CANNABIDIOL IN VIVO SUPPRESSES Aβ INDUCED REACTIVE GLIOSIS

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Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder characterized by extracellular accumulation of Aβ fibrils in senile plaques (SP), and intraneuronal fibrillary tangles (NFTs). At present, biochemical events leading to Aβ neurotoxicity still remain unclear. Recently, besides cytotoxic mechanisms directly impacting on neurons, Aβ 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 Aβ induced models of neurotoxicity, including antioxidant and anti-apoptotic effects, tau protein hyperphosphorilation inhibition through the Wnt pathway rescue, and marked iNOS protein expression and nitrite production decrease in Aβ 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 Aβ (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-1β protein expression. Under the same experimental conditions, ELISA assay of IL-1β 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 Aβ 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 ± 4.1% and -81 ± 6.7%) and protein expression (-30 ± 3.12% and -64.14 ± 6.2% respectively) versus Aβ injected hippocampi. Moreover a marked inducible nitric oxide synthase (-33.3 ± 5.2% and -61.5 ± 4.25% respectively) and relative NO·production (-30 ± 1% and -51 ± 3.71% respectively) as well as IL-1β protein expression (-30.5 ± 5.7% and -68 ± 4.23% respectively) and release (-75 ± 6% and -50 ± 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 Aβ evoked neuroinflammatory response.