

Inhibition of TNF- α by infliximab restores adiponectin production in perivascular adipose tissue from streptozotocin-treated type 1 diabetic mice

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Hyperglycemia, oxidative stress and inflammatory response contribute to cardiovascular complications of type 1 diabetes (T1DM). In both patients and animal models of T1DM such as the streptozotocin (STZ)-diabetic mice, circulating levels of proinflammatory cytokines TNF- α and IL-6 are increased (Mohamed-Ali V et al. 2001), whereas levels of adiponectin (Ad), an adipocytokine with anti-inflammatory and anti-atherogenic properties, have been found dysregulated (Galler A et al. 2007). Since TNF- α negatively modulates Ad synthesis and release in various tissues and cells (Kim KY et al. 2005), it is likely that increased levels of TNF- α may affect Ad concentration and activity in T1DM. Treatment with infliximab, the TNF- α blocking monoclonal antibody, has been recently suggested to improve diabetic features in animals (Araujo LP et al. 2007) and patients (Gupta-Ganguli M et al. 2011). Whether pharmacological inhibition of TNF- α would improve Ad profile in T1DM is unknown. The aim of this study was to elucidate whether treatment with infliximab may modulate Ad and Ad receptor expression at the early stage of T1DM in different cardiovascular tissues and adipose depots of STZ-treated mice.

Male Balb/c mice were treated once with STZ (200 mg/kg, IP) or vehicle (citrate buffer; CTRL group, n=10). After 72 hours, diabetic condition was assessed by measuring the blood glucose obtained by tail tip cut. Diabetic animals (glycemia >240 mg/dl) were randomly assigned to treatment with infliximab (10 mg/Kg, IP, I-STZ group, n=10) or no treatment (STZ group, n=10). Glycemia and body weight were monitored daily for the 10 days following STZ treatment in all groups. Serum levels of total and high-molecular weight (HMW) Ad were compared by ELISA assay among groups. The mRNA and protein expression of Ad and Ad receptors AdipoR1 and AdipoR2 in epididimal (EAT), subcutaneous (SAT), visceral (VAT) and perivascular adipose (PAT) tissues, as well as in mesenteric vessels and in the heart homogenates were evaluated by RT-PCR and WB techniques, respectively.

In STZ diabetic mice, Ad serum levels were slightly increased when compared to CTRL (p<0.05). mRNA and protein levels of Ad and AdipoR2 were significantly reduced in PAT (p<0.01 vs. CTRL) and unmodified in EAT and SAT. Conversely, both Ad and AdipoR2 were significantly increased in VAT (p<0.01 vs. CTRL), and likely responsible for the increased Ad serum levels observed in STZ mice. In heart homogenates, Ad expression was unaffected, whereas AdipoR1 expression was reduced (p<0.05 vs. CTRL). Infliximab did not restore body weight loss and did not reduce hyperglycemia observed in STZ mice, but further increased total Ad concentrations (p<0.05 vs. STZ), without affecting the HMW isoform. Treatment with infliximab did not improve AdipoR1 expression in the heart, nor did affect mRNA and protein levels of Ad and AdipoR2 in EAT and SAT. Interestingly, infliximab completely restored both mRNA and Ad protein expression in PAT (p<0.05 vs. STZ). At molecular level, this effect was associated to normalization of phosphorylated/total c-Jun N-terminal kinase (JNK) ratio, which was increased in both PAT and mesenteric arteries from STZ group (p<0.05 vs. CTRL).

Taken together, these findings suggest that, during the onset of T1DM, PAT displays an early inflammatory profile with respect to other visceral fat depots, and may be more prone to TNF- α -induce deregulation of Ad production. Short-term treatment with infliximab is able to inhibit JNK activation and restore Ad profile in PAT, thus implying that treatment inactivating TNF- α may have potential therapeutic applications for diabetes-associated vascular complications.

References:

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