Cannabinoid 2 Receptor Modulation In The Iris Microcirculation During Experimental Endotoxemia

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Introduction: Endotoxemia produces systemic leukocyte activation [1]. In the iris, the interaction of activated leukocytes with the vascular endothelium can result in ocular inflammation (uveitis) and cause tissue damage. The endocannabinoid system is involved during systemic inflammation [2] and cannabinoid drugs that interact with endogenous cannabinoid receptors (CB1R and CB2R) have immunomodulatory properties in experimental studies [3]. However, the effects of modulating the endocannabinoid system in the iris during acute endotoxemia are currently unknown. The aim of this study, therefore, was to examine the impact of CB2R modulation on leukocyte activation during experimental endotoxemia using intravital microscopy (IVM).

Methods: Four groups of Lewis rats (n=4-5 in each group) were studied: LPS-treated animals (20 mg LPS/kg i.v.); LPS-treated animals + the CB2R agonist, HU208, 2.5 mg/kg i.v.; LPS-treated animals + the CB2 antagonist, AM630, 2.5 mg/kg i.v.; and saline control animals. All treatments were given 15 minutes after LPS administration. Intravital microscopy of the iridial microcirculation was performed at 0, 1, and 2 hours post-LPS/saline administration. Leukocyte adhesion was measured in a blinded fashion.

Results: At 0 hours, the baseline number of adhering leukocytes was established using animals from all groups. In the LPS-treated group, at 1 and 2 hours, a significant increase in the number of rolling and adhering leukocytes was observed in iris vessels of all sizes. CB2R activation with 2.5 mg/kg HU308 was able to attenuate leukocyte activation to baseline levels at both 1 and 2 hour intervals in vessels less than 25 µm in diameter. In larger vessels, HU308 was only effective in significantly reducing leukocyte activation at 1 hour post-LPS administration. Inhibiting CB2R with 2.5 mg/kg AM630 had no effect on leukocyte activation in LPS-challenged animals at all time points.

Summary and Conclusion: The data suggests that endocannabinoid signaling is involved in leukocyte activation in the iris. Activation of CB2R with HU308 significantly reduces leukocyte activation following an acute endotoxemic challenge, but does so to a greater extent in smaller vessels (< 25µm) than in larger vessels. Drugs targeting CB2R may have future utility in the treatment of inflammatory conditions such as uveitis.