Salvinorin A has antiinflammatory and antinociceptive effects mediated by KOR and CB1 receptors

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The hallucinogenic compound, salvinorin A (SA)[1], the main active component of *Salvia Divinorum* is a potent κ-opioid receptor (KOR) agonist[2,3]. However, other target(s) than the KOR, such as the cannabinoid CB1 receptor, have been proposed to explain its multiple pharmacological actions[4]. Here we have investigated the effect of SA (administered intraperitonealy ones a day) on acute pain, oedema and formali-induced persistent pain in mice. The SA effects on long-term behavioural dysfuctions and changes in neuronal activity occurring at spinal level after single peripheral formalin injection, have been investigated. Furthermore, the involvement of microglial and glial cells in formalin-induced chronic pain condition and in SA-mediated effects has been evaluated. In vivo, SA reduced the LPS- and the carrageenan-induced paw oedema and formalin-induced inflammatory pain, in a nor-binaltorphimine and rimonabant-sensitive manner. Formalin induced a significant decrease of mechanical withdrawal threshold at the injected and contralateral paw as well as an increase in the duration and frequency, and a rapid decrease in the onset of evoked activity of spinal nociceptive neurons 7 days after formalin injection. SA daily treatment significantly reduced mechanical allodynia in a KOR and CB1 receptor sensitive manner. SA treatment also normalized the spinal nociceptive neurons evoked activity. SA significantly reduced the formalin-mediated microglia and astrocytes activation and modulated pro and anti-inflammatory mediators in the spinal cord. In conclusion SA exerts analgesic actions and also shows moderate antinflammatory effects in vivo via KORs and CB1 receptors.

References

1. Gonzàlez D, Riba J, Bouso JC, Gómez-Jarabo G, Barbanoj MJ: Pattern of use and subjective effects of Salvia divinorum among recreational users. Drug Alcohol Depend 2006, 85: 157 – 162

2. Ortega A: Salvinorin, a new trans-neoclorodane diterpene from Salvia divinorum (Labiatae). J Chem Soc Perkins Trans 1982, I:2505 – 2508.

3. Valdés LJ 3rd: Salvia divinorum and the unique diterpene hallucinogen, Salvinorin (divinorin) A. J Psychoactive Drugs 1994, 26: 277 – 283. Review

4. Capasso R, Borrelli F, Cascio MG, Aviello G, Huben K, Zjawiony JK, Marini P, Romano B, Di Marzo V, Capasso F, Izzo AA: Inhibitory effect of salvinorin A, from Salvia divinorum, on ileitis-induced hypermotility: cross-talk between kappa-opioid and cannabinoid CB(1) receptors. Br J Pharmacol 2008, 155: 681 – 689