THE ARYLPIPERAZINYLALKYL PYRIDAZINONE ET1AS A POTENT ANTINOCICEPTIVE AGENT AFTER ORAL ADMINISTRATION IN MICE

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Introduction: Pyridazine derivatives such as arylpiperazinylalkyl pyridazinones displayed antinociceptive effects to thermal and chemical stimuli in mice comparable to that of morphine. Among these derivatives, we have previously identified ET1as a very promising compound, several fold more potent than morphine in reducing thermal nociception. Here, we extended the knowledge on the pharmacological profile of ET1by describing its effects on other models of nociception in mice.

Materials and methods: We evaluated the mouse behavioural responses to acute chemical nociception (capsaicin test), inflammatory-based models of nociception (formalin test, writhing test and carrageenan-induced thermal hyperalgesia) and neuropathic pain (chronic constriction injury model), after oral administration of increasing doses of ET1. We also evaluated the effect of ET1on the inflammatory response in the murine model of zymosan-induced paw oedema.

Results: In the formalin test, oral ET1caused the reduction of the neurogenic pain and the abolition of the inflammatory phase of nociception induced by the aldehyde. Similarly, ET1abolished the paw licking response in the capsaicin test, the abdominal stretching in the writhing test and the carrageenan-induced thermal hyperalgesia. We also demonstrated that ET1reduced thermal hyperalgesia and mechanical allodynia in neuropathic mice after a single oral administration. Furthermore, ET1produced a long-lasting anti-inflammatory effect in the zymosan-induced mouse paw edema.

Discussion and conclusion: In the present study, we evaluated the potential anti-nociceptive effects of ET1using several animal models of pain. We found that ET1caused significant reduction of nociception and edema development, and this effect is most likely due to the inhibition of different aspects and mediators of inflammation, as already known for arylpiperazinylalkyl pyridazinone derivatives. These results indicate ET1as a potent antinociceptive agent after oral administration, and support the possibility that ET1may be suitable for clinical applications in a wide-range of pain syndromes.