Relationship between Increases in Body Weight, Endocannabinoids, Leptin and Coronary Circulatory Dysfunction

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Background: Over the last ten years there has been a dramatic increase in the incidence of overweight and obesity in Switzerland between 37-58% in male and 22-38% in female. The mechanisms by which increases in body weight initiates and accelerates coronary artery disease (CAD) remain largely unexplored. We have shown recently that obesity is independently predictive of coronary circulatory dysfunction as an early functional precursor of CAD process. Adipocytokines such as leptin and endocannabinoids may be involved in the regulation and modulation of coronary circulatory function.

Increases in leptin plasma levels in obesity may exert beneficial effects on the coronary endothelium to counteract the adverse effects of increases in body weight on coronary circulatory function. More recently, it has also been suggested that increases in adipose-derived endocannabinoids may exert proatherosclerotic effects by receptor signaling via CB1 receptors in the vascular wall. Further, a genetic malfunctioning of the degradation of endocannabinoids, owing to a missense polymorphism in fatty acid amide hydrolase (FAAH), may contribute to increases in endocannabinoids in obesity. Notably, the endocannabinoid system underlies a negative feedback control regulation by increases in leptin levels mediated through stimulation of PPAR-γ in the adipose tissue.

Working hypothesis: Increases in proatherosclerotic endocannabinoids in obesity, which may be reinforced by a missense polymorphism in FAAH, causes coronary circulatory dysfunction, while increases in leptin may protect the coronary endothelium against a worsening of its function. We hypothesize that the benefical effects of leptin on coronary circulatory function in individuals with increased body weight may also be mediated by a leptin-induced down-regulation of adipose-derived and proatherosclerotic endocannabinoids.

Aims: The overall aims of the present research proposal are:

1) to assess whether increases in endocannabinoids in overweight and obesity, possibly reinforced by a missense polymorphism in FAA, leads to coronary circulatory dysfunction;

2) to assess whether beneficial effects of leptin on coronary endothelial function in overweight/obesity are also mediated by a leptin-induced negative feedback regulation of the endocannabinoid system (cross-sectional analysis); and

3) to investigate whether surgical bypass-induced weight loss (i.e. BMI □40) after 12 months improves coronary circulatory dysfunction, and how this beneficial effect on the coronary circulation is related to changes in body weight and adipocytokines such as leptin and endocannabinoids (longitudinal analysis to evaluate cause-and-effect relationships).

Design and Methodology: The study will be conducted in normal weight (BMI>20 25kg/m2,n=40), overweight (BMI□25-30 kg/m2,n=40), obese (BMI>30kg/m2,n=40) and morbidly obese (BMI□40kg/m2,n=40) individuals without traditional coronary risk factors. Dual X-Ray Absorptiometry (DXA) and Computerized Tomography (CT) will determine the extent of the fat mass and its distribution (visceral/subcutaneous). Concentrations of endocannabinoids, leptin and adiponectine will be determined in the plasma and adipose tissue. Coronary circulatory function will be assessed by cardiac 13N-ammonia PET.

Potential Significance: If our hypothesis as outlined above holds true, then new medical therapy strategies may target the production and/or release of leptin, while at the same time aiming to diminish endocannabinoid concentrations in the prevention of the CAD process in overweight and obesity.