## Role of the endocannabinoid system in different models of absence epilepsy

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Absence epilepsy is a generalized non-convulsive epileptic syndrome characterized by bilaterally synchronous spike and wave discharges (SWDs). SWDs are generated within a cortico-thalamo-cortical loop that comprises cortical pyramidal neurons and GABAergic interneurons, thalamic relay neurons and inhibitory neurons of the reticular thalamic nucleus (nRT) (Blumenfeld, 2005). CB1 receptor is expressed pre-synaptically in both glutamatergic and GABAergic neurons of the cortico-thalamo-cortical network and its activation leads to the inhibition of neurotransmitters release (Kano et al., 2009). Previous findings in our laboratory demonstrated that CB1 receptor expression is decreased in the thalamus of WAG/Rij rat, a validated animal model of absence epilepsy, and CB1 receptor activation reduces SWDs (Van Rijn et al., 2010). The aim of this study was to investigate long and short-term responses of the endocannabinoid system in the cortico-thalamo-cortical network during absence seizures. Here, we used both genetic and pharmacological models of absence epilepsy/seizures to mimic respectively chronic and acute stages of the disease. The genetic model is represented by stargazer mutant mice ($stg^{-/-}$), which develop spontaneous SWDs (5-7 Hz) around P18 continuing for the rest of their life. The pharmacological model consists of a single injection of low dose of PTZ (20 mg/kg i.p.) inducing SWDs with a frequency of 4–8 Hz comparable to human absence seizures. Data so far obtained point toward the following results: as compared to wild-type mice, $stg^{-/-}$ showed a reduction of CB1 mRNA expression in the nRT and an upregulation of CB1 mRNA expression in the somatosensory cortex. Noteworthy, CB1 mRNA alterations occurred in the caudal region but not in the rostral region of the nRT of $stg^{-/-}$. Concerning the pharmacological model, the EEG study showed that PTZ treatment triggered SWDs within 15 minutes from the administration and the effect lasted for about 3 hours. The potent cannabinoid receptors agonist WIN 55,212-2 (5 mg/kg, i.p.) significantly reduced both the number and the duration of SWDs induced by PTZ. This result is consistent with our previous observation demonstrating that WIN 55,212-2 decreases the incidence of spontaneous SWDs in the WAG/Rij rat model (van Rijn et al., 2010). In situ hybridization analysis showed lower CB1 mRNA expression in the nRT of PTZ treated rats as compared to control rats. No CB1 mRNA alteration was found in cortex. To identify the specific regions where PTZ and WIN 55,212-2 might be acting on the network, we analyzed the neuronal activation by c-fos mRNA expression. PTZ induced neuronal activation in a particular subregion of the somatosensory cortex, the S1FL cortex, leaving the other brain regions of the cortico-thalamo-cortical network unaffected. WIN 55,212-2, administered alone, had no effect on neuronal activation while, when administered after PTZ, it increased neuronal activity in all brain regions involved in the network. These data confirm the involvement of the endocannabinoid system in the cortico-thalamo-cortical network, suggesting that CB1 receptor might be a suitable target for the development of novel anti-absence drugs.

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