The non-psychotropic plant cannabinoid cannabidivarin ameliorates Rett syndrome-like phenotype in MeCP2 mutant mice

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Rett syndrome (RTT) is an X-linked dominant neurodevelopmental disorder with a prevalence rate of 1 in 10,000 females. RTT patients have apparently normal perinatal development until about 6–18 months of age, after which they undergo a period of rapid regression, characterized by the appearance of autistic features, stereotypic hand movements and loss of language. RTT girls also have seizures during childhood, breathing arrhythmias, dysautonomia, and develop scoliosis at later stages, which ultimately lead to loss of mobility.

In the last years, there has been growing interest in the therapeutic potential of phytocannabinoids in the context of neurological diseases. Several preclinical and clinical data support the ability of some phytocannabinoids to modulate cognitive functions, mood, anxiety, motor dysfunctions and convulsions, all of which are present in RTT. Epilepsy in particular has been reported in 60-80% of patients with RTT and very recent data have highlighted the potential of the phytocannabinoids cannabidivarin (CBDV) as effective antiepileptic agent both in vitro and in vivo. Remarkably, clinical trials have proven CBDV to be safe and well tolerated even at the higher doses tested.

In this study, we explored for the first time the ability of chronic administration of the non-psychotropic phytocannabinoid CBDV to affect neurological defects as well as cognitive deficits in MeCP2-null mice on a CD1 background strain. Furthermore, biochemical analyses were carried out in brain lysates from MeCP2 WT and KO mice to assess the ability of CBDV to modulate brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1) protein levels as well as components of the endocannabinoid system.

Chronic administration of the non-psychotropic phytocannabinoid CBDV prolongs survival and attenuates the appearance of neurological and motor signs (tremor, hindlimb clasping, breathing, general condition and gait) in MeCP2 KO mice in a time window between 6 and 8 weeks of age. During the last week of the observation period, CBDV still elicits a protective effect against impairments in mobility whereas its beneficial effect on the other motor and neurological signs is lost. Remarkably, CBDV administration completely recovers short- and long-term memory deficits in MeCP2 KO animals during the whole treatment schedule, and this improvement persists at later stages of the disease progression.

At biochemical level, CBDV chronic treatment simultaneously elevates the expression of BDNF and IGF-1 in the brain of MeCP2 KO mice and restores their common downstream PI3K/AKT/mTOR intracellular signaling pathway at behaviorally efficacious doses. Furthermore, CBDV also modulates components of the endocannabinoid system in the brain of MeCP2 KO mice, enhancing AEA and PEA levels and greatly reducing 2-AG content.

As a whole, the present findings indicate that chronic CBDV administration ameliorates neurological and motor signs and exerts an enduring and complete rescue of short- and long-term memory deficits in male MeCP2 KO mice, suggesting a potential to alleviate some of the clinical signs present in RTT, possibly via modulation of the endocannabinoid system as well as the trophic molecules, BDNF and IGF-1.

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