**Antinociception induced by the inhibition of the soluble epoxide hydrolase enzyme in an orofacial chronic pain model in mice**

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Orofacial pain (OFP) is extremely debilitating and refers to pain associated with the hard and soft tissues of the head, face, and neck, affecting about 26% of the population. The treatment for OFP conditions is still a challenge for the health care services and pharmaceutical industry and some individuals are resistant and/or refractory to conventional approaches, motivating research in search of new therapeutic options. The sEH is an enzyme found in the mitochondria; it converts the epoxyeicosatrienoic acids (EETs) into 1,2-dihydroxy-fatty acids, reducing the EETs effects. EETs are bioactive lipids resulted from the arachidonic acid metabolism and are associated with the generation of pain and inflammation. The 1-(1-propanoylpi-peridin-4-yl)-3-[4-(trifluoromethoxy)phenyl] urea (TPPU) is an inhibitor of soluble epoxide hydrolase (sEH) enzyme, that shows anti-inflammatory and antinociceptive effects, including chronic pain, being a good option to test against orofacial pain. Thus, this study aimed to evaluate the possible antinociceptive effects of TPPU in a chronic model of orofacial pain induced by infraorbital nerve constriction (CION). C57/BL6 adult mice were trained for 3 days before the surgery to obtain baseline values and then tested on postoperative days 1, 3, 5, 7, 10, 15, and 20. For the CION procedure, the animals were anesthetized with ketamine and xylazine and two constrictive ligatures were placed around the infraorbital nerve (CEUA 117/16). We used a “Sham-operated” group, a “CION” non-treated group, and a “CION+TPPU” group. The treatment with TPPU (3mg/Kg) was done daily and started on the third day after CION. The mechanical sensitivity was assessed in the vibrissal area using Von Frey filaments and the “up and down” method. For the non-evoked pain behavior, the animals were observed for 30 minutes and the rubbing response was recorded. To assess the cold hypersensitivity, acetone was applied in the vibrissal area and the response was measured for 60 seconds. Acetone was applied three times and the average nociceptive time was calculated. The results were analyzed by two-way ANOVA, followed by the post hoc Bonferroni’s test. The CION caused non-evoked nociceptive behavior and mechanical hypersensitivity throughout the days observed but did not induce hypersensitivity to cold in comparison to sham-operated mice. The treatment with TPPU reduced the mechanical allodynia in all of the days observed caused by the infraorbital nerve constriction, and, from day 7 to 20, the non-evoked pain behavior was prevented by the treatment. Our data suggest that the treatment using TPPU has antinociceptive effects in a model of infraorbital nerve constriction. More studies are necessary to understand the molecular mechanisms involved in these effects.

Keywords: orofacial pain, antinociceptive, treatment