PALMITOYLETHANOLAMIDE REDUCES PAIN PERCEPTION ALTERATIONS IN A CENTRAL POST-STROKE PAIN (CPSP) MODEL

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Background: Central post-stroke pain (CPSP), including thalamic syndrome, is one of the most serious sequelae that can occur after a cerebrovascular accident involving any tract of central somatosensory system. The persistent, and often refractory, painful sensation can be a major problem that affects the quality of life of patients. The pharmacological treatment is still modest since the mechanisms at its basis are still poorly understood. Dosage adjustments are limited by side-effects, particularly in elderly patients. Thus, the development of new strategies to manage CPSP is eagerly awaited. CPSP is characterized by spontaneous and evoked pain, with typical manifestations of neuropathic pain such as hyperalgesia and allodynia. Clinical evidence strongly suggests a dysfunction in central pain pathways as an important pathophysiological factor in the development of CPSP, but the accurate underlying mechanisms remain poorly understood. In this study, we characterized the nociceptive and affective behavior of CPSP mouse model in order to clarify the pathophysiology of this syndrome.

Material and methods: Intrathalamic hemorrhage was induced by administration of a 0.3ml volume containing 0.07U collagenase Type IV in the ventral posterior nucleus (VPN) of the right thalamus (anterior-posterior to bregma 1.6mm, lateral to the midline 1.8mm, ventral to the skull surface 3.2mm). Control injections consisted of an equal volume of saline. Behavioral tasks were performed at different time points and scheduled in order to avoid carry-over effects from prior testing experience. Precisely, was evaluated tactile allodynia by Von Frey Test, cold hyperalgesia (cold plate and cold allodynia through Acetone test) 7days post-stroke, motor coordination (rotarod test) 7, 14and 21days, and depressive- like behavior (tail suspension test) 14days after stroke induction. Single injection of PEA, PEA-OXA and PEA/PEA-OXA combination was performed in both stroke and sham mice.

Results: Stroke mice developed tactile allodynia, cold hyperalgesia and cold allodynia in the controlateral hind paw associated with depressive-like behavior as compared with sham mice. Whereas, stroke mice did not show impairment in motor coordination at different time points. A single dose of PEA (10 mg/kg, o.s.), PEA-OXA (10 mg/kg, o.s.) or PEA/PEA-OXA (30 mg/kg, o.s.) combination, ameliorated allodynia with a peak between 30 and 60 minutes post-injection.

Discussion and conclusions: Preliminary behavioral data show that allodynia development observed in this study is comparable to the sensory abnormalities common in human patients suffering from CPSP. Moreover, we found a depressive-like behavior in stroke mice, similarly to other chronic pain conditions. In this context, the modulation of endocannabinoid system by endocannabinoid-like substances, such as palmitoylethanolamide (PEA) and its derivates, improved altered pain behaviors. These results suggest that the pharmacological manipulation of the endocannabinoid system, given its neuro-immuno-modulatory role, may represent a new therapeutic target for CPSP pain-related management.