PALMITOYLETHANOLAMIDE, VIA PPAR-ALPHA RECEPTOR, RESTORES THE ALTERED SYNAPTIC PLASTICITY AND AMELIORATES THE COMPROMISED PAIN-RELATED BEHAVIOURS IN THE HIPPOCAMPUS IN NEUROPATHIC MICE.

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The hippocampus is an integral part of the Papez circuit involved in learning, memory, emotion, and motivation. Patients with chronic pain exhibit increased anxiety, depression, and deficits in learning and memory. Long-term potentiation (LTP) in the hippocampus has received attention as the biological substrate at the base of learning and memory. The activation of cannabinoid receptors, either directly by natural or synthetic agonists, or indirectly by selective inhibitors of the inactivation of endogenous cannabinoid receptor ligands (endocannabinoids), is widely supported by recent studies on neuropathic pain management (Goya et al.,2003; Cravatt et al., 2004; Maione et al., 2006). There is evidence that palmitoylethanolamide (PEA) is able to reduce pain-related behaviors and to restore glutamatergic synapses homeostasis in the medial prefrontal cortex of neuropathic mice (Guida et al., 2015). In this study, to investigate the impact of chronic pain condition on the hippocampal synaptic plasticity and on the related behavioral responses, electrophysiological, behavioural and biochemical analysis were performed, in a murine model of spared nerve injury (SNI), 30 days post-surgery (Decostered and Woolf, 2000). Moreover, the possible neuroprotective effect of chronic treatment with PEA, was evaluated, in both wild-type and Ppar-α -/- SNI mice. Our results showed, in 30 days SNI mice, a reduction of alternation in the Y-maze task, of recognition index in the Novel Object Recognition (NOR) test and of open-arm choice in the elevated plus-maze test, whereas neuropathy induced an increase of the time of immobility in the tail suspension test, as compared to the control group (Sham mice). Moreover both neuropathic wild-type and PPARα null mice showed either an altered spatial memory retention and an impairment of LTP in the granule cells of dentate gyrus induced by theta-burst stimulations (TBS) of the perforant path (PP) in the entorhinal cortex (Jedlicka et l., 2009). In fact when the entorhinal cortex was electrically stimulated, a great potentiation of the EPSP (LTP), was observed in the ipsilateral hippocampus, in sham mice. PEA chronic treatment (14 days) increased the alternation in the Y-maze task, the recognition index in the NOR test and decreased the immobility time in the tail suspension test, suggesting that PEA was able to improve memory deficits and the depressive-like behavior but not the anxiety-like behavior associated to neuropathic pain. Finally, PEA partially restored the LTP in the dentate gyrus and ameliorated the altered spatial memory in wild-type SNI mice but not in PPARα/SNI null mice. These results suggest that neuropathic pain negatively affect the limbic and cognitive functions, which may underlie the deficiency of LTP and memory. Moreover, it opens new perspectives for the possible use of natural compounds such as PEA for the treatment of neuropathic pain and its central behavioural sequelae.

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