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Electrophysiological study of the effect of cannabidiol on the dorsal raphe nucleus serotonergic neurons

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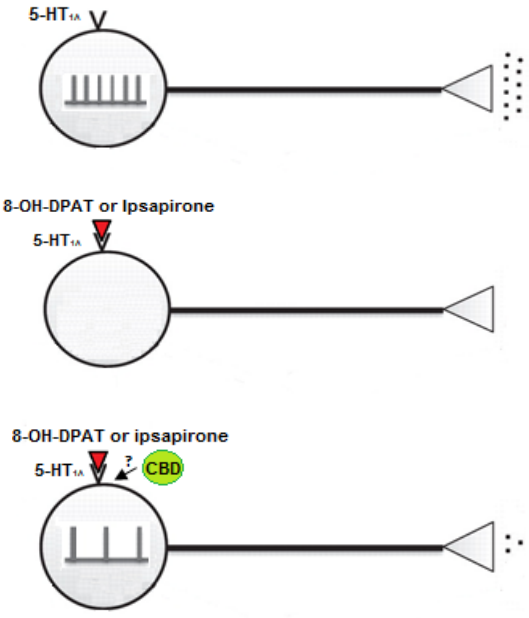
Graphical Abstract



Abstract

Cannabidiol (CBD) is the main non-psychoactive cannabinoid found in the *Cannabis* plant, which exerts several pharmacological effects including anxiolytic, antiemetic, antidepressant, antiepileptic and motor effects. *In vivo* evidence suggests that these pharmacological effects could be mediated by serotonergic 5-HT$_{1A}$ receptors. The dorsal raphe nucleus (DRN), which is the main serotonergic cluster in the brain, expresses 5-HT$_{1A}$ receptor and plays a key role in the regulation of different functions such as mood and anxiety. To date, the nuclei involved in the action of CBD and the mechanisms by which it regulates 5-HT$_{1A}$ receptor are still unknown. Therefore, the aim of this study was to characterize the effect of CBD on the firing rate of dorsal raphe 5-HT neurons and 5-HT$_{1A}$ receptor activation by single-unit extracellular electrophysiological recordings *in vitro*. Direct perfusion with CBD (30 μM) slightly but significantly reduced the firing activity of DRN 5-HT cells. In order to study the effect of CBD on 5-HT$_{1A}$ receptor activation, we applied the cannabinoid in the presence of two different 5-HT$_{1A}$ receptor agonists: 8-OH DPAT (10 nM) and ipsapirone (100 nM). Application of 8-OH-DPAT or ipsapirone completely inhibited the firing activity of DRN 5-HT cells. However, in the presence of CBD (30 μM) the inhibitory effects of 8-OH-DPAT and ipsapirone were reduced by 66% and 53%,

	respectively. Finally, to discard the possible role of CBD as a competitive 5-HT_{1A} receptor antagonist, we administrated CBD once the cells had been totally inhibited with ipsapirone. Perfusion with CBD (30 μM) failed to recover the firing activity of inhibited 5-HT cells, whereas 5-HT_{1A} antagonist WAY 100635 (30 nM) recovered the firing rate of all 5-HT cells. In conclusion, these results suggest that CBD regulates the activity of 5-HT_{1A} receptor in an indirect manner since it does not displace the agonist from the binding site.

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