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ORIGINAL ARTICLE

Tapentadol in an Experimental Animal Model of Acute Orofacial Pain

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Abstract

OBJECTIVE: Tapentadol exhibits a synergistic dual effect effect (MOR / NRI) -agonist effect on noradrena-line reuptake inhibition (NRI). Tapentadol is effective on pain with neuropathic characteristics, therefore we decided to use it in an experimental model of acute orofacial pain.
METHODS: The Orofacial Stimulation Test, developed by Ugo Basile, measures hypersensitivity to thermal or mechanical stimulation of the trigeminal area. In the experiment, rats had to voluntarily contact a thermal or mechanical stimulator with their unshaved vibrissal pad in order to access a food reward. Twenty adult laboratory rats (average weight 345 grams) were tested. Intraperitoneal tapentadol was used in doses of 1 mg/kg and 2 mg/kg.
RESULTS: The results of the pilot study indicate that intraperitoneal administration of tapentadol (2 mg/kg) increased mechanical anti-nociception in rats.

INTRODUCTION

Tapentadol has dual synergistic agonistic effects (MOR/NRI) on μ opioid receptors (MOR) and noradrenaline reuptake inhibition (NRI). Tapentadol also activates alpha-2 receptors in the spinal cord (Bee *et al.* 2011).

This mechanism may be responsible for its very good analgesic effect on neuropathic pain. Several 3rd phase studies have produced favorable results. Reports from approximately 4,000 followed patients with severe chronic lower back pain (LBP) and osteoarthritis treated with tapentadol (at doses of 100–250 mg twice a day (BID)) have found the same positive analgesic effect as patients treated with oxycodone 20–50 mg BID. During 12 weeks of therapy, patients treated with tapentadol reported a significantly lower incidence of side effects with the same analgesic effects. (Buynak *et al.* 2010, Steigerwald *et al.* 2013; 2012a; 2012b). The pharmacological profile of tapentadol is also positive in that it does not have any active metabolites, has low plasma protein binding, and does not depend on cytochrome P450 (CYP) metabolism. In comparison with other opioids, tapentadol has a lower incidence of side effects and tolerance develops relatively slowly. Potential antidepressant and anxiolytic effects described in clinical experience by numerous doctors are also very interesting, although, this feature has not been the subject of studies so far. Diabetic polyneuropathy is a new indication (DNP) for tapentadol, which has shown a very good effect and slow tolerance compared to placebo for this diagnosis. It was administered in

doses of 100 mg up to 250 mg BID and was compared to placebo in patients with moderate to severe pain as a result of chronic DNP. At the onset of therapy in patients with DPN, pain relief was assessed after three weeks of treatment when a titration was performed. This study (ClinicalTrials.gov identifier: NCT01041859), which was done only in the U.S., showed the safety, effectiveness, and good tolerance of tapentadol. Clinical assessments were sufficient for FDA approval (April 2012) and for the treatment of neuropathic pain associated with DPN. The use of tapentadol in combination with other anti-neuropathic medication also works well in patients with chronic neuropathic pain (Fricová, 2014; Hakl, 2015). The most frequent diagnoses in which tapentadol holds potential benefits are fibromyalgia, post-amputation pain, the neuropathic pain component in patients suffering from chronic lower back pain, and in various tumor pain syndromes.

AIM OF INVESTIGATIONS

We used tapentadol in our animal model of orofacial pain, in which we evaluated the anti-nociceptive effects of tapentadol in experimentally (thermal and mechanical stimulation) induced orofacial pain.

METHODS

The Orofacial Stimulation Test, developed by Ugo Basile, measures hypersensitivity to thermal or mechanical stimulation of the trigeminal area. In the experiment, rats voluntarily contact a thermal or a mechanical stimulator with their unshaved vibrissal pad in order to access a food reward (Fig. 1). Data were obtained regarding the duration of feeding and the number of feeding attempts; attempts were determined based on the interruption of an infrared barrier traversing the opening to the reward. Feeding duration and number of attempts were found to be very dependent on changes in the applied thermal or mechanical stimulus.

Neuronal responses to multimodal peripheral stimulation of animals with spinal nerve ligation or sham surgery were recorded before and after two different doses of tapentadol. After the higher dose of tapentadol either naloxone or yohimbine was administered.Twenty adult laboratory rats (average weight = 345 grams) were tested. Tapentadol was applied intraperitoneally (i.p.) at doses of 1 mg/kg or 2 mg/kg. During the first day of the experiment, rats had an opportunity to get acquainted with the environment and look for food and find food, without pain.

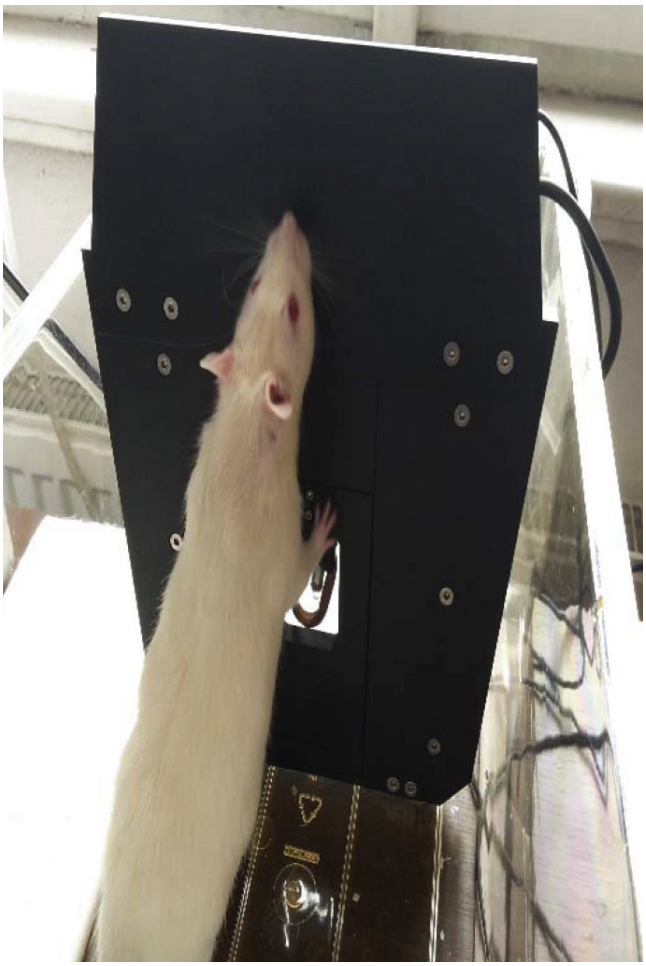


Fig. 1. Thermal stimulation

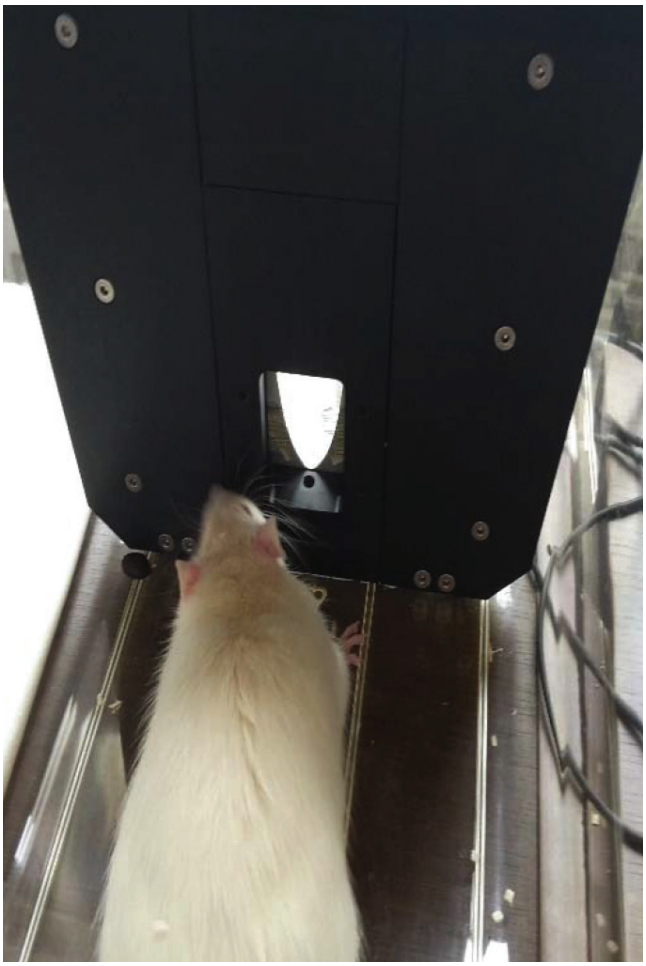


Fig. 2. Mechanical stimulation

Each group was administered alternately physiological solution 0.1 ml/100 g i.p. or tapentadol 1 mg/kg i.p. one hour before testing.

In the sham group, saline (0.1 ml/100 grams) was injected intraperitoneally. Dosing was done one hour before testing. The first group of animals was tested with the help of thermal stimulation (70°C). Mechanical testing was performed using Von Frey Hairs. Test periods lasted 10 minutes for all groups.

The Orofacial Stimulation Test (Ugo Basile)

The thermal stimulator relies on a copper tubing loop and a circulating water bath, the temperature of which can be adjusted from ambient to 70°C, to reach nociceptive thresholds. Chin inserts were included to test animals of different size. The mechanical stimulator relies on thin wires attached to a mounting plate. The system comes with several plates, each with a different number of wires in order to apply different force levels to the animal's vibrissal pad.(Figure 1, Figure 2)

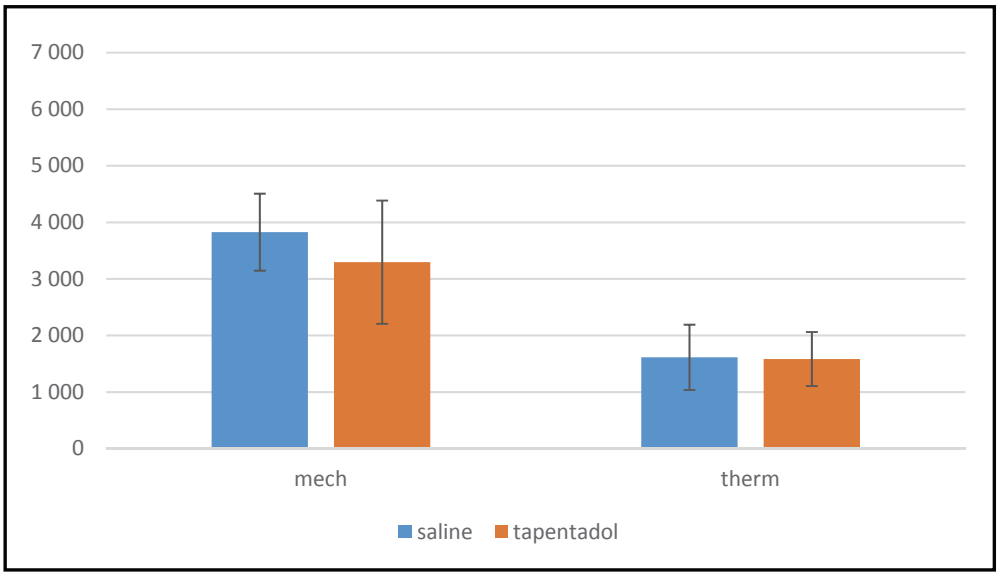
RESULTS

We assessed tapentadol at 1 mg/kg and 2 mg/kg and compared it to a physiological solution. Tapentadol at 1 mg/kg had no effect on the thermal and mechanical stimulation. Tapentadol at 2 mg/kg prolonged the sensitivity of rats to mechanical stimulation. Of special note, there were differences between the results of experiments held in September/December vs. February, with more intensive anti-nociceptive effects observed in February (Graph 1 and 2 vs. Graph 3). Average time of drinking (in milliseconds) is demonstrated.

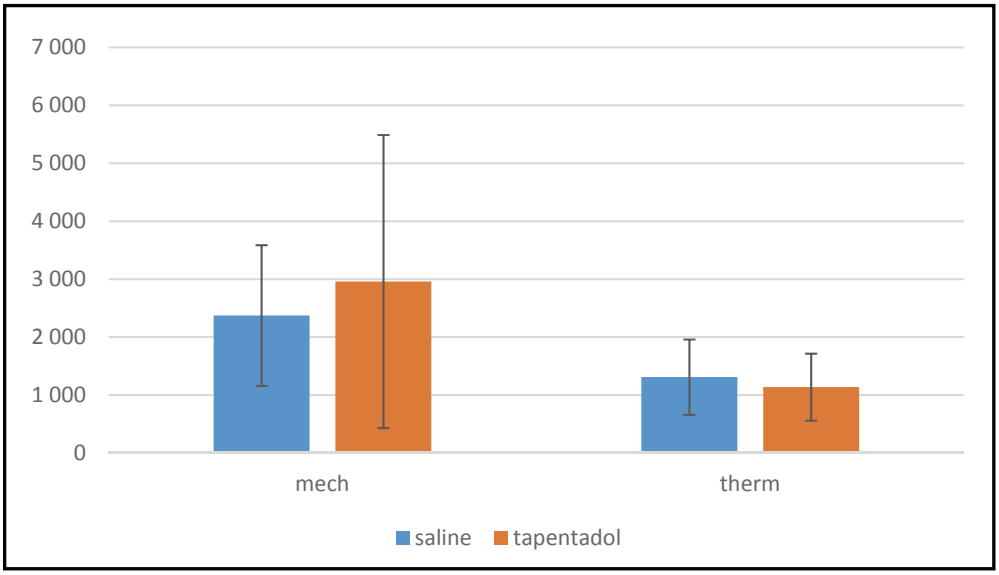
Systemic tapentadol resulted in a dose-dependent decrease in right CeA neuronal activity but only in neuropathy. Both naloxone and yohimbine reversed this effect to the extent that it was modality selective. The interactions of the components of tapentadol are not limited to the synergy between the MOR and α2-adrenoceptors seen at spinal levels but are seen at the CeA supraspinal site where suppression of responses may relate to the ability of the drug to alter the affective components of pain (Gonçalves *et al.*).

DISCUSSION

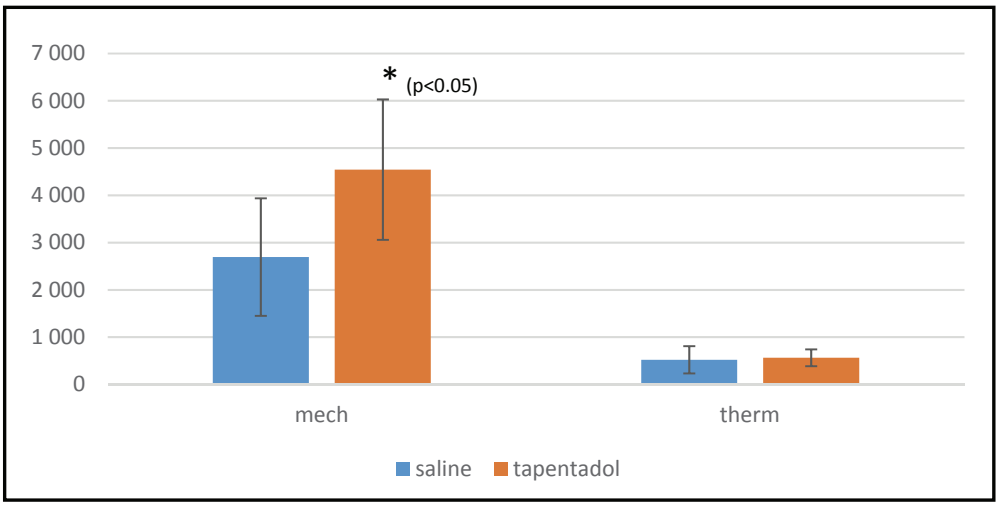
Tapentadol was injected into laboratory rats and its effect on food rewards was observed. The right central nucleus of the amygdala (CeA) is a critical part of the lateral spinal ascending pain pathway, regulates descending pain pathways, and is key in the emotional-affective components of pain. Few studies have investigated the pharmacology of limbic brain areas in pain models. In this study, we determined the actions of intraperitoneal tapentadol on the right CeA of animals with neuropathy, which should be susceptible to one of the components of tapentadol Tapentadol has a dual mechanism of action; some support the norepinephrine reuptake inhibition pathway as being primarily responsible for it analgesic effects. Thus, it is possible that TT- Thermal treshold testing is not an ideal model for evaluating the anti-nociceptive effects of drugs with a dual mechanism of action. However, tramadol has a similar mechanism of action as tapentadol, and oral administration of tramadol produces thermal antinociception in a dose-dependent manner (Pypendop *et al.* 2009). Nonetheless, it is clear that clinical pain is complex and that more than one type of nociceptive stimulus (i.e., mechanical and thermal) should be used to comprehensively evaluate analgesia (Steagall *et al.* 2007, Doodnaught *et al.* 2017).



Graph. 1. Mechanical and Thermal stimulation (September)



Graph. 2. Mechanical and Thermal stimulation (December)



Graph. 3. Mechanical and Thermal stimulation (February)

CONCLUSIONS

We showed that tapentadol anti-nociceptive effects are realized only at dosages of 2 mg/kg and only in association with mechanical stimulation. We also observed that experiments performed in February were more effective than those performed in September/December. Further experimentation with higher dosages of tapentadol is indicated. The results of this pilot study indicate that intraperitoneal administration of tapentadol (2 mg/kg) increased mechanical anti-nociception in rats.

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