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Letters

Comments

Free Fatty acids (FFA) and endothelial dysfunction; role of increased oxidative stress and inflammation

–to: Steinberg et al. (2002) Vascular function, insulin resistance and fatty acids

To the Editor: The review by Steinberg and Baron on the role of FFA in the pathogenesis of abnormal vascular reactivity and diminished responses to insulin at the endothelial/vascular level and in terms of glucose utilization is of interest [1]. In insulin-resistant states of obesity and Type 2 diabetes, nitric oxide (NO) release could be impaired because of the action of FFA on PI3 kinase mediated mechanisms resulting in diminished release of NO [2]. There are two other important contributing factors which could decrease NO bioavailability. Firstly, oxidative stress (and reactive oxygen species; ROS generation) is increased in obesity and Type 2 diabetes. Not only is there an increase in ROS generation, there is oxidative damage of lipids, proteins, amino acids and DNA [3]. Superoxide is known to be the major ROS generated by leucocytes, which binds NO to form peroxynitrite ($ONOO^-$), which is toxic and does not vasodilate. Indeed, we have recently shown that an FFA increase in FFA acutely induces a diminution in post-ischaemic flow-mediated vasodilatation of the brachial artery [4]. Thus, FFA could account for the previously described abnormalities of vascular reactivity in diabetes and obesity in both arterial and venous vascular beds [5].

It has been shown that FFA might also contribute to the induction of ROS generation in the endothelial and vascular smooth muscle cells [6]. Also, as an indirect evidence of increased oxidative stress, vitamin C, an anti oxidant has been shown to reverse the FFA-induced endothelial dysfunction in healthy subjects [7]. Additionally, we have shown that FFA increase the formation of ROS by leukocytes and inflammatory changes in the circulating mononuclear cells (MNC), the cells which initiate an inflammatory process on the endothelium [4]. Thus, an acute FFA increase in plasma results in a rapid increase in intranuclear NF-κB in MNC. Such an action, similar to that observed following glucose challenge, can potentially result in the activation of pro-inflammatory genes which are modulated by NF-κB [8]. Thus, pro-inflammatory cytokines like TNF-α and IL-6, chemokines like MCP-1 and enzymes which produce ROS, like NADPH oxidase, might increase since inflammation is the final common pathway/mechanism underlying atherosclerosis. Thus, increased concentrations of FFA in plasma could also contribute to atherogenesis. Another pro-inflammatory cytokine, TNF-α, which is known to be constituitively expressed by adipose tissue and whose tissue expression and plasma concentrations are increased in obesity and Type 2 diabetes, causes a suppression of NOS expression in human aortic endothelial cells (HAEC) in the basal state and following stimulation by insulin. TNF-α also causes the suppression of insulin receptor phosphorylation and the expression of insulin receptor protein in human aeortic endothelial cells (HAEC) [9].

Thus, the absence of insulin-induced vasodilation, as well as impaired endothelium-mediated vasodilation by other stimuli in insulin-resistant states like obesity and Type 2 diabetes, is probably due to multiple mechanisms of which an increase in FFA is one. These factors also contribute to atherosclerosis in insulin-resistant states like obesity and Type 2 diabetes.

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