The role of leptin in endothelial dysfunction and cardiovascular disease

Manuel Cruz González García

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie/medicine doktorsexamen framläggs till officiellt försvar i Salens E04 By 6E, den 27 September, kl. 13:00.

Avhandlingen kommer att förvaras på svenska.

Fakultetsopponent: Professor Jan Engvall,
Institutionen för medicin och hälsa, avdelning för kardiovaskulär medicin, Linköpings universitet, Sverige.
Abstract

Objective: Obesity has become the leading cause of mortality worldwide; however, the fundamental pathophysiology underlying this association remains unclear. The discovery of adipokines, i.e., cytokines produced by adipose cells (adipocytes), revealed that adipose tissue is a highly endocrine organ, thus opening new lines of investigation. The prototypical adipokine leptin increases in obesity, and leptin receptors are found in vascular cells. However, results are contradictory regarding the role of leptin in vascular and endothelial functions. Leptin has been shown to elicit vasodilatation, but it has also been linked with atherosclerotic and thrombotic disease. The main aim of the present thesis was to study the association of circulating levels of leptin with markers of endothelial function, and to analyze the effects of leptin infusion in vivo on vasomotor function and endogenous fibrinolysis.

Material: Four associative studies and two interventional studies were conducted. The former included DISARM (studies 1 and 2), the PIVUS study (study 3), and the Scottish post-infarction study (study 4). The DISARM studies and study 4, respectively, recruited 20 men and 83 men and women with stable ischemic heart disease. Study 3 included a random sample of 1016 subjects (54% women, 70 years old) living in the community of Uppsala, Sweden. For the interventional studies (studies 5 and 6), 10 healthy men were recruited for each study.

Methods: In all studies, endothelial function was estimated based on forearm blood flow (FBF) as measured by strain-gauge venous occlusion plethysmography, at rest or during infusion of vasodilators. In study 3, additional measurement techniques were used, such as brachial ultrasound flow-mediated dilation (FMD) and the aortic augmentation index (AoAIx) by tonometry in the radial artery. Fibrinolytic status was estimated based on basal and stimulated levels of tissue plasminogen activator antigen (t-PA), and by assessment of the endothelial release of t-PA (net t-PA release). Plasma leptin levels were measured by radioimmunoassay. In the associative studies, endothelial function and fibrinolytic status were related to circulating plasma leptin levels. In the experimental studies, exogenous leptin was administered in the brachial artery and endothelial function was assessed by strain-gauge plethysmography.

Results: In elderly men and women, leptin was independently associated with decrease endothelial-dependent and -independent vasodilatation, reflecting disturbed endothelial function in resistance vessels. This association was attenuated after adjustment for BMI, and when analyzed among subjects with high plasma leptin levels. FMD (a measure of endothelial function in conduit vessels) was not associated with leptin. Exogenous leptin infusion did not alter vasomotor tone, but the endothelium-dependent and -independent vasodilatation was impaired during concomitant infusion of leptin and vasodilators. Infused leptin in the forearm did not affect blood pressure or pulse rate. Chronic hyperleptinemia, but not acutely induced hyperleptinemia, was associated with release of endothelial tissue plasminogen activator (net t-PA).

Conclusions: In humans, leptin was associated with decreased endothelial-dependent and -independent vasodilatation, reflecting disturbed endothelial function in resistance vessels. This association was attenuated after adjustment for BMI, and when analyzed among subjects with high plasma leptin levels. FMD (a measure of endothelial function in conduit vessels) was not associated with leptin. Exogenous leptin infusion did not alter vasomotor tone, but the endothelium-dependent and -independent vasodilatation was impaired during concomitant infusion of leptin and vasodilators. Infused leptin in the forearm did not affect blood pressure or pulse rate. Chronic hyperleptinemia, but not acutely induced hyperleptinemia, was associated with release of endothelial tissue plasminogen activator (net t-PA).

This thesis addresses several controversial issues regarding the action of leptin on vascular tissue in humans. The final results indicate that the in vivo action of leptin on vasularity is complex and mediated by several mechanisms. Our findings suggest that leptin is an important mediator between obesity and endothelial dysfunction, and should stimulate further investigation of this matter.