Salvinorin A inhibits leukotriene biosynthesis in experimental models of acute inflammation

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Salvia divinorum is a hallucinogenic plant utilized for the treatment of inflammatory disorders especially referred to the gastrointestinal tract. The main active component of this herb is Salvinorin A (SA), a hallucinogenic diterpene, already known as potent and highly selective agonist of the k-opioid receptor (KOR) (Capasso et al., 2008). Moreover, the anti-inflammatory effects of this compound were also connected to a potent inhibitory capability of nitrite production as well as tumor necrosis factor alpha and interleukin 1-beta in activated murine macrophages (Aviello et al., 2011).
Here, we present novel insights on the anti-inflammatory effect of SA due to the inhibition of leukotriene (LT) biosynthesis, key players in several inflammatory and autoimmune diseases (Rådmark et al., 2015).
The effect of SA has been evaluated making use of *in vitro* (rat peritoneal macrophages activated with calcium ionophore A23187) and *in vivo* (mouse zymosan-induced peritonitis and rat carrageenan-induced pleurisy) models of inflammation.
SA inhibited LTB_4 production in a concentration-dependent in activated rat peritoneal macrophages and exerted anti-inflammatory effects in *in vivo* models of acute inflammation.
In a mouse peritonitis model, SA dose-dependently inhibited LTC_4 formation in peritoneal exudates. Interestingly, LTC_4 suppression was accompanied with a potent inhibition of the acute inflammatory reaction evaluated in terms of vascular permeability (50% at 10 mg/kg) and of cell recruitment (63% at 10 mg/kg) as well as myeloperoxidase (MPO) activity (71% at 10 mg/kg), a specific marker of polymorphonuclear cells.
In carrageenan-induced pleurisy in rats, SA significantly reduced LTB_4 (58% of inhibition) levels in pleural exudates as well as the inflammatory parameters connected to LT such as exudate volume (61%), leukocyte afflux (60%) and lung MPO activity (30%).
Histological examination of lungs revealed that SA reduced lung injury as well as extracellular signal-regulated kinase activation.
Taking together, these data clearly demonstrate the capability of SA in the inhibition of LT biosynthesis *in vitro* and *in vivo* in models of acute inflammation with promising potential for further therapeutic application.

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