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Basic Science

(Abstracts and Case Report/Series)

Cannabinoid Type 2 Receptor Activation Ameliorates Acute Lung Injury Induced Systemic Inflammation

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Introduction:
The COVID-19 pandemic has highlighted the danger of immune dysregulation in severe cases of lung infection. These cases are characterized by life-threatening complications including pneumonia, acute respiratory distress syndrome, and multi organ failure. Elevated pro-inflammatory cytokine levels are described as contributing to disease progression. Activation of the cannabinoid type 2 receptor (CB2R) exerts immunomodulatory effects in numerous pre-clinical models, including protective effects in lung inflammation. Thus, we hypothesize that experimental CB2R activation can lead to reductions in systemic inflammation in a murine model of acute lung injury (ALI).

Methods:
12-week-old C57BL/6 mice were challenged with intranasal *Pseudomonas aeruginosa* (5 mg/kg) or vehicle, followed by intravenous administration of experimental CB2R agonist, onternabez, vehicle, and/or dexamethasone (0.1 mg/kg). At t = 6 hours, lung tissue was scored for histological changes and plasma cytokines were analyzed with Luminex™ technology. In separate groups, intravital microscopy (IVM) of the intestinal or pulmonary microcirculation, respectively, was performed. IVM recordings were analyzed to quantify leukocyte adhesion, leukocyte rolling, and functional capillary density (FCD). All experiments and procedures were approved by the institutional animal care committee.

Results:
Vehicle-treated LPS mice displayed a marked increase in lung histopathology scores consistent with ALI and significant increases in plasma CXCL2, IL-6, IL-10, and TNF-Alpha. This effect was recapitulated by intestinal IVM results which demonstrated significant increases in leukocyte adhesion in V1 and V3 venules and a significant reduction in muscularis FCD. Treatment with onternabez significantly reduced leukocyte adhesion in V1 venules. Dexamethasone treatment abolished leukocyte adhesion in V1 venules, significantly reduced leukocyte adhesion in V3 venules and significantly increased muscularis FCD. It also abolished lung histopathology and significantly reduced plasma levels of TNF-alpha. Combination treatment displayed similar effects to dexamethasone-only treatment, as well as significant decreases in CXCL2 and IL-6. Lung IVM showed similar trends of leukocyte adhesion and capillary perfusion (FCD) in selected micro-vessels.

Discussion:
Intranasal administration of LPS from *P. aeruginosa* induced ALI and a systemic inflammatory response evidenced by increased plasma cytokine levels and leukocyte activation in intestinal and pulmonary microvasculature. Dexamethasone and combination treatment exhibited immunosuppressive action, abolishing immune responses in most, but not all cases. Conversely, onternabez treatment exhibited milder immunomodulatory effects, with significant reductions in leukocyte adhesion and trends toward baseline

across all other parameters. Further studies will aid in establishing its utility in treating ALI-induced systemic inflammation.

References:

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