

Summary of research (group Steffens)

Role of the endocannabinoid system in atherosclerosis

Atherosclerosis and its major adverse cardiovascular events, heart disease and stroke, are the leading cause of morbidity and mortality worldwide. It is an inflammatory disease of the arteries, characterized by lesions containing immune cells, smooth muscle cells, lipids and extracellular matrix. Both innate and adaptive immunity are involved in atherosclerosis. In recent years, exciting discoveries have revolutionized our current understanding of the molecular pathways underlying the disease, providing potential new targets for clinical therapy.

A dysregulation of the endocannabinoid system has been linked to a variety of pathologic conditions, including atherosclerosis and its related cardiovascular risk factors, obesity, dyslipidemia and diabetes. The endocannabinoid system comprises at least two distinct membrane receptors, CB₁ and CB₂, their endogenous ligands (named endocannabinoids) as well as enzymes for ligand biosynthesis and inactivation. It is well established that endocannabinoids are synthesized and released “on demand” and that this process can be regulated both physiologically and under pathological conditions.

As to cardiovascular disease, blocking of CB₁ receptors reduces several cardiometabolic risk factors in rodents and humans, indicating a potential relevance for the process of atherosclerosis. A modulation of endocannabinoid levels was reported in patients with coronary artery disease as well as in atherosclerotic mice. The first evidence for a causal role of CB₁ activation in atherosclerosis has been provided in mice treated with a pharmacological CB₁ receptor antagonist. In vitro, CB₁ antagonism mediates anti-inflammatory effects in macrophages and smooth muscle cells. We have shown that the phytocannabinoid delta-9-tetrahydrocannabinol inhibited atherosclerotic plaque progression in mice, mainly by inhibiting macrophage recruitment. The effect was inhibited by pharmacological CB₂ antagonism. However, some controversy exists about the effects of genetic CB₂ deficiency in atherosclerotic mice.

In the future, we would like to clarify whether the activated endocannabinoid system in atherosclerosis indeed plays a causal role to increase the risk of acute thrombotic events or rather counterbalances atherogenic processes. The existing data so far suggest opposing effects of CB₁ and CB₂ activation in the pathogenesis of atherosclerosis; however, the underlying cellular and molecular mechanisms remain largely elusive and deserve further investigations.