Endocannabinoid signalling as an anti-inflammatory therapeutic target in atherosclerosis: does it work?

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This editorial refers to 'CB1 and CB2 cannabinoid receptors differentially regulate the production of reactive oxygen species by macrophages' by K.H. Han et al., pp. 378–386, this issue.

The endocannabinoid system is a physiological signalling network that has attracted major attention in recent years because of its therapeutic potential for the treatment of various pathological conditions, including cardiovascular disease. More specifically, targeted modulation of the major receptors of this system, the G-protein-coupled cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors, has been implicated in the protection against atherosclerosis. Accumulating evidence suggests that specific blockage of these receptors may have beneficial effects on classical cardiovascular risk factors such as hypercholesterolaemia, obesity, and impaired glucose tolerance. In a pioneering report, it was demonstrated that low levels of the cannabinoid derivative delta-9-tetrahydrocannabinol reduced the progression of atherosclerosis in an apolipoprotein E knock-out mouse model of established atherosclerosis via the CB2 receptor. This protective effect has been shown to be mediated via the immunomodulatory, anti-inflammatory actions of this receptor. Subsequently, CB2 receptor-dependent anti-inflammatory therapeutic effects have also been observed in other conditions such as sepsis. More recently, the CB1 receptor antagonist rimonabant (SR141716) has been shown to provide anti-inflammatory protection against atherosclerosis. Since the majority of these studies have been performed in mouse models, the relevance of the findings for humans has remained largely elusive. Moreover, the regulatory role of cannabinoid signalling for specific interactions of immune cells with the vascular system during the inflammatory response is not well understood.

Such pertinent questions have been addressed by Han et al. The authors present novel, interesting findings on how the endocannabinoid system may modulate the inflammatory activity of mononuclear immune cells such as monocytes and macrophages. These cells are major players in the development and progression of atherosclerosis, and Han et al. show that cannabinoid receptor expression on these cells is regulated in a species-specific manner. Expression of CB1 and CB2 receptors in mouse and human shows a distinct pattern of regulation in response to pro-inflammatory and pro-atherogenic stimuli that is dependent on the degree of differentiation of monocyctic cells. Importantly, the differential expression of CB1 and CB2 receptors on mononuclear cells is functionally significant. The ratio of CB1:CB2 receptor expression regulates the inflammatory activity of these cells and their ability to produce reactive oxygen species. Thus, the findings of this report give interesting insights into the association of inflammation and oxidative stress in the context of atherosclerosis. Although this association has been known for a long while, the detailed underlying molecular and cellular mechanisms that link these conditions are less well understood. The present study is complementary to previous work on the significance of the endocannabinoid system for immune modulation and adds further information to the puzzle on how cannabinoid receptors may be involved in inflammation. Furthermore, this report is the first to show in an experimental system of human mononuclear cells that inhibition of the activity of CB1 receptors together with a selective up-regulation of CB2 receptor activity markedly attenuates the inflammatory response. This combined modulation of CB1 and CB2 receptors in macrophages may therefore be an important novel therapeutic approach to treat inflammatory disease, which may have implications beyond atherosclerosis. With respect to the role of endocannabinoid signalling in macrophages for the development and progression of atherosclerosis, it is noteworthy that selective blockade of the CB1 receptor has also been shown to be beneficial via reducing the accumulation of oxidized low-density lipoproteins in these cells.

Historically, due to its psychotropic effects, the endocannabinoid system has been considered to be primarily involved in signal transduction of the central nervous system. Within the past decade, however, it has been appreciated that this system also plays a major physiological regulatory role in other peripheral tissues and organs. Endocannabinoids are endogenous lipid mediators that are released immediately at the site of their biosynthesis. Under physiological conditions, they are rapidly inactivated via degradation by a number of specific metabolic pathways. The endocannabinoid system is a physiological signalling network that has attracted major attention in recent years because of its therapeutic potential for the treatment of various pathological conditions, including cardiovascular disease. More specifically, targeted modulation of the major receptors of this system, the G-protein-coupled cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors, has been implicated in the protection against atherosclerosis. Accumulating evidence suggests that specific blockage of these receptors may have beneficial effects on classical cardiovascular risk factors such as hypercholesterolaemia, obesity, and impaired glucose tolerance.

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enzymes. The high complexity of the endocannabinoid system has been further revealed by the identification of endocannabinoid-like molecules that have effects partially overlapping with those of endocannabinoids. In addition, a number of atypical cannabinoid receptors have been characterized whose significance still needs to be elucidated in further detail.

An important aspect of conflicting regulatory pathways of the endocannabinoid system under pathological conditions is emerging from recent studies in experimental disease models. Observations from these studies appear to be highly relevant for future clinical applications, because independent groups have demonstrated that pharmacological approaches that modulate the same specific targets of the endocannabinoid system can have both positive and negative effects in comparable disease models. As an example, it has been shown in inflammatory disease models that the up- or down-regulation of a particular pathway of this signalling system may be pro- or anti-inflammatory under comparable conditions. These contradictory findings, which may be explained by a significantly altered endocannabinoid metabolism in a pathophysiological environment, add another level of complexity to this system and give a preview of future challenges in potential therapeutic applications.

Despite these conflicting findings, a number of promising pharmacological compounds have been characterized in recent years that function both as agonists and antagonists of CB1 and CB2 receptors. Difficulties that may be encountered when applying such compounds in a clinical setting have been demonstrated for the CB1 receptor antagonist rimonabant. Clinical trials in which rimonabant has been applied for the treatment of patients with atherosclerosis have recently been stopped because of serious adverse psychiatric effects. Moreover, the manufacturer of the CB1 receptor antagonist taranabant has announced that the clinical development of this drug has been discontinued for similar reasons.

Thus, although the endocannabinoid system has raised many expectations for the development of innovative pharmacological compounds, it still seems precocious to speculate on a single agonist or antagonist of the endocannabinoid system that may ultimately be applicable for targeted clinical interventions. In conclusion, a number of critical questions remain to be answered. A better understanding of cell- and tissue-specific regulation is crucial and needs further attention. In addition, issues that deal with the species-specific differences between mouse and human should be addressed more closely. Finally, the regulation of this highly complex signal transduction system in distinct pathological conditions has to be investigated in more detail.

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