Neurotransmitters involved in the antinociception evoked from the APN on neuropathic pain in rats.

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Background and aims: The Anterior Pretectal Nucleus (APN) is a structure from which descending pathways originate and act to modulate spinal nociceptive inputs. Previous experiments indicate that serotonergic and opioid, but not muscarinic cholinergic receptors in the APN participate in descending inhibitory modulation of pain. Villarreal and Prado (2007) suggested that the activation of a serotonergic mechanism in the APN modulates incision pain, and is under GABAergic inhibitory control, which is negatively controlled by the local release of endogenous opioids. The present study investigates whether the release of endogenous opioids also modulates the GABAergic inhibitory control of the APN against neuropathic pain in rats. Methods: The experiments were approved by the Ethical Committee for Animal Experimentation of the Faculty of Medicine of Ribeirão Preto/USP (No. 199/2009). Unilateral guide cannula were implanted in male Wistar rats (140g-160g; n = 36) and directed to the APN. Five days later, baseline paw withdrawal thresholds (PWT) to mechanical stimulation were recorded with an electronic von Frey test. The animals were then submitted to sciatic nerve ligation using a method modified from Bennett and Xie (1988). Two days after nerve ligation an opioid antagonist (naloxone, 10 ng / 0.25 µl) or a GABA B receptor antagonist (CGP 35348, 2 mg / 0.4 µl) was injected into the APN and the PWT were measured before and 15 minutes after the injection and then at 5-min intervals for up 30 minutes. At this moment, the µ-opioid receptor agonist DAMGO (1.5 µg/ 0.08 µl) was injected into the same nucleus. The PWT were considered in terms of force (in grams) required to evoke the reflex paw withdrawal. Thresholds in each subgroup were analyzed and presented in graphs as mean ± standard error of mean (SEM). The subgroups were compared using analysis of variance (MANOVA). The factors analyzed were treatments, time and treatment-time interaction. For each time, was performed analysis of variance (one-way) followed by Bonferroni test with significance set at P <0.05 in all cases. Results: Rats with nerve lesion had significant reduction of the PWT, this effect been further reduced after injection of naloxone or CGP35348 into the APN. The administration of DAMGO into this nucleus partially reversed the effect of naloxone. The results obtained were different in the treatment (F3,20 = 998.46 ; p < 0.001 ) and time (F9,180 = 115.01 ; p < 0.0001 ) and demonstrated significant interaction treatment x time (F27,180 = 42.57 ; p < 0.0001 ). The effect of DAMGO was partially reduced by CGP35348. The results obtained were different in the treatment (F3,20 = 1120,43 ; p < 0.001 ) and time (F9,180 = 121.51 ; p < 0.0001 ) and demonstrated significant interaction treatment x time (F27,180 = 45.95 ; p < 0.0001 ). Conclusions: We conclude that the descending inhibitory pathway activated in the APN by persistent noxious inputs generated during the development of neuropathic pain depends on the activation of pretectal opioid receptors, which modulates the inhibitory activity of GABAergic neurons also present in this nucleus. Financial Support: FAPESP.

References:


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