Published in final edited form as:

Am J Physiol Heart Circ Physiol. 2008 March ; 294(3): H1133–H1134.

Pleiotropic effects of the CB₂ cannabinoid receptor activation on human monocyte migration: implications for atherosclerosis and inflammatory diseases

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Endocannabinoids are endogenous lipid mediators, generated by practically all cell types both in the central nervous system and in peripheral tissues, which exert wide range of biological effects (e.g. psychoactive, analgesic, cardiovascular, and anti-inflammatory, etc.) similar to those of cannabis via activation of two main G protein-coupled cannabinoid (CB) receptors: the CB₁ and the CB₂ receptors (7,9,13,17,20). Emerging recent evidence also supports the possible existence of additional yet unidentified CB receptors, and endocannabinoids may also exert multiple effects unrelated to CB receptors (5). The dysregulation of the endocannabinoid system (ES) has recently been implicated in many human diseases, and its pharmacological modulation holds tremendous promise in the treatment of pain, neurodegenerative, metabolic, cardiovascular, and inflammatory disorders, and cancer (7,9,17,20).

The CB₂ receptor was previously considered to be expressed predominantly in immune and hematopoietic cells (overviewed in (17)), but more recent studies have also found it in the brain (26), myocardium (11,16) and endothelial cells of various origins (overviewed in (18)). Since CB₂ receptor activation mediates various beneficial effects in preclinical disease models, the development of selective CB₂ receptor agonists for therapeutic indications, which are devoid of psychoactive properties of CB₁ agonists, has attracted considerable interest over the past couple of years (9,17,20). Indeed, numerous recent studies have demonstrated anti-inflammatory effects of CB₂ receptor activation in a multitude of disparate diseases and pathological conditions, ranging from neurodegenerative disorders (2,19), inflammatory pain (8), atherosclerosis (24,25), myocardial (6,11), cerebral (28) and hepatic ischemia/reperfusion (I/R) injury (3,18,23), to gastrointestinal inflammatory disorders (27), liver inflammation and fibrosis (12), to mention just a few.

The migration of inflammatory cells, mainly monocytes, into the arterial wall is a crucial event during atherogenesis. This process is orchestrated by chemokines, chemokine receptors as well as adhesion molecules. Steffens and colleagues using the apolipoprotein E knockout mice have previously provided experimental evidence on a possible role of CB₂ receptors in atherosclerosis progression (25). Oral administration of low doses of delta-9-tetrahydrocannabinol (THC), which exerts various effects on both CB₁ and CB₂ receptors,

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Comment on: **The CB₂ cannabinoid receptor agonist JWH-015 modulates human monocyte migration through defined intracellular signaling pathways.** by Fabrizio Montecucco, Fabienne Burger, Francoise Mach, and Sabine Steffens. *Am J Physiol Heart Circ Physiol*, Jan 2008; 10.1152/ajpheart.01328.2007.

inhibited atherosclerotic plaque progression in mice. They have also demonstrated CB₂ receptor expressing immune cells in mouse and human atherosclerotic plaques. Furthermore, lymphoid cells isolated from THC-treated mice had reduced proliferation capacity and decreased interferon-gamma production, and THC inhibited macrophage chemotaxis in vitro. Since all the above mentioned effects could largely be attenuated by a selective CB₂, but not CB₁ receptor antagonist, Authors hypothesized the crucial involvement of CB₂ receptors on immune cells in atherosclerosis progression (25).

Several previous, mostly in vitro studies, have investigated the role of CB₁/CB₂ receptor activation on baseline or stimulated inflammatory and other cell migration, with both increases and decreases of cell migration being reported, depending on the trigger/condition, endocannabinoid, synthetic agonist/antagonist, and cell type used (overviewed in (9,10,14)). Therefore, it is important to better understand the complex role of endocannabinoid signaling in inflammatory cell chemotaxis/migration and potential consequences of its pharmacological modulation by selective agonists and/or antagonists.

In their current study (15), Montecucco and colleagues have investigated the effect of CB₂ cannabinoid receptor activation on the chemotactic response of human monocytes. They found that the CB₂ receptor agonists JWH-015 and/or JWH-133 modulated the recruitment of human monocytes by various immediate and delayed effects. Prolonged (12 to 18h) preincubation with JWH-015 reduced monocyte migration to chemokines CCL2 and CCL3. This effect was likely due to reduced expression of the cognate chemokine receptors CCR2 and CCR1 and reduced IFN- γ -induced ICAM-1 expression. These interesting findings should provide a basis for further research into the role of CB₂ receptors in cardiovascular inflammatory diseases using genetically modified mice. Montecucco et al. convincingly showed that short term incubation with JWH-015 itself was chemoattractant for monocytes. Migration experiments using increasing JWH-015 gradients suggested that the cannabinoid-induced migration was rather directed chemotaxis than random movement. Moreover, JWH-015 cross-desensitized human monocytes for migration to CCL2 and CCL3. Indeed, it has been reported that certain chemoattractants desensitize the cells towards a further stimulation with other chemoattractants (1). This may have physiological relevance, as systemic administration of JWH-015 may desensitize the cells towards migration to inflammatory sites. Authors have also shown that the above mentioned effects of JWH-015 could be mimicked by another selective CB₂ agonist JWH-133, and largely attenuated by CB₂ selective antagonist SR144528 supporting the involvement of CB₂ receptors. Finally, the authors provided evidence that both short and long term effects were dependent on PI3K/Akt and ERK 1/2 signaling. Further studies are evidently needed to elucidate the role of the aforementioned pathways in animal models of inflammatory diseases.

In conclusion, these new findings, coupled with recent evidence demonstrating that CB₂ receptor activation also attenuates TNF- α -induced endothelial cell activation, transendothelial migration of monocytes and monocyte/neutrophil-endothelial adhesion (3,4,21,23), and decreases TNF- α -induced proliferation and migration of human coronary vascular smooth muscle cells by (22) by modulating distinct signaling pathways, provide important new mechanistic insights on the possible pleiotropic effects of CB₂ activation in atherosclerosis and other inflammatory disorders.

Acknowledgements

This publication was supported by grants from the National Institute of Health (HL-077256; HL-43023 to Z.U.) and the Intramural Research program of NIH/NIAAA (to P.P.)

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