Palmitoylethanolamide reduces pain-related behaviors and restores glutamatergic synapses homeostasis in the medial prefrontal cortex of neuropathic mice

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Enhanced supraspinal glutamate levels following nerve injury are associated with pathophysiological mechanisms responsible for neuropathic pain. Chronic pain can interfere with specific brain areas involved in glutamate-dependent neuropsychological processes, such as cognition, memory, and decision-making. The medial prefrontal cortex (mPFC) is thought to play a critical role in pain-related depression and anxiety, which are frequent co-morbidities of chronic pain. Using an animal model of spared nerve injury (SNI) of the sciatic nerve (Decostered and Woolf 2000), we assess bio-molecular modifications in glutamatergic synapses in the mPFC that underlie neuropathic pain-induced plastic changes at 30 days post-surgery. Moreover, we examine the effects of palmitoylethanolamide (PEA) administration on pain-related behaviours, as well as the cortical biochemical and morphological changes that occur in SNI animals. At 1 month, SNI was associated with mechanical and thermal hypersensitivity, as well as depression-like behaviour, cognitive impairments, and obsessive-compulsive activities. Moreover, we observed an overall glutamate synapse over-activation in the mPFC, characterized by changes in synaptic density proteins and amino acid levels. Finally, with regard to the resolution of pain and depressive-like syndrome in SNI mice, PEA restored the glutamatergic synapse proteins and changes in amino acid release. Given the potential role of the mPFC in pain mechanisms, our findings may provide novel insights into neuropathic pain processes and indicate PEA as a new pharmacological tool to treat neuropathic pain and the related negative affective states.

Decosterd I, Woolf CJ. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. PAIN 2000;87:149–58.