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Exenatide modulates metalloproteinase expression in human cardiac smooth muscle cells via the inhibition of Akt signaling pathway

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ABSTRACT

Background: Incretin analogue drugs, a FDA-approved treatment in diabetes, has been tested for its therapeutic properties as modulators of atherosclerosis. We investigated the effects of incretin drugs on the modulation of gene expression and protein levels of matrix metalloproteinases (MMPs) as well as their inhibitors - tissue inhibitors of metalloproteinases (TIMPs) in coronary artery smooth muscle cells (hCASMC) in the context of atherosclerotic plaque formation and inflammation.

Methods: TNFα-stimulated hCASMC were treated with Glucagon-like Peptide 1 (GLP-1) (10nM and 100nM) and Exendin-4 (1nM and 10nM). Messenger RNA (mRNA) levels and protein concentrations of MMP-1, MMP-2, MMP-9 and TIMP-1, TIMP-2 were measured and the effects on extracellular matrix turnover under TNFα-mediated microenvironment were evaluated. Intracellular signaling pathways were also examined.

Results: Our experiments reveal that GLP-1 receptor agonists downregulate the expression of MMP-1, MMP-2, MMP-9 in hCASMC under TNFα mediated inflammatory conditions. Signaling pathway analysis show that GLP-1 receptor agonists induced inhibition of AKT-Thr308 phosphorylation, PRAS40 and S6 proteins but not AKT-Ser473.

Conclusions: These findings indicate that GLP-1 receptor agonists modulate the expression of MMPs through inhibition of AKT-Thr308 phosphorylation in hCASMC. These results suggest a possible role of incretin analogue drugs in therapy of coronary atherosclerosis.

Key words: atherosclerosis, incretins, Exenatide, matrix metalloproteinases, human coronary artery smooth muscle cells

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