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Target regulation of PI3K/Akt/mTOR pathway by cannabidiol in treatment of experimental multiple sclerosis.

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Abstract

This study was aimed to investigate whether treatment with purified cannabidiol (CBD) may counteract the development of experimental multiple sclerosis (MS), by targeting the PI3K/Akt/mTOR pathway. Although the PI3K/Akt/mTOR pathway was found to be activated by cannabinoids in several immune and non-immune cells, currently, there is no data about the effects of CBD in the PI3K/Akt/mTOR activity in MS. Experimental Autoimmune Encephalomyelitis (EAE), the most common model of MS, was induced in C57BL/6 mice by immunization with myelin oligodendroglial glycoprotein peptide $(MOG)_{35-55}$. After EAE onset, which occurs approximately 14days after disease induction, mice were daily intraperitoneally treated with CBD (10mg/kg mouse) and observed for clinical signs of EAE. At 28days from EAE-induction, mice were euthanized and spinal cord tissues were sampled to perform immunohistochemical evaluations and western blot analysis. Our results showed a clear downregulation of the PI3K/Akt/mTOR pathway following EAE induction. CBD treatment was able to restore it, increasing significantly the phosphorylation of PI3K, Akt and mTOR. Also, an increased level of BNDF in CBD-treated mice seems to be involved in the activation of PI3K/Akt/mTOR pathway. In addition, our data demonstrated that therapeutic efficacy of CBD treatment is due to reduction of pro-inflammatory cytokines, like IFN-γ and IL-17 together with an up-regulation of PPARγ. Finally, CBD was found to promote neuronal survival by inhibiting JNK and p38 MAP kinases. These results provide an interesting discovery about the regulation of the PI3K/Akt/mTOR pathway by cannabidiol administration, that could be a new potential therapeutic target for MS management.

KEYWORDS: BDNF; Cannabidiol; Inflammation; Multiple sclerosis; Neuronal survival; PI3K/Akt/mTOR pathway

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