PHARMACOLOGICAL EFFECT OF PERAMPANEL, A NEW AMPA ANTAGONIST, IN ANIMAL MODELS OF ACUTE AND CHRONIC PAIN.

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Perampanel (PER), a selective non-competitive a-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid (AMPA)-receptor antagonist, had a anticonvulsant activity in several seizure models (1), but its effect on pain have not been investigated. However, AMPA receptor has been shown to play a critical role in animal pain models. It is known that up regulation of AMPA receptors (AMPARs) in the dorsal horn (DH) neurons causes central sensitization, a specific form of synaptic plasticity in the DH, sustainable for along period of time (2-3). Peripheral inflammatory pain induces up regulation of Ca2+ permeable AMPARs (CP-AMPARs) at both synapses (4,5) and the extra synaptic membranes of DH interneurons, two of those are causally linked to the persistent pain (6). Neuropathic pain is a multifactorial condition caused by damage or dysfunction of the nervous system resulting in loss of afferent sensory function, hyperalgesia and allodynia (7,8). Several drugs such as anticonvulsants, antidepressants, and opioids are available for the treatment of neuropathic pain, the balance of efficacy to safety remains far from satisfactory (9). Thus, the development of better therapeutic options through investigational activities including the assessment of efficacy in preclinical animal models is needed.

Aim of this study was to evaluate the effects of PER in models of acute pain (acid acetic test, tail flick test and hot plate test) and neuropathic pain induced by chronic constriction injury (CCI) of sciatic nerve.

We first tested PER capability to reduce the nocifensive behavior in acetic acid-induced writhing. Acute oral dose of PER (5 mg/kg) produced a significant reduction of writhing numbers. Furthermore, single oral administration of PER (5 mg/kg) showed increase of pain threshold at tail flick and hot plate test.

Finally we tested PER in a model of chronic pain. Results showed that the oral dose of PER (5 mg/kg) produced analgesic activity, leading to a significant reduction of mechanical allodynia and hyperalgesia after ligation.

Our data suggest that AMPA receptor are involved in reduction of pain perception and that PER is able to reduced mechanical hyperalgesia and allodynia.

1. Citraro R. et al. (2017). Epilepsia, 58:231-238

2. Woolf CJ. et al. (2000). Science, 288:1765-9

3. Ji RR. et al. (2003). Trends Neurosci., 26:696-705

4. Hartmann B. et al. (2004). Neuron., 44:637-50

5. Park JS. et al. (2009). J Neurosci., 29:3206-19

6. Kopach O. et al. (2012). Front Physiol., 3:391

7. Ueda H., (2006). Pharmacol Ther, 109:57-77

8. Bridges D. et al. (2001). Br J Anaesth, 87:12-26

9. Jongen JL. et al. (2013). Pain Pract., 14:283-295