Possible dysregulation of the endocannabinoid system in a cohort of patients with Dravet syndrome

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Dravet syndrome (DS), also known as Severe Myoclonic Epilepsy of Infancy (SMEI), is a rare genetic pediatric epilepsy (Dravet, 1978) that affects 1:20.000 subjects and it occurs more often in males than females (2:1) (Hurst, 1990). DS is caused by mutations in the SCN1A gene, which encodes the α-subunit of the voltage-gated sodium channel Nav1.1 involving a loss of channel function. This particularly affects subpopulations of GABAergic neurons losing the ability to inhibit neurons that synapse with, implying an increase in the excitability which is responsible for the frequent seizures. The onset of DS is generally in the first year of life with febrile seizures that progress to severe partial or generalized tonic-clonic seizures, myoclonic seizures and episodes of status epilepticus in otherwise healthy infants. Cognitive impairment, behavioral disturbances with hyperactivity and sometimes autistic traits were also described (Guerrini, 2012). Since DS is one of the most pharmacoresistant epilepsy syndromes, novel therapies are urgently needed for its treatment (Kassaï et al., 2008). Recent anecdotal data (Porter and Jacobson, 2013) and on-going clinical trials in EEUU and Europe have shown as the use of cannabidiol (CBD) was able to reduce approximately 80% frequency and intensity of epileptic episodes in about 42% of DS treated children. CBD is the major non-psychoactive component of *Cannabis sativa* whose mechanism of action, including those involved in its anti-convulsant properties, is presently unknown. It has no direct activity on the classical cannabinoid type 1 receptor (CB_1) and type 2 (CB_2), but it may indirectly activate both receptors for their ability to inhibit the activity of the fatty acid amide hydrolase (FAAH), a key enzyme in the degradation of endocannabinoids (Fernández-Ruiz et al., 2013). It is possible that the apparent efficacy of CBD in DS may be due to the normalization of an underlying dysregulation of the endocannabinoid signaling system (Fernández-Ruiz et al., 2013). In this study, we investigated the possible dysregulation of the endocannabinoid signaling in patients affected by DS through the analysis of specific endocannabinoid elements in peripheral cells. In particular, we analyzed the gene expression for endocannabinoid elements using their lymphocytes, employed as a peripheral marker of possible changes occurring in the central nervous system. We also analyzed the levels of endocannabinoids and related lipid derivatives in the plasma of the same patients. Results showed a significant increase of CB_2 receptor gene 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. Since CB_2 receptor has been connected with the control of inflammatory processes, we also evaluated the expression of CD70, a marker of lymphocyte activation, whose expression was significantly increased in DS patients. We also analyzed some inflammation-related genes encoding PPAR-γ receptors and cytokines (e.g. TNF-α, IL-1β) which showed certain trends towards an increase, although they were not statistically significant. Plasma levels of endocannabinoids and related N-acylethanolamines were also similar in both DS and controls, in agreement with lymphocyte gene expression data for endocannabinoid-related enzymes which showed no changes in DS patients. Taken together these results may significantly contribute to understand the neurobiology of the endocannabinoid system in DS.

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