CB2 Receptor Activation is Anti-Inflammatory in an Endotoxin-Induced Uveitis Model

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Uveitis is an inflammatory disease of the uvea, which can affect vision. Experimental endotoxin-induced uveitis (EIU) can be generated with an intravitreal injection (IVT) of lipopolysaccharide (LPS). LPS induces leukocyte activation and leukocyte-endothelial interactions, resulting in the release of proinflammatory mediators that cause tissue damage. The endocannabinoid system (ECS) modulates immune cell activity, and cannabinoid drugs that interact with cannabinoid 2 receptors (CB2R) have immunosuppressive effects. The purpose of this study was to investigate the effects of CB2R activation on leukocyte-endothelial interactions in the rat iridal microcirculation, using intravital microscopy (IVM), and to compare the efficacy of CB2 modulating drugs to current agents used to treat ocular inflammation.

The Lewis rats (n=5-10/group) were divided into 11 experimental groups: control (saline, IVT), EIU (100 ng LPS, IVT), EIU + vehicle (Tocrisolve®), EIU + vehicle (DMSO), EIU + vehicle (DMSO) + vehicle (Tocrisolve®), EIU + CB2R agonist, HU308 (1.5 µg/µL eye drop), EIU + CB2R antagonist, AM630 (2.5 mg/kg, i.v.), EIU + CB2R agonist, HU308 + CB2R antagonist AM630, EIU + Maxidex® (0.1% dexamethasone, eye drop), EIU + Predforte® (1% prednelasone, eye drop), EIU + Nevanac® (0.1% nepafenac eye drop). All drug treatments were given 15 min after IVT of LPS. IVM of the iridal microcirculation was performed for 30 seconds in 4 regions of interest at 1, 2, 3, 4, 5, and 6 hrs post-LPS administration. Leukocyte adhesion was measured offline in a blinded manner. Statistical analysis was conducted by a two-way ANOVA with a Bonferroni post hoc test.

The LPS-treated group (EIU) had a significant increase in leukocyte adhesion by 6 hrs after induction of LPS in all iridal microvessels (p<0.05), as compared to the control group. Application of vehicle in the EIU group did not result in a significant change in leukocyte-endothelial adhesion (p>0.05). No significant difference in iridal leukocyte-endothelial adhesion in EIU animals and those treated in combination with AM630 and HU308 (p>0.05). Application of AM630 alone in the EIU group significantly increased leukocyte adhesion at 4, 5 and 6 hrs (p<0.05). Administration of the selective CB2R agonist, HU308, significantly attenuated leukocyte adhesion at 4, 5 and 6 hrs (p<0.05) in the iris’s microcirculation while clinical drugs, Maxidex®, Predforte® and Nevanac® did not significantly reduce leukocyte adhesion during the 6 hrs of EIU.

This data demonstrates CB2R modulation of leukocyte adhesion in the iris microcirculation in EIU. Activation of CB2R by HU308 significantly attenuates leukocyte adhesion in the iridal microvasculature after EIU while clinical treatments Maxidex®, Predforte® and Nevanac® failed to significantly mitigate leukocyte adhesion. These results are consistent with the immunosuppressive action of CB2R agonists, and indicates that future drugs targeting CB2R could aid in the treatment of ocular inflammatory diseases, such as uveitis.
