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Neuronatin: a new inflammation gene expressed on the aortic endothelium of diabetic mice.

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Abstract

OBJECTIVE: Identification of arterial genes and pathways altered in obesity and diabetes.

RESEARCH DESIGN AND METHODS: Aortic gene expression profiles of obese and diabetic db/db, high-fat diet-fed C57BL/6J, and control mice were obtained using mouse Affymetrix arrays. **Neuronatin** (Nnat) was selected for further analysis. To determine the function of Nnat, a recombinant adenovirus (Ad-Nnat) was used to overexpress the Nnat gene in primary endothelial cells and in the mouse aorta in vivo.

RESULTS: Nnat, a gene of unknown vascular function, was upregulated in the aortas of db/db and high-fat diet-fed mice. Nnat gene expression was increased in db/db mouse aorta endothelial cells. Nnat protein was localized to aortic endothelium and was selectively increased in the endothelium of db/db mice. Infection of primary human aortic endothelial cells (HAECs) with Ad-Nnat increased expression of a panel of nuclear factor-kappaB (NF-kappaB)-regulated genes, including inflammatory cytokines, chemokines, and cell adhesion molecules. Infection of mouse carotid arteries in vivo with the Ad-Nnat increased expression of vascular cell adhesion molecule 1 protein. Nnat activation of NF-kappaB and inflammatory gene expression in HAECs was mediated through pathways distinct from tumor necrosis factor-alpha. Nnat expression stimulated p38, Jun NH(2)-terminal kinase, extracellular signal-related kinase, and AKT kinase phosphorylation. Phosphatidylinositol 3-kinase and p38 inhibitors prevented Nnat-mediated activation of NF-kappaB-induced gene expression.

CONCLUSIONS: Nnat expression is increased in endothelial cells of obese and diabetic mouse blood vessels. The effects of Nnat on inflammatory pathways in vitro and in vivo suggest a pathophysiological role of this new gene in diabetic vascular diseases.

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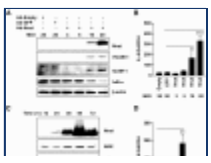

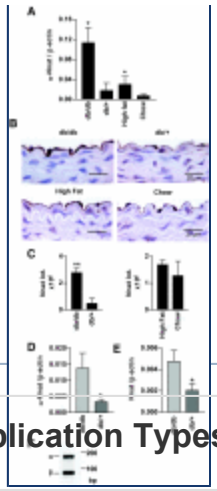

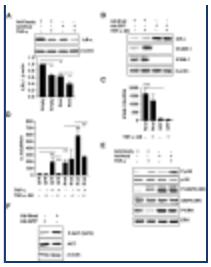

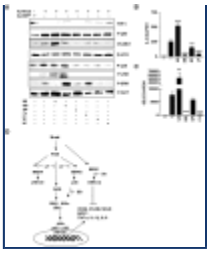

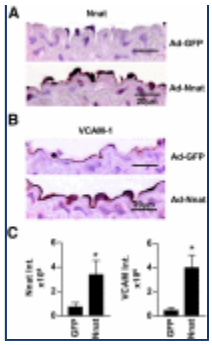

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