

Editorial Focus

Leptin, obesity and platelet responsiveness: Another piece in the puzzle

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The effects of leptin on platelet aggregation in morbidly obese subjects in comparison to normal-weight controls are examined in this issue of *Thrombosis and Haemostasis* by Dellas et al (1). They found that a) aggregatory response to increasing concentrations of ADP was significantly increased in platelets from obese compared to lean donors; b) plasma leptin levels were significantly higher in subjects with stronger platelet aggregation response to ADP; c) leptin was able to induce phosphorylation of JAK2 and STAT3 to a similar extent in platelets from both obese and lean donors; d) the expression of mediators of leptin resistance, such as SOCS3 and PTP1B did not differ in platelets from obese patients and controls.

The pattern of plasma leptin distribution in relation to platelet aggregation response to ADP observed by Dellas et al. differs from that observed in former studies. Indeed, body mass index (BMI) and circulating leptin levels were higher in subjects whose platelets did not respond to the pre-incubation with leptin in a recent study of ours (2). This finding, together with the demonstration that normal weight subjects undergoing complete caloric deprivation had greater sensitivity in haemostatic responses to leptin (3), gave rise to the hypothesis that the sensitivity of leptin receptors on platelet membranes might change in relation to body composition, and that human obesity might be associated with resistance to the pro-aggregatory action of leptin. Such platelet resistance to leptin in overweight or obese patients might represent a finalistic protective mechanism against the excess pro-thrombotic stimulation produced by obesity-related hyperleptinemia (2).

Differences in methodology, such as use of platelet-rich plasma versus washed platelets, leptin concentrations used in the experimental procedures, time points chosen to measure the effects of leptin, and overall design of the study, could partially explain these discrepancies. Furthermore, the cross-sectional design does not allow Dellas et al. (1) to verify whether leptin-dependent platelet aggregation reduces with weight loss and consequent fall of leptin levels, and this issue remains to be settled.

Whatever the explanation for this discrepancy is, Dellas and coworkers merit to be commended for their very elegant study denying the former hypothesis, providing convincing evidence about the absence of resistance to leptin in platelets from obese donors, and putting another important piece in the puzzle of leptin actions in the human pathology. Indeed, platelet-priming and -potentiating molecules and/or their mechanisms are an attractive novel target of antiplatelet therapy, and their inhibition might drive us out of the narrow passage between insufficient efficacy and excessive bleeding typical of currently available platelet inhibitors. However, the challenge we must overcome in the future development of antiplatelet agents targeting molecules able to prime and potentiate aggregation is that of cell- and tissue-selectivity and/or of possible paradoxical receptor-agonistic activity (4). While molecules acting on leptin or its receptor have been extensively described (e.g. soluble leptin receptors that bind free leptin in the circulation, leptin-receptor antagonists such as leptin mutants, peptide antagonists, and anti-leptin-receptor monoclonal antibodies) (5), no studies have so far explored the potential platelet modulatory activity of leptin inhibition. The most relevant and immediate implication of the new findings reported by Dellas et al (1) is the beginning of a new era in search of a pharmacological strategy specifically targeting the leptin-platelet axis against the thrombotic complications from obesity.

While clinical evidence supports experimental studies that suggest a link between hyperleptinaemia and increased risk of vascular thrombosis (6, 7), pharmacological interventions aimed at reducing circulating leptin levels may produce more harms than benefits by inducing weight gain and consequent comorbidities. Therefore, weight loss still remains the only safe strategy to reduce plasma leptin and its potentiating effects on thrombosis. Nevertheless, a drug selectively acting on the platelets leptin receptor and/or post-receptorial mechanisms, provided it can be achieved, could produce benefit independent of changes in leptin (8). The work of Dellas et al. indicates that it is time to accept this challenge.

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