

### **Antinociceptive effects of delta-9-tetrahydrocannabinol and cannabidiol alone and in combination in the mouse hypertonic saline foot assay**

Y. I. Asiri, T. Fung, B. A. MacLeod, E. Puil. Anesthesiology, Pharmacology, & Therapeutics, University of British Columbia, Vancouver, Canada.

**Introduction:** There is a growing interest in using cannabis for the treatment of various conditions such as pain. Many preclinical animal assays show varying degrees of antinociception for cannabinoids, predominantly  $\Delta^9$ -tetrahydrocannabinol (THC) and cannabidiol (CBD) either alone or as a combination.<sup>1</sup> However, this has not been investigated in the newly characterized intraplantar hypertonic saline (HS) assay.<sup>2</sup> The aim of this study was to examine the antinociceptive effects of THC and CBD both as pure compounds or in combination.

**Method:** Experiments were performed in a randomized and blinded fashion. Naïve female CD-1 mice (25–30 g) were used. Following 2 h of habituation in testing chambers, mice received THC (0.03–10 mg/kg; i.v.; n=8 per dose), CBD (1–45 mg/kg; i.v.; n=8 per dose) or THC+CBC in a 1:10 ratio (0.01/0.1–1/10 mg/kg; i.v.; n=8 per dose). Five minutes later, 10  $\mu$ l of 10% HS was injected into the right hind paw and responses were video recorded for 5 min. Videos were analyzed by a blinded observer to record the time each animal spent licking and nibbling the injected paw. THC and THC+CBD were dissolved in (ethanol, ethoxylated castor oil, and saline; 1:1:18). CBD was dissolved in 100% DMSO. Dose response curves were obtained using a non-linear square fit with a log[inhibitor] vs response [variable slope] model.

**Results:** THC dose dependently reduced licking and nibbling with an ID<sub>50</sub> of 0.5 mg/kg (95% CI, 0.2–1.2) and Hill slope of -1.1 (95% CI, -2.1– -0.2) while CBD failed to produce any detectable reduction. The combination of THC+CBD produced antinociception in a dose dependent manner with an ID<sub>50</sub> of 0.3 mg/kg (95% CI, 0.15–0.6) and Hill slope of -2.3 (95% CI, -7– 2.302). A comparison of ID<sub>50</sub> and Hill slope values of THC+CBD with THC values show no differences.

**Conclusions:** Based on the HS foot assay, the main driving force for antinociception is THC. While the results of other assays suggest an antinociceptive effect of CBD alone or combined, the inability of the HS assay to detect CBD antinociception or potentiation of THC effect may stem from a different mechanism.

#### **References:**

1. Cascio MG Pertwee RG (2014). In: Pertwee RG (ed). Handbook of Cannabis. Oxford University Press: USA, pp 115–156
2. Asiri YI *et al.* (2017). *Anesth Analg*. Accepted for publication.