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Study Of Trpv1, Tprv2 And Trpa1 Channel Activation By Cannabidiol (CBD) And Cannabidivarine (CBDV) In Whole-Cell Patch Clamp Analysis

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Transient receptor potential (TRP) channels are a superfamily of non-selective cation channels (mainly permeable to Na^+, Mg^{2+}, Ca^{2+}) which can be divided into six main subfamilies based on amino acid homologies: TRPC ("C" for canonical), TRPV ("V" for vanilloid), TRPM ("M" for melastatin), TRPA (“A” for ankyrin repeats), TRPP ("P" for polycystic) and TRPML ("ML" for mucolipin) (1). To date, TRP channel expression is considered to be ubiquitous in the human organism, and their activity has been associated with a remarkable range of functions including regulation of body temperature, mechanical and osmotic stimuli, hot or cold sensations, inflammation, pain transmission and also neuronal excitability. Accordingly, mutations in TRP genes are closely related to human disorders affecting the intestinal, renal, urogenital, respiratory, cardiovascular systems and neurological diseases (2). For instance, changes in TRPV1 (the “capsaicin receptor”) and TRPA1 (the “mustard oil receptor”) channel functionality have been described during acute and chronic inflammatory conditions in A□. and C fibers and dorsal root ganglia (DRG). Changes in TRPV1 channel expression were also described in patients affected by mesial temporal lobe epilepsy (3). However, despite the physiological importance of this class of ion channels, the exact molecular mechanisms by which they detect incoming stimuli and orchestrate molecular responses still need to be elucidated. In this context, the aim of this study was to clarify if two active constituents of Cannabis sativa, cannabidiol (CBD) and cannabidivarine (CBDV), can modulate TRP channel functionality. Through the use of patch clamp electrophysiology, we have demonstrated that both CBD and CBDV (1, 3, 10 and 30 □M) dose dependently evoked TRPV1, TRPV2 and TRPA1 whole cell currents in HEK293 over-expressing these channels, as revealed by the increased cell amplitude (pA) observed across a voltage range (ramp protocol from -80 to + 80 mV) in both inward and outward directions (n=12). The CBD as well as CBDV effects on TRPV1, TRPV2 and TRPA1 currents were mitigated in the presence of capsazepine (10 □M), a selective TRPV1 antagonist or Ruthenium Red (10 □M) (n=14). We further investigated endogenous TRP current activation by CBD and CBDV in rat cultured DRG neurons, showing that both CBDV and CBD (10 □M each) evoked a TRP channel-mediated current with similar kinetic proprieties to those found in HEK293 cells transiently transfected with TRP channels (n=5). Moreover, in our experiments we have also evaluated the potential mechanism of TRP channel desensitization by using high doses of or prolonged exposure to CBDV and CBD. In conclusion, based on these findings we advocate the possibility that pharmacologically modulating TRP channels by CBDV and CBD may represent a new potential therapeutic prospective to treat mammalian disorders in which these channels are involved, such as pain and epilepsies.

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