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OC.6-ULTRA-MICRONIZED PALMITOYLETHANOLAMIDE RESCUES THE COGNITIVE DECLINE-ASSOCIATED LOSS OF NEURAL PLASTICITY IN THE NEUROPATHIC MOUSE ENTORHINAL CORTEX-DENTATE GYRUS PATHWAY

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Chronic pain is associated with cognitive deficits. Palmitoylethanolamide (PEA) has been shown to ameliorate pain and pain-related cognitive impairments by restoring glutamatergic synapses functioning in the spared nerve injury (SNI) of the sciatic nerve in mice. SNI reduced mechanical and thermal threshold, spatial memory and LTP at the lateral entorhinal cortex (LEC)-dentate gyrus (DG) pathway. It decreased also postsynaptic density, volume and dendrite arborization of DG and increased the expression of metabotropic glutamate receptor 1 and 7 (mGluR1 and mGluR7), of the GluR1, GluR1s845 and GluR1s831 subunits of AMPA receptor and the levels of glutamate in the DG. The level of the endocannabinoid 2-arachidonoylglycerol (2-AG) was instead increased in the LEC. Chronic treatment with PEA, starting from when neuropathic pain was fully developed, was able to reverse mechanical allodynia and thermal hyperalgesia, memory deficit and LTP in SNI wild type, but not in PPARα null, mice. PEA also restored the level of glutamate and the expression of phosphorylated GluR1 subunits, postsynaptic density and neurogenesis. Altogether, these results suggest that neuropathic pain negatively affects cognitive behavior and related LTP, glutamatergic synapse and synaptogenesis in the DG. In these conditions PEA treatment alleviates pain and cognitive impairment by restoring LTP and synaptic maladaptative changes in the LEC-DG pathway. These outcomes open new perspectives for the use of the Nacylethanolamines, such as PEA, for the treatment of neuropathic pain and its central behavioural sequelae.