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Leptin: The missing link between obesity and heart disease?

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Two papers in this issue of *Atherosclerosis* explore different aspects of the role of leptin in cardiovascular disease, and here we review each paper in turn. Leptin plays a key role in the regulation of body weight and inflammatory responses, and its role in atherosclerosis has been described in several studies [1,2]. Elevated plasma concentrations of leptin are independently associated with the intima-media thickness of the common carotid artery, and with the degree of coronary artery calcification in patients with type 2 diabetes mellitus, after controlling for adiposity and CRP. Hyperleptinemia is also involved in the increased risk of post-angioplasty restenosis. Obesity and the co-existing metabolic syndrome eventually lead to leptin resistance with attenuation of leptin signalling at a cellular level. The development and mechanism of leptin resistance however is still poorly understood, and it is likely that it encompasses different events that are distinct in underlying mechanisms and pathophysiological implications. As to how leptin resistance develops in the vascular system and whether it is a cause or an effect of atheroma formation is still unclear. A key early event in atherosclerosis is endothelial dysfunction. Caveolin-1 is a structural protein of caveolae, which plays an important regulatory role in cell signalling, development of atherosclerosis and obesity. Caveolin levels are increased with obesity and caveolin deficiency results in a lean phenotype [3,4]. However, the interaction between leptin and caveolin has not been studied so far.

In the current issue of *Atherosclerosis* Singh et al. [5] describe a novel feed-back loop of caveolin-1-mediated down regulation of leptin signalling. The important and novel findings reported are that leptin induces caveolin-1 protein expression, and in addition, increased caveolin-1 expression impairs leptin signalling. As caveolin-1 is pro-atherogenic, leptin may cause a direct atherogenic effect, while increased caveolin-1 expression may contribute to the development of endothelial leptin resistance and eventually, atherosclerosis. *In vivo* studies are necessary to confirm the relevance of these findings and also to elucidate the time course of the events establishing the cause and effect relationship between leptin, caveolin-1 upregulation and leptin resistance. Also, the mechanisms leading to these effects need to be delineated.

Leptin levels increase with obesity. Despite being discovered more than a decade ago, human studies investigating the relationship of leptin to coronary artery disease are still conflicting. Thus, this relationship needs to be investigated in large prospective studies. In this issue of *Atherosclerosis* Ku et al. [6] report the results of such an analysis, in The Heart and Soul Study, a prospective cohort study investigating the effect of psychosocial factors on

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prognosis in 981 patients with chronic stable CAD. The authors report that low baseline leptin levels predicted subsequent CV events and death. Although subjects with low leptin had fewer co-morbidities and more favorable metabolic and inflammatory profiles, they had a worse prognosis than subjects with high leptin. Furthermore, BMI modified the effect of leptin on mortality, and lower leptin predicted mortality in patients with normal BMI but not in patients with high BMI. Again, these effects may be explained by increased leptin resistance in obesity. Leptin has been shown to have both protective as well as atherogenic effects, depending on the dose of leptin used in the different studies. Unfortunately, in this paper, no functional effects of leptin were studied, thus understanding the mechanistic effects of leptin in the cardiovascular system may provide insights into the relationship between obesity and heart disease. Also, most patients in this study were men and had coronary artery disease, so whether these effects apply to the general population, who do not have heart disease, is unclear and this still needs to be delineated.

Overall these studies give interesting insights into the multiple roles this novel hormone is having in influencing human health and disease, but many areas remain to be explored to elucidate in detail the mechanisms involved.

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