Effects of cannabinoid receptors and gpr55 modulation in experimental sepsis

Hyewon Yang¹, Juan Zhou¹, Andrew W. Stadnyk¹, Christian Lehmann¹
¹Dalhousie University

Sepsis is the systemic inflammatory response to an infection and is associated with tissue hypoperfusion, multi-organ dysfunction and a high mortality. Based on accumulating evidence suggesting that the endocannabinoid system is up-regulated in acute inflammation, we investigated the impact of cannabinoid receptor (CBR) and GPR55 modulation on leukocyte-endothelial interactions and capillary perfusion within the microcirculation using intestinal intravital microscopy (IVM) in experimental sepsis induced by endotoxin (5 mg/kg lipopolysaccharide). Endotoxemic male C57BL/6 mice (WT or CBR2 knockouts) were treated using the following substances: endocannabinoid degradation enzyme inhibitor (JZL184); CBR1 antagonist (AM281); CBR2 antagonist (AM630); GPR55 agonists (LPI, O-1602); or GPR55 antagonists (CID16020046, O-1918). Endocannabinoid degradation enzyme inhibition and GPR55 blockade reduced endotoxin-induced intestinal leukocyte activation and improved the capillary perfusion in experimental sepsis in WT mice. Contradictory results were found in the CBR2 knockout animals suggesting alternative molecular targets of endocannabinoids to be further investigated. Taken together, these findings implicate that CBR2 activation as well as GPR55 inactivation would be potential therapeutic targets to regulate the host immune system in the early hyperinflammatory phase of sepsis.