The role of neuropeptides in the pathomechanism of atherosclerosis

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Previous studies and the aim of the present study

In our earlier studies, we found that signal transduction of some neuropeptides and LDL particles was altered in leukocytes obtained from patients with hypercholesterolemia (HC). The aim of the present study was to elucidate whether cytokine-like neuropeptides, e.g., angiotensin II (Ang II) and leptin - which are involved in atherosclerotic plaque formation - do affect control and HC leukocytes in different ways. We showed that there is free radical generation through the statin-sensitive Rac1/2 activation as well, as a consequence of the mevalonate cycle's increased intensity. We also investigated the effect of enhanced free radical generation on membrane composition and $[Ca^{2+}]i$ homeostasis of leukocytes that were obtained from patients with different entities of metabolic syndrome (MS). Finally, based on the finding of neuropeptide-induced increase of the mevalonate cycle, we studied leptin's effect on endogenous cholesterol biosynthesis in monocytes of HC patients.

Results

1.) According to our results, the Ang II and leptin-induced superoxide and leukotriene generation in HC cells were higher than in control leukocytes, even through Rac1/2 activation, as a consequence of statin-inhibitable increased intensity of the mevalonate cycle. In contrast with the "canonical" signalling pathway in control cells, the signal processing of HC leukocytes involved Ca^{2+}-influx, PI3 kinase and MAP kinase

activation. Additionally, the PI3 kinase-activated alternative pathways through Ins(3,4,5)P3, and ξ protein kinase C play significant roles in the altered signal processing of HC leukocytes. 2.) We have clarified that in different entities of MS, increased free radical generation have influence on membrane rigidity and membrane composition. As a "vicious circle", neuropeptides generate free radicals in leukocytes of obese and HC patients, and the free raducals, in turn, injure ion channels resulting in altered Ca^{2+} signals. This finding manifested itself in the different form of $[Ca^{2+}]i$ time curve and in the increase of the "area under time curve" (AUC) value. The disturbed Ca^{2+} signal in leukocytes of obese patients was partially corrected by in vitro treatment with fluvastatin. 3.) We have described it for the first time that leptin has a concentration dependent effect on intracellular cholesterol synthesis in human monocytes. At 10-100 ng/mL concentrations, leptin increased cholesterol synthesis in HC cells more intensely than in control monocytes, through the SREBP-SCAP-Insig protein system.