NEURAL REGENERATION RESEARCH
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Cannabidiol preferentially binds TRPV2: a novel mechanism of action

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Plants from the genus *Cannabis*, and strains of *Cannabis sativa* in particular, have been used in medicine since ancient times. The *Cannabis* plant contains more than 500 chemical compounds, with two main phytocannabinoids consisting of Δ9-tetrahydrocannabinol (THC), the psychoactive constituent, and cannabidiol (CBD), which does not bear this effect. This paper aims at providing a perspective on the potential therapeutic effects of CBD based on its preferential interaction with transient potential receptor V2 (TRPV2).

Many formulations based on *Cannabis* extract have been licensed for therapeutic use in some Western countries. Among these, the most relevant are Sativex (THC + CBD, used mainly for the treatment of spasticity in multiple sclerosis) and Epidyolex (purified plant-derived CBD, used for some rare childhood epilepsies). Dronabinol, a pharmaceutical form constituted by THC, has been approved by the Food and Drug Administration as an appetite stimulant for people affected by acquired immunodeficiency syndrome and as an antiemetic for patients receiving chemotherapy.

CBD possesses an extensive therapeutic potential against several conditions, including neurological diseases (epilepsy, neurodegenerative diseases, traumatic and ischemic brain injuries) and psychiatric disorders (schizophrenia, addiction, major depressive disorder, and anxiety) (Bergamaschi et al., 2011). In particular, successful results of the treatment of patients with epileptic encephalopathies were recently reported (Lattanzi et al., 2020, 2021). CBD is also characterized by a good safety profile when compared to other cannabinoids such as THC. Several studies suggest that CBD lacks toxicity in non-transformed cells and does not induce changes in food intake or catalepsy. Moreover, it does not affect physiological parameters such as heart rate, blood pressure and body temperature, it does not affect gastrointestinal transit and neither alters psychomotor or psychological functions. In any case, very high doses of CBD (up to 1500 mg/d) are safe and well-tolerated both in animals and humans (Bergamaschi et al., 2011).

The mechanisms responsible for the broad range of CBD neuroprotective effects in neurological disorders are not completely known, and several studies conducted in recent years envisage the involvement of various pharmacological targets. A recent review (Patricio et al., 2020) summarized the controversial pharmacology of CBD and its ability to interact with cannabinoid receptors CB1 and CB2. In contrast to THC, CBD displays a very low affinity for these receptors. In detail, CBD exerts an agonist-like effect on the peroxisome proliferator-activated receptor γ (PPARγ), transient potential receptor V1 (TRPV1), and indirectly on CB1 and CB2 receptors, by inhibiting the enzyme fatty acid amide hydrolase that degrades anandamide, with an increase in anandamide concentration. In addition, CBD inhibits G protein-coupled receptor 55 and transient potential receptor M8 and exerts an effect as an inverse antagonist or negative allosteric modulator on CB1 and CB2 receptors. The reader is invited to refer to the cited review for more details on these studies and for reference to original research articles.

The neuroprotective effects of CBD are based on a direct interference with the synthesis of pro-inflammatory cytokines and on the stimulation of the synthesis of anti-inflammatory cytokines. CBD also reduces inflammation by stimulating PPARγ.

Several examples of studies focused on the neuroprotective effects of CBD can be retrieved from the literature. Hind et al. (2016) investigated whether CBD could also affect blood-brain barrier permeability following ischemia and observed that CBD prevented the increase in permeability caused by oxygen and glucose deprivation. The effects were maximal when CBD was administered before the oxygen and glucose deprivation and the protective effect was inhibited by a PPARγ antagonist and partly reduced by a 5-hydroxytryptamine 1A (5-HT1A) receptor antagonist, but was unaffected by antagonists of CB1, CB2, TRPV1 channels and adenosine A2A receptors. In an *in vivo* model of cerebral ischemia represented by middle cerebral artery (MCA) occlusion in mice, CBD significantly reduced the infarct volume induced by MCA occlusion in a bell-shaped curve. Moreover, the neuroprotective effect of CBD was inhibited by WAY100135, a serotonin 5-HT1A receptor antagonist, but not by capsazepine, a vanilloid receptor 1 antagonist. CBD increased cerebral blood flow to the cortex, and the cerebral blood flow was partly inhibited by WAY100135 in mice subjected to MCA occlusion (Mishima et al., 2005). In a model of transient global cerebral ischemia in mice, Mori et al. (2005) explored the neuropharmacological mechanisms of CBD action and its impact on functional recovery. Using a multi-task behavioral testing battery CBD prevented anxiety-like behavior, memory impairments, and despair-like behaviour induced by bilateral common carotid artery occlusion in mice. The anxiolytic-like effects of CBD in bilateral common carotid artery occlusion mice were attenuated by CB1, CB2, 5-HT1A, and PPAR-γ receptor antagonists (Mori et al., 2021), shedding light on the possible involved molecular mechanisms.

In a recent paper from our laboratory (Landucci et al., 2021), we reported the neuroprotective effect of CBD in an *in vitro* model of cerebral ischemia and, by contrast, the detrimental effect of THC. Moreover, we observed the same behavior using a FM2 extract rich in CBD and Bedrocan, which contains THC. FM2 is a therapeutic variety of *C. sativa* produced by the Italian Institution Florence Military Pharmaceutical Chemical Works, while Bedrocan is produced by the homonymous company from the Netherlands. In this study, we investigated the possible mechanism of action of CBD and THC, and we showed that the neurotoxic effect of THC is mediated only by the CB1 receptor, whereas the neuroprotective effect of CBD is mediated by 5-HT1A, PPARγ and TRPV2 in agreement with other studies. Importantly, we observed that capsazepine, an antagonist of TRPV1 cannot reverse the neuroprotective effects of CBD, in accordance with other previous studies (Mishima et al., 2005; Hind et al., 2016).

Computational studies can be enrolled to complement the elucidation of the more marked effect of CBD on TRPV2 over TRPV1 observed in the above mentioned research work. More specifically, molecular docking, a structure-based *in silico* technique, allows investigating the interaction motif of ligands with target proteins. This method was previously adopted by our group to predict the profile of target interactions of CBD with biologically relevant macromolecules (Mastinu et al., 2021). Importantly, the 3D structure of CBD in complex with TRPV2 solved by electron microscopy was recently made available (Pumroy et al., 2019), confirming the possibility for this interaction to occur. The results of the CBD docking experiment performed with AutoDock Vina (Trott and Olson, 2010) on the 3D structures of TRPV1 and TRPV2 retrieved from the Protein Data Bank (PDB, PDB IDs: 6U8A and 5IS0) support the experimental observations from our previous work (Landucci et al., 2021). In fact, calculated binding energy values of –7.1 kcal/mol and –7.6 kcal/mol were computed for the interaction of CBD with TRPV1 and TRPV2, respectively, suggesting that CBD may preferentially interfere with the latter (**Figure 1**).

CBD was reported as a potent TRPV2 activator. THC was also found to interact with TRPV2, even if this compound lacks selectivity (Muller et al., 2019).

Our finding that TRPV2 but not TRPV1 is a modulating receptor in case of CBD-treatment on our slices opens a whole new area (Landucci et al., 2021), especially

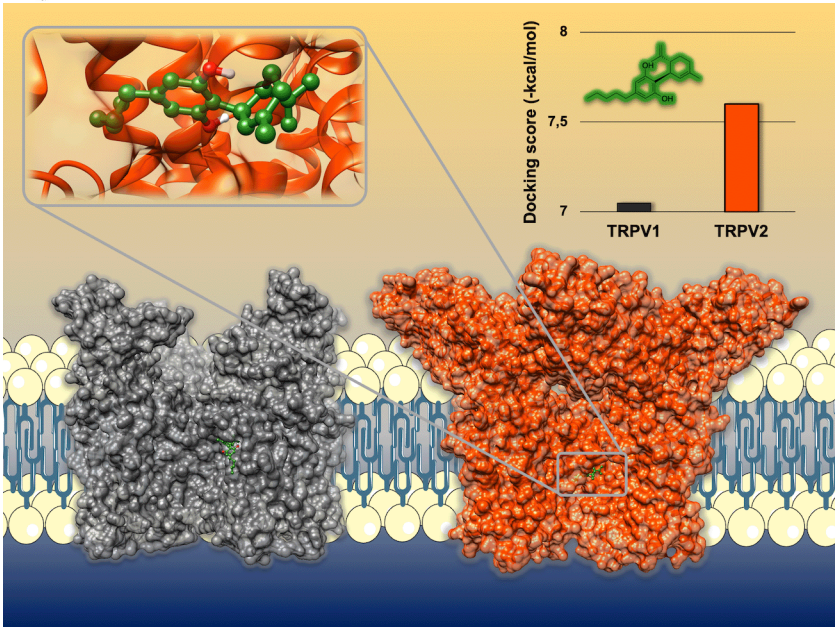

Figure 1 | **Representation of the interaction motif of CBD with transient potential receptor V1 (TRPV1, grey) and transient potential receptor V2 (TRPV2, orange) based on the models obtained by molecular docking.**
The chemical structure of cannabidiol (CBD) is depicted in green. Computational studies predicted a more promising calculated binding energy towards TRPV2 rather than TRPV1 for CBD, suggesting that the compound may preferentially interact with the first. The artwork was prepared using resources from Servier Medical Art (smart.servier.com) and UCSF Chimera (Pettersen et al., 2004).

since previous reports were almost exclusively focused on the investigation of phytocannabinoids, including CBD, as TRPV1 interactors (Starkus et al., 2019). More specifically, so far, multiple studies have suggested that hippocampal neuronal-synaptic modulation by TRPV1 could have been a possible mechanism. However, it is not known how CBD might interact in this microenvironment and why TRPV1 may not respond to the CBD treatment, even though TRPV1 receptors are prevalent in the hippocampus (Gibson et al., 2008). The expression of transcripts encoding for TRPV1, TRPV2 and TRPA1 channels in the rat hippocampus using real-time quantitative polymerase chain reaction experiments was performed with gene-selective primers by the laboratory of Iannotti. The study revealed that the genes encoding both TRPV1 and TRPV2 are expressed in ipsilateral and contralateral sides of the adult rat hippocampus but the TRPA1 mRNA expression was barely detectable. TRPV2 was expressed at significantly higher levels than TRPV1. The authors confirmed the polymerase chain reaction data with Western blot through which they claim that TRPV2 is more strongly expressed than TRPV1 in rat hippocampal tissue. In the same study, the researchers tested the effects of CBD on rat recombinant TRPV2 channels. They observed that, as for the effects observed for TRPV1 channels and compared to vehicle, CBD dose-dependently evoked a bidirectional current across the voltage range (–80 to +80 mV) with a reversal potential near to 0 mV (Iannotti et al., 2014).

In conclusion, computational and experimental evidence, together with structural data testifying the interaction of CBD with TRPV2 (Pumroy et al., 2019), suggest that this channel is among the preferential interactors of CBD and that this macromolecular partner may be directly involved in the observed neuroprotective effects.

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Date of submission: November 2, 2021
Date of decision: December 3, 2021
Date of acceptance: December 14, 2021
Date of web publication: April 29, 2022

https://doi.org/10.4103/1673-5374.335821
How to cite this article: *Landucci E, Pellegrini-Giampietro DE, Gianoncelli A, Ribaudo G (2022) Cannabidiol preferentially binds TRPV2: a novel mechanism of action. Neural Regen Res 17(12):2693-2694.*

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C-Editors: Zhao M, Liu WJ, Wang Lu; T-Editor: Jia Y