Progression of Intravenous (IV) Lipopolysaccharide (LPS)-induced hypotension can be prevented by Intra-Cerebral Ventricular injection (ICV)

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We previously showed that progression of Intravenous (IV) Lipopolysaccharide (LPS)-induced hypotension can be prevented by Intra-Cerebral Ventricular injection (ICV) of the endocannabinoid type 1 (CB1) receptor inverse agonist/antagonist rimonabant. However, the role of brain CB1 receptors on LPS-induced pulmonary inflammation, an additional characteristic of endotoxemia, is not known. Hence, we tested the hypothesis that CB1 receptor antagonists in the brain will prevent lung inflammation in response to IV LPS. Male Sprague-Dawley rats received an initial ICV injection of rimonabant (500ng) or vehicle 5 minutes prior to IV injection of either LPS (5 mg/kg) or saline, followed by additional ICV injections at 1.5 and 3 hours post-LPS in the 4 hour treatment group. Lungs were removed at 30 minutes or 4 hours after IV LPS injection. The isolated-perfused lung was assessed for hemodynamics. Lung homogenates were assessed for TLR-4 signaling cascade markers and α7-nicotinic acetylcholine receptor activity. There was a decrease in Pulmonary Capillary Pressure (Ppc) and increases in the (Wet-Dry)/Dry lung weight ratio (W–D/D) and (W–D/D)/(Ppc) ratio in the ICV-vehicle/IV-LPS group at 4 hours. In lung homogenate of the same treatment group there were decreases in levels of IRAK1, IκBα, phospho-RAF(Ser259) and phospho-Src (Tyr416) at 30 minutes and increases in IL-6, VCAM and Myeloperoxidase (MPO) at 4 hours. The ICV injection(s) of rimonabant attenuated or completely prevented the changes in hemodynamics, W–D/D, (W–D/D)/(Ppc), IRAK1, IκBα, pRAF (Ser259), pSrc (Tyr216), IL-6, VCAM and MPO in response to LPS injection. The data indicate that inhibition of the brain's central CB1 activity modulates the initiation and progression of the lung inflammatory response to LPS.

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