ser1177 activatory phosphorylation and eNOS dimerization were performed on aortic tissue lysates.

Results: GLP-1- and insulin-induced vasodilation improved in RYGB and tended to improve in SP compared to AL rats. The specific JNK inhibitor DJNK completely mimicked the beneficial effects of RYGB surgery on endothelial function 8 days after surgery. Ex vivo aortic pre-incubation with DJNK impaired the vascular relaxation of TAT rats, but did not further ameliorate the already restored vasodilation of rats receiving the in vivo DJNK treatment. Aortic protein phosphorylation of JNK2, but not of JNK1 were specifically decreased. IRS-1 ser307 phosphorylation was decreased, and the axis Akt-IRS-ser1177 phosphorylation and dimerization were increased in SP and DJNK rats similarly to RYGB, in comparison with their respective controls.

Conclusion: Pharmacological JNK inhibition mimics the beneficial effect of RYGB against obesity-induced vascular dysfunction by specifically blunting JNK2-endothelial activation. Our study suggests a novel JNK2-targeted mechanism for the vascular benefits after RYGB.

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Involvement of the Fgf21 system in obesity-associated cardiomyopathy
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Introduction: High-fat diet-induced obesity leads to development of cardiac dysfunction through molecular mechanisms poorly known. We have recently shown that fibrolast growth factor-21 (Fgf21), an endocrine member of the FGF family, is produced by the heart and exerts protective effects preventing cardiac hypertrophy development. The aim of this study was to determine the effects of Fgf21 on the cardiomyopathy associated to obesity development.

Methods: Studies in vivo were performed in wild-type (wt) and Fgf21-null mice. Two-month old mice were fed a high-fat diet (45% fat content) for 16 weeks to induce obesity. Systemic metabolic and hormonal profile, echocardiographic measurements, cardiac gene expression analysis, oil-red O staining, and dynamic measurement of fatty acid oxidation rates were determined.

Results: We found that high-fat diet-induced obesity significantly increased the plasma levels of Fgf21. Furthermore, high-fat feeding was associated with an increase in the heart weight/body length (HW/TL) ratio in wt mice. In contrast, Fgf21-null mice presented enhanced HW/TL compared with wt mice after high-fat feeding. In keeping with this, echocardiographic measurements (LVID, IVS, PWT and EDV) confirmed enhanced cardiac hypertrophy in Fgf21-null mice. At the cellular level, the area of the cardiomyocytes was increased in Fgf21-null mice treated with the high-fat diet and was accompanied by induced expression of the hypertrophic marker gene α-Actinin. Furthermore, fatty acid oxidation in the hearts of mice fed a high-fat diet was induced in Fgf21-null mice. Finally, the mRNA expression levels of genes involved in lipolysis such as hormone-sensitive lipase (Hsl) and adipocyte triglyceride lipase (Atgl) were down-regulated in Fgf21-null mice compared to wt mice fed with a high-fat diet. Oil-red O staining revealed the presence of higher amounts of lipid droplets in the hearts of Fgf21-null mice fed with a high-fat diet relative to wild-type mice fed this same diet.

Conclusion: Our data indicate that lack of Fgf21 confers more susceptibility to the cardiomyopathy induced by obesity. Furthermore, we demonstrate that this cardiac dysfunction was associated with deleterious lipid accumulation in the heart.

Oil-red O staining of cardiac samples

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Is low ATM protein responsible for myocardial insulin resistance associated with obesity?
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Atlases-proteasome (A-T), an auto-somal recessive disorder caused by mutations in the ataxia-telangiectasia mutated gene, is coupled to low or no expression of ATM, a ser/thr protein kinase. A-T patients have a high incidence of insulin resistance/type 2 diabetes mellitus, atherosclerosis and ischaemic heart disease. Aim: Since obesity may alter ATM expression, its myocardial levels and role in obesity-induced insulin resistance were studied.

Methods: Male Wistar rats were rendered obese and insulin resistant by diet (HFD) and compared to chow-fed controls (C). Measurements: iPTTs, biometric and biochemical parameters, ex vivo perfused working hearts to determine functional performance, resistance to ischaemia/reperfusion and infarct development. Insulin sensitivity, measured by accumulation of [3H]2DG in ventricular cardiac myocytes, was determined by western blotting and NO measured by FAC5 analysis.

Results: (i) HFD cardiocytes were insulin resistant with reduced ATM and PKB/Akt expression: insulin-stimulated 2DG uptake in C and HFD cells to 17 ± 4.6 vs 27.5 ± 3.2 pmol/mg prot/30min in C (p = 0.05). (ii) KU inhibited insulin-stimulated 2DG uptake in C and HFD cells to 17 ± 4.1 and 12.3 ± 3.9 pmol/mg prot/30min respectively (p = 0.05). (iii) HFD lowered expression of both ATM and PKB/Akt in myocytes by 60% (1 ± 0.1 vs 0.4 ± 0.1 ADU, p = 0.002) and (1 ± 0.05 vs 0.37 ± 0.09, respectively)
(iv) KU significantly inhibited insulin-stimulated phosphorylation of both ATM (p<0.001) and PKB/Akt (p=0.04). (iii) KU increased coronary flow of both C and HFD hearts (P<0.0001), NO production by AEC’s (23% increase in DAF fluorescence) and eNOS-mediated aortic relaxation. However, (iv) hearts from HFD but not C animals had significantly decreased coronary flow recovery on reperfusion following ATM inhibition. In contrast, KU in HFD animals was infarct sparing. Conclusion: This is one of the first studies aimed to elucidate the importance of ATM in cardiac function. We showed downregulated expression of ATM in the heart in obesity coupled to insulin resistance in cardiomyocytes. Inhibition of ATM with KU mimicked this, also resulting in inhibition of insulin-stimulated PKB/Akt activation. ATM is therefore a prerequisite for insulin-mediated PKB/Akt activation and glucose uptake in cardiomyocytes and low ATM in HFD may be partly responsible for insulin resistance. In addition, we demonstrated an important role for ATM in vascular responsiveness.