Possible dysregulation of the endocannabinoid system: study in lymphocytes of patients with Dravet syndrome

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Dravet syndrome (DS) is a rare genetic pediatric epilepsy that occurs in the first year of life with febrile seizures that progress to severe partial or generalized tonic-clonic seizures. DS is caused by mutations in the SCN1A gene, which encodes the Î±-subunit of the voltage-gated sodium channel Nav1.1 involved in the rising phase of the action potential in neurons (Bender et al., 2013). DS is pharmacoresistant syndrome and novel therapies are urgently needed for its treatment. Recent data suggest that a promising therapy for DS may be based on the use of cannabidiol (CBD). CBD had been investigated for its anticonvulsant properties in seizure models of adult epilepsy, but the first evidence of its potential for infantile epileptic syndromes was collected in 2013 when a number of US families, having children affected by DS or related epileptic syndromes, used CBD-enriched cannabis to attenuate the frequency and intensity of epileptic episodes. In particular, CBD was able to reduce approximately 80% frequency and intensity of epileptic episodes in about 42% of DS treated children (Porter and Jacobson, 2013). At the end of 2013, three US and one UK hospitals initiated a clinical trial with oral CBD formulated as Epidiolex® (GWPharmaceuticals), in which it was demonstrated that CBD was efficacious and well-tolerated (Devinsky et al., 2016).

In this study we investigated the status of the endocannabinoid system, which contains the potential pharmacological targets for CBD, in DS patients.

The study was conducted in DS patients lymphocytes DS patients and compared with control subjects, which have no clinical diagnosis of DS. Lymphocytes were isolated and, by the quantitative real-time PCR (qPCR-RT), we analyzed the gene expression of different elements related to the endocannabinoid system: a) receptors (CB1, CB2, GPR55, GPR18, TRPV1 and TRPV2 receptors); b) enzymes the synthesis and degradation of endocannabinoids (NAPE-PLD, FAAH, DAGL and MAGL); c) proteins related to inflammation such as CD70, a marker of lymphocyte activation, several cytokines (TNF-alfa, IL-1beta, iNOS) and the PPAR-gamma receptor; and d) some proteins downstream the endocannabinoid signaling (NFkB, Nrf-2, Keap-1, beta-arrestin-1 and 2). We also studied different elements potentially related to CBD action (Fernández-Ruiz et al., 2013) such as the voltage-dependent calcium channel a-1h subunit (CACNA1h) and several transmitter receptors, such as serotonin1A receptor (5HT1A) and adenosine 2A receptor (A2A), as well as the transporters for glutamate (GLT-1 and GLAST), GABA (GABA-T), dopamine (DAT), serotonin (5HTT), and adenosine (equilibrative nucleoside transporter).

We found a significant increase of CB2 receptor expression in lymphocytes from patients with DS compared with control subjects, whereas there were no differences in the expression of other receptors related to the endocannabinoid system. In agreement to the role of CB2 in the control of inflammatory processes, the expression of CD70 was found significantly increased in DS patients. PPAR-gamma receptors and TNF-alfa/IL-1beta showed certain trends towards an increase, although they were not statistically significant. We did not detect any difference in transcription factors such as NFκB or Nrf-2, its inhibitory protein Keap-1, the kinase Akt, and the receptor regulatory proteins beta-arrestin-1 and -2. Furthermore, we found CACNA1h gene expression to be signi?cantly elevated in DS patients, but no changes were found for A2A receptors, adenosine transporter, GLAST and GLT-1 and DAT.

In conclusion, our results support the idea of a possible endocannabinoid dysregulation in DS, whose correction with CBD might underlie in the benefits reached with this phytocannabinoid.

References

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