Involvement of the endocannabinoid system in a genetic animal model of absence epilepsy.

F. Scicchitano[1], E. Russo[1], R. Citraro[1], M. Menniti[1], BJ. Whalley[2], A. Calignano[3], G. De Sarro[1]
[1]Dept of Health Science, School of Medicine, University of Catanzaro, Catanzaro, Italy. [2]School of Chemistry, Food and Nutritional Sciences and Pharmacy, The University of Reading, Whiteknights, Reading, Berkshire, RG6 6AP, United Kingdom. [3]Department of Experimental Pharmacology, University of Naples 'Federico II', Naples, Italy

It is widely recognized that modulation of the endocannabinoid system might be useful for the treatment of several neurological disorders associated with neural excitability changes[1;2].
Drugs that modulate the endocannabinoid system and endocannabinoids typically play an anticonvulsant role although some proconvulsant effects have been reported both in humans and animal models[3;4]. Moreover, no evidence for a role of the cannabinoid system in human absence epilepsy has been found although limited evidence of efficacy in relevant experimental animal models has been documented [5;6]. This study aims to characterize the role of cannabinoids in specific areas of the cortico-thalamic network involved in oscillations that underlie seizures in a genetic animal model of absence epilepsy, the WAG/Rij rat. We assessed the effects of focal injection of the endogenous cannabinoid, anandamide (AEA), a non-selective CB receptor agonist (WIN55,212) and a selective CB1 receptor antagonist/inverse agonist (SR141716A) into thalamic nuclei of the cortico-thalamic network: the reticular thalamic nucleus (NRT), an area crucially involved for the communication between the cortex and thalamus and the ventroposteromedial thalamic nucleus (VPM), an area of SWD resonance generated by the cortex. We also assessed the effects of focal injection of these cannabinoid compounds into primary somatosensory cortex (S1po) which has been indicated as origin of SWDs [7].
AEA and WIN both reduced absence seizures independently from the brain focal site of infusion while, conversely, SR141716A increased absence seizures but only when focally administered to the ventroposteromedial thalamic nucleus (VPM). These results, together with previous reports, support therapeutic potential for endocannabinoid system modulators in absence epilepsy and highlight that attenuated endocannabinergic function may contribute to the generation and maintenance of seizures. Furthermore, the entire cortico-thalamic network responds to cannabinoid treatment, indicating that in all areas considered, CB receptor activation inhibits the pathological synchronization that subserves absence seizures. In conclusion, our result strongly suggest that eCB modulators might represent an alternative target for the treatment of absence seizures in epileptic patients.

References

1. Drysdale AJ, Platt B. (2003) *Curr Med Chem* 10:2719-2732.
2. Hill AJ, et al., (2012) Pharmacol Ther 133:79-97.
3. Wallace MJ, et al., (2003) J Pharmacol Exp Ther 307:129–37
4. Deshpande, L.S., et al., (2007) Neurosci. Lett. 411, 11–16.
5. Citraro R, et al., (2013) Neuropharmacology. 69:115-26.
6. Vilela LR, et al., (2013) *Epilepsy Res*. 104(3):195-202
7. Meeren HK, et al., (2002) *J Neurosci* 22:1480-1495.