Endocannabinoid system modulation of hippocampal excitability in normal and epileptic conditions

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It has been established that temporal lobe epilepsy (TLE), the most common type of complex partial seizures, strongly impairs memory performance. The brain region mainly involved in cognitive functions such as acquiring new memory, retaining memory and spatial coding, is the hippocampus. The dentate gyrus, the input region of the hippocampus, plays a critical role in these processes by acting as preprocessor of incoming information from the perforant path (PP) that project from the entorthinal cortex. It has been shown that high-frequency train of stimuli (HFS) delivered to the PP pathway cause a long-term increase in the amplitude of the evoked excitatory postsynaptic potentials of granule cells of the dentate gyrus. This facilitation, called long-term potentiation (LTP), has been shown to be associated with structural alterations at the synapses, and it is thought to be a strong candidate for the molecular mechanism underlying memory processes.

The endocannabinoid system (EC), comprises G protein-coupled cannabinoid CB1 and CB2 receptors, endogenous cannabinoid receptor ligands and enzymes responsible for their synthesis and degradation. EC is key regulator of synaptic transmission in the central nervous system (CNS). CB1 receptor activation is anticonvulsant in several experimental models of epilepsy, however, detrimental effects on long-term synaptic plasticity have been reported.

For this study, male adult Sprague-Dawley rats weighing 260g-300g, were administered either with the CB1 agonist WIN55, 212-2 (WIN, 0.3-2 mg/kg, i.p.), or the fatty acid amide hydrolase (FAAH) inhibitor URB-597 (3 mg/kg, i.p) and then tested for synaptic plasticity in normal and epileptic conditions. Two different paradigms of HFS were delivered to the PP dentate gyrus synapses to induce either LTP (200 Hz for ten seconds, one stimulus per second) or maximal dentate activation (MDA, 20 Hz, 10 s repeated 14 times every 10 min). To evaluate seizure-induced changes in neuronal excitability and synaptic plasticity, before and after MDA, single and paired pulse stimulations were delivered to construct an input/output (I/O) response curve and to assess short-term synaptic plasticity.

Both URB597 and WIN 55,212-2 significantly decreased MDA duration with respect to the vehicle group. The CB1 receptor antagonist AM 251 (2 mg/kg, i.p.) completely prevented WIN 55,212-2 antiepileptic effect. When AM 251 and URB 597 were administered together, a significant increase in the duration of the MDA was observed. The antiepileptic dose of WIN 55, 212-2 significantly impaired both LTP and paired pulse facilitation (PPF), which were then reverted by the AM 251 treatment. Conversely, antiepileptic dose of URB597 had no effect neither on LTP or PPF. These results suggest that endocannabinoid modulations might be a suitable candidate for the treatment of epilepsy without having detrimental effects on synaptic plasticity and memory related processes.