

MEETING ABSTRACT

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The role of CB₂ receptor ligands in human eosinophil function

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Background

Eosinophils play a key role in allergic diseases such as bronchial asthma and atopic dermatitis. A prominent feature of these diseases is the accumulation of eosinophils in inflamed tissue induced by several chemoattractants like prostaglandin (PG) D₂ or eotaxins. After the discovery of the endocannabinoid system and investigation of several endogenous and synthetic ligands, evidence has accumulated that cannabinoids, especially CB₂ receptor ligands, may play a major role in mediating inflammatory responses. Elevated levels of 2-arachidonoylglycerol (2-AG; a CB₁/CB₂ agonist) were found in tissues of mouse models of allergic inflammation, suggesting a possible involvement in leukocyte recruitment.

Methods

Blood was sampled from healthy volunteers, erythrocytes were removed by dextran sedimentation and polymorphonuclear leukocytes were obtained via Histopaque gradients. For all assays eosinophils were further purified by negative magnetic isolation. Shape change was recorded immediately after stimulation on a FACSCalibur flow cytometer. For chemotaxis assays an AP48 microBoyden chamber was used and migration time was 1h at 37°C. Intracellular Ca²⁺ levels were analyzed by flow cytometry after treating eosinophils with Fluo-3-AM for 60min at room temperature.

Results

We found that CB₂ receptor agonists like the endocannabinoid 2-AG or the synthetic selective agonist JWH-133 significantly increased eosinophil responses in shape change assays induced by PGD₂ or eotaxin-1. The

observed effects could be abolished by pretreatment with the selective CB₂ receptor antagonists SR144528 or AM630. As cytoskeletal changes are required for firm arrest and leukocyte diapedesis, transmigration assays were conducted subsequently, confirming the shape change data as eosinophil migration induced by PGD₂ was increased by pretreatment with JWH-133. Calcium flux assays showed Ca²⁺ mobilization induced by JWH-133 and the tendency to increase PGD₂-induced Ca²⁺ release.

Conclusions

We could show that JWH-133 can influence human eosinophil activation/migration via activation of CB₂ receptors as chemoattractant effects were significantly modulated, suggesting a possible pro-inflammatory role in allergic inflammation which may further lead to cannabinoid-based treatment options in allergic inflammatory diseases.

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