ROLE OF THE ENDOCANNABINOID SYSTEM IN ATHEROSCLEROSIS

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Introduction

Atherosclerosis is an inflammatory disease that involves vascular and immune cell types. Endothelial cells, smooth muscle cells, resident macrophages, as well as circulating leukocytes and platelets are the active players in the atherosclerotic inflammatory processes. Recently, basic research studies, animal models, and clinical trials have strongly suggested that the endocannabinoid system (ECS) is a crucial modulator of these cells in atherosclerosis.

State of the Art

The ECS comprises several endogenous agonists of the cannabinoid type 1 (CB1) and type 2 (CB2) receptors and their degrading enzymes, which are secreted on demand. Endocannabinoid activity is mainly mediated by the binding and activation of CB1 or CB2 receptors, which are differentially expressed in inflammatory cell types and organs. However, endocannabinoids can also exhibit immunomodulatory activities through pathways that are independent of "classical" cannabinoid receptors. For instance, they can activate transient receptor potential vanilloid type-1 receptors (TRPV1), peroxisome proliferator-activated receptor-α (PPAR-α), and the orphan G protein-coupled receptor GPR55. There is mounting evidence for immunomodulatory effects of endocannabinoids, suggesting their crucial role in atherosclerotic inflammatory processes. In particular, the endocannabinoid anandamide has been shown to reduce the pro-inflammatory effects of tumor necrosis factor-α in human coronary artery endothelial cells and the adhesion of THP-1 monocytes to human coronary artery endothelial cells in a CB1 and CB2-dependent manner. More recently, we have shown that the activation of CB2 receptors inhibits human monocyte migration in response to classical chemoattractants, which are expressed in atherosclerotic plaques. Furthermore, endothelial cells, macrophages, or platelets themselves increase their endocannabinoid synthesis during atherosclerosis, thus triggering platelet activation. These cells are also able to metabolize anandamide. Although some studies have also shown a possible pro-thrombotic effect of endocannabinoids, the majority of *in vitro* experimental evidence supports their possible anti-inflammatory role in atherosclerosis. Several animal models have confirmed *in vitro* studies by showing that treatment with cannabinoid agonists reduced blood pressure and atherosclerosis progression in rodents. In spontaneously hypertensive rats, prevention of endocannabinoid anandamide degradation by an inhibitor of fatty acid amide hydrolase (FAAH) was shown to lower blood pressure and heart rate through reductions in both car-

diac contractility and vascular resistance. These effects were prevented by CB1 antagonists. These findings suggest that the ECS represents a therapeutic target for the treatment of hypertension, which is a major risk factor for atherosclerosis. A more recent study investigated the age-associated decline of cardiac function and changes in inflammatory gene expression, nitrative stress, and apoptosis in FAAH-/-mice as compared to wild type mice. Enhanced anandamide levels in the FAAH-/-animals were protective, which further supports the protective role of endocannabinoids in inflammatory disorders such as atherosclerosis. Nevertheless, direct experimental evidence supporting a direct role of the ECS in atherosclerosis is still missing.

Obesity is a metabolic disease and a major risk factor for atherosclerosis. The ECS plays a crucial role in obesity. In particular, overactivity of the ECS promotes excessive food intake and fat accumulation in animal models and humans. In rodents, pharmacologic blockade or genetic ablation of CB1 receptors reduces appetite and weight and prevents obesity and insulin resistance. CB1 blockade in rodents acts on adipocytes to increase adiponectin expression, on hepatocytes to decrease *de novo* lipogenesis and increase fatty acid oxidation, and in the gastrointestinal tract to increase satiety. Clinical trials investigating treatment with rimonabant (a selective antagonist of the cannabinoid type 1 receptor) have suggested a beneficial effect of this drug in the management of obesity in humans. The first study on the efficacy of rimonabant against atherosclerosis and coronary artery disease (CAD) in obese subjects was published recently (in 2008). The Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant - The Intravascular Ultrasound Study (STRADIVARIUS) was a prospective, multicentre, multinational, randomized, double-blind placebo-controlled 2-group, parallel-group study, involving 112 centres in North America, Europe, and Australia. Patients were randomly assigned to two groups (placebo vs. 20 mg/day rimonabant) and followed for 18 months. Although rimonabant ameliorated the normalized total atheroma volume (TAV, secondary endpoint), the study failed to show a decrease in percent atheroma volume (PAV, primary endpoint). These controversial results indicated that the use of rimonabant in the management of coronary disease in patients with central obesity or metabolic syndrome requires further investigation. However, the elevated incidence of adverse events in this study raises some doubts regarding the safety of rimonabant.

Priorities for Future Studies

Basic research, animal models, and clinical trials clearly show that the ECS is a crucial player in the modulation of inflammatory processes in atherosclerosis. In particular, the majority of the studies indicate that endocannabinoids are anti-inflammatory rather than pro-inflammatory agents. Further studies are needed to clarify a possible use of rimonabant, the selective antagonist of CB1 receptors, in acute and chronic events in atherosclerosis.