

CANNABIDIOL IN VIVO SUPPRESSES A β INDUCED REACTIVE GLIOSIS

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Alzheimer’s disease (AD) is the most common age-related neurodegenerative disorder characterized by extracellular accumulation of A β fibrils in senile plaques (SP), and intraneuronal fibrillary tangles (NFTs). At present, biochemical events leading to A β neurotoxicity still remain unclear. Recently, besides cytotoxic mechanisms directly impacting on neurons, A β induced glial cell activation, triggering release of neurotoxic cytokines, has been proposed to occur in AD brain. Pharmacological inhibition of reactive gliosis may be regarded as a novel rationale to develop drugs which may blunt neuronal damage and slow AD course. Cannabidiol (CBD), the main non-psychotropic component of the glandular hairs of *Cannabis sativa*, exhibits a plethora of actions, including anti-inflammatory properties. CBD has been proved to exert in vitro a combination of neuroprotective effects in A β induced models of neurotoxicity, including antioxidant and anti-apoptotic effects, tau protein hyperphosphorylation inhibition through the Wnt pathway rescue, and marked iNOS protein expression and nitrite production decrease in A β challenged differentiated rat neuronal cells.

Despite the amount of data describing the significant neuroprotective and anti-inflammatory properties of CBD, to date no evidence has been yet produced about its in vivo effects. To this purpose 3-5 months old C57Bl/6 mice were inoculated with 10 ng of human A β (1-42) into the right dorsal hippocampus (AP = + 2.0 mm; ML = - 1.8 mm; DV = - 2.3 mm). Starting by the 3rd day after surgery, mice were intraperitoneally treated daily with vehicle or cannabidiol (2.5 or 10 mg/kg) until their sacrifice at 10th day. In situ hybridization technique was performed to investigate GFAP mRNA expression and immunofluorescence analysis was carried out to determine GFAP, iNOS and IL-1 β protein expression. Under the same experimental conditions, ELISA assay of IL-1 β level and the measurement of nitrite (NO₂-) release, as stable metabolites of NO, were performed in dissected and homogenized mice ipsilateral hippocampi, derived from vehicle, and A β inoculated mice, in the absence or presence of CBD (2.5-10 mg/kg).

The results indicated that CBD (2.5-10 mg/Kg) dose dependently and significantly inhibited GFAP mRNA (respectively -31.3 \pm 4.1% and -81 \pm 6.7%) and protein expression (-30 \pm 3.12% and -64.14 \pm 6.2% respectively) versus A β injected hippocampi. Moreover a marked inducible nitric oxide synthase (-33.3 \pm 5.2% and -61.5 \pm 4.25% respectively) and relative NO-production (-30 \pm 1% and -51 \pm 3.71% respectively) as well as IL-1 β protein expression (-30.5 \pm 5.7% and -68 \pm 4.23% respectively) and release (-75 \pm 6% and -50 \pm 4.71%) have been also observed. Taken together, the present study highlights the importance of CBD as a promising novel pharmacological tool able to attenuate in vivo A β evoked neuroinflammatory response.