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Antidepressant-like effects of tramadol and other central analgesics with activity on monoamines reuptake, in helpless rats

M.O. Rojas-Corrales, E. Berrocoso, J. Gibert-Rahola, J.A. Micó*

Unit of Neuropsychopharmacology, Department of Neuroscience, Faculty of Medicine, University of Cádiz. Plz Fragela 9, 11003 Cádiz, Spain

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Abstract

Affective states are regulated mainly by serotonin and noradrenaline. However the opioid system has been also related to antidepressant-induced mood improvement, and the μ-opioid receptor has been involved in affective responses to a sustained painful stimulus. Similarly, antidepressant drugs induce an antinociceptive effect *via* both the monoaminergic and opioid systems, probably involving sensorial and affective dimensions of pain. The aim of this study was to test three opiate analgesics, which also inhibit monoamine reuptake, in the learned helplessness model of depression in rats. Helpless rats receiving (±)tramadol (10, 20 mg/Kg) or (−)methadone (2, 4 mg/Kg) showed a decreased number of failures to avoid or escape aversive stimulus (shock) in both the second and the third daily sessions, compared with controls. Rats receiving levorphanol (0.5, 1 mg/Kg) showed a decreased number of such failures in the third session. The number of crossings in the intertrial interval (ITI) was not significantly modified by (±)tramadol or (−)methadone. Levorphanol enhanced ITI crosses at 1 mg/Kg. These results, together with other clinical and experimental data, suggest that analgesics with monoaminergic properties improve mood and that this effect may account for their analgesic effect in regulating the affective dimension of pain. From this, it seems probable that the analgesic effect of opiates could be induced by adding together the attenuation produced of both the sensorial and the affective dimensions of pain.

Keywords: Tramadol; Opiates; Monoamines; Learned helplessness; Rats; Affective; Analgesics

* Corresponding author. Tel.: +34-956-015247; fax: +34-956-015225.
E-mail address: juanantonio.mico@uca.es (J.A. Micó).

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Introduction

It is widely accepted that affective states are regulated mainly by serotonin and noradrenaline [1]. Given the involvement of these neurotransmitters, in order to regulate mood, classical and atypical antidepressants have been designed to interfere with the action of these neurotransmitters [2–4]. However, it is also claimed that the mechanism of action of mood improvement induced by some antidepressants is related in some way with the regulation of the opioid system [5,6]. In fact several opiate antagonists are capable of attenuating the effects of a number of clinically effective antidepressants in various tests to predict antidepressant activity [7–9].

It has been proposed very recently that the endogenous opioid system is involved in the attenuation of sensory and pain-specific affective responses to a sustained painful stimulus through the activation of μ-opioid receptors in specific brain regions (both cortical and subcortical) [10]. Thus it seems probable that the analgesic effect of opiates is produced by the sum of two components, the attenuation of the sensorial dimension of pain added to the attenuation of the affective dimension. In this respect it should be borne in mind that, in addition to their effects on affectivity, antidepressants have been shown, both experimentally and clinically, to induce analgesia [11–14] and that their antinociceptive activity can be antagonized by naloxone and other selective opiate antagonists [15,16]. Thus it also seems probable that the analgesic effect of antidepressants is also produced by the combined or cumulative action of both the monoaminergic and the opioid systems in attenuating both the sensorial and affective dimensions of pain [17].

Learned helplessness (LH) is a construct in which rats exposed to an inescapable and unpredictable aversive stimulus show a typical behaviour that reflects, to a certain extent, a deteriorated affective status in humans. In fact, this paradigm has been claimed to be a good model of human depression [18] and, according to some authors, also constitutes a possible model of post-traumatic stress disorder (PTSD) [19,20], a condition very similar to the anxiety-depression continuum. In animals, this paradigm is frequently used to predict antidepressant activity [21]. In humans, depression and PTSD has been extensively related to a dysfunction in the monoaminergic system [1,22,23]. However other neurotransmitters, such as the opioid system, have also been implicated; for example, an increase in the number of endogenous opioid receptors in the central nervous system of depressed suicide victims has been demonstrated [24,25].

Tramadol is a centrally-acting analgesic [26]. It binds weakly but effectively to opioid μ-receptors [27]. Nevertheless, a non-opioid mechanism is involved in tramadol analgesia. In accordance with the recognized implication of noradrenaline and serotonin in pain modulation [28] tramadol has been shown to inhibit the reuptake of noradrenaline and serotonin [29,30], thereby increasing the concentration of these two neurotransmitters in selected brain areas, and thus raising the pain threshold.

In a previous study [31], we showed that tramadol induces an antidepressant-type effect in the forced swimming test in mice. In the present study, we have aimed to explore the possible antidepressant-like effects of the tramadol by means of a depression model that is more valid, in terms of face and construct, than the forced swimming test in mice. Moreover, we have included in the study methadone and levorphanol, two opiate analgesics that are different from tramadol but have similar capability to inhibit the reuptake of noradrenaline and serotonin [32].

Methods

Animals

Experiments were performed using male Wistar rats (250–300 g). All the animals were provided by the "Servicio de Experimentación y Producción Animal" (SEPA) of the University of Cádiz. Animals were maintained under standard conditions: 12-h light-dark schedule (light on at 8 h 00 min a.m.) with *ad libitum* food and water and constant temperature (21 ± 1 °C). The experimental protocols were reviewed and approved by the Local Committee for Animal Experimentation of the Faculty of Medicine at the University of Cádiz (License number 079604). Animal care and use procedures conformed to International European Ethical Standards (86/609-EEC) and Spanish Law (RD 223/1988) for the care and use of laboratory animals.

Drugs

Tramadol (Grünenthal-Andrómaco, Spain), (−)Methadone (R.B.I., Natick, USA) and Levorphanol (R.B.I., Natick, USA) were i.p. administered 20 minutes before each daily shuttle-box session. All substances were dissolved in saline (NaCl 0.9%). Control animals received saline only. Drugs were injected in a volume of 0.1 ml/100 g of body wt to groups of 9–10 rats.

Learned helplessness model

The animals were selected for their high emotional level, since it has been shown that there exists a relationship between a high emotional level and high susceptibility to learned helplessness [33]. Emotional level was established by submitting the animals to a five-minute session conducted in an open field (50 cm high, 1 m diameter) with white floor and walls. The open field was placed in a light- and sound-proof room, and was illuminated with a 100 W bulb installed 60 cm over the open field. The number of faecal boluses was recorded as an index of emotional level [34] and only animals with five or more boluses excreted (high emotional level) were selected.

Selected animals were placed individually in Plexiglas chambers (20 × 20 × 10 cm) where sixty scrambled, randomised and inescapable electric foot-shocks (AC 50 Hz, 0.8 mA, 15 seconds duration and 10–90 seconds of inter-shock interval) were delivered through a stainless-steel grid floor.

Forty-eight hours after this inescapable shock pre-treatment, the animals were submitted to a daily shuttle box session for three consecutive days, always in the morning. Avoidance and escape learning was evaluated in automated two-way shuttle-boxes (52 × 22 × 29 cm) divided in two compartments linked by a gate (7 × 7 cm). Animals were placed individually in the shuttle-boxes and each was subjected to 30 avoidance trials, with 30 seconds between consecutive trials. A light signal (conditioned stimulus) was presented during the first 3 seconds of each trial, allowing animals to avoid the shock (0.8 mA) delivered for the next 3 seconds *via* the grid floor. If there was no response (avoidance or escape) within this period (6 seconds), shock and light were terminated. The response required of the rat, either avoidance prior to the shock or escape during the shock, was to cross through the gate into the other compartment of the shuttle-box. Failures to avoid or escape shock were recorded as escape failures. The number of crossings from one compartment to the other during the 30-second inter-trial interval (ITI) was also recorded.

Statistical analyses

The results are expressed as the mean ± S.E.M. of the number of escape failures recorded during the 30 trials in each of the 3 daily shuttle-box sessions. The number of failures was analyzed using one-way analysis of variance followed by the Student-Newman-Keuls *post-hoc* test. A p value of < 0.05 was considered to be significant. The number of inter-trial crossings (ITI activity) was submitted to the same statistical analysis.

Results

Effects induced by tramadol in the learned helplessness model

Fig. 1 shows the results obtained with tramadol in the learned helplessness model. ANOVA analysis shows a main effect induced by tramadol treatment in both the second ($F = 4.245$, $p = 0.025$) and the third ($F = 14.212$, $p = 0.001$) daily sessions. In the first session a tendency for escape failures to be reduced in comparison with controls, was observed, but it was not significant ($F = 2.808$, $p = 0.078$). The *post hoc* analysis shows that in the second session 10 and 20 mg/Kg of tramadol significantly reduced the number of escape failures, to 9.10 ± 3.32 (n = 10, $p < 0.05$) and 12.20 ± 3.94 (n = 10, $p < 0.05$) respectively, compared with 21.50 ± 1.68 (n = 10) failures in the control animals. In the third shuttle-box session the escape failures were reduced by 10 and 20 mg/Kg of tramadol to 11.40 ± 3.30 (n = 10, $p < 0.05$) and 5.00 ± 2.34 (n = 9, $p < 0.05$) respectively, compared with 24.90 ± 2.20 (n = 10) in the control group.

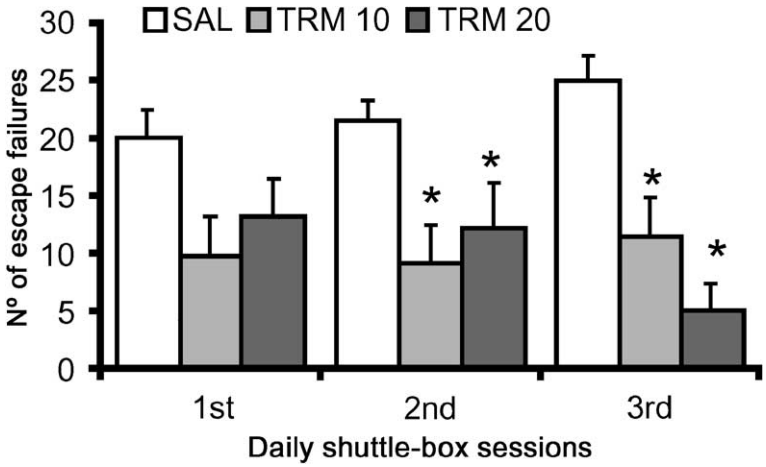

Fig. 1. Effect of tramadol (TRM) in the learned helplessness model in rats. Bars show the mean ± S.E.M. of the number of escape failures in the 30 trials performed in each of 3 daily shuttle-box sessions. Drugs were i.p. administered 20 minutes before each daily shuttle-box session (started 48 hours after inescapable, unpredictable foot-shock pretreatment). Tramadol significantly reduced the number of escape failures at 10 (grey bars) and 20 (black bars) mg/Kg in the second and third shuttle-box sessions. * $p < 0.05$ vs saline treated control animals (white bars) (Student Newman-Keuls *post hoc* test, after significant ANOVA analysis).

Tramadol did not induce any significant change in the ITI activity in the first ($F = 0.696$, $p = 0.507$), in the second ($F = 2.873$, $p = 0.075$) nor in the third ($F = 3.070$, $p = 0.064$) daily session.

Effects induced by (−)methadone in the learned helplessness model

Fig. 2 shows the reduction in the number of escape failures induced by (−)methadone at 2 and 4 mg/Kg in the learned helplessness model. In the first session, the reduction in the number of escape failures was not significant ($F = 2.206$, $p = 0.131$) but it was significant in both the second ($F = 5.570$, $p = 0.010$) and third ($F = 4.621$, $p = 0.020$) shuttle-box sessions. Administration of 2 mg/Kg of (−)methadone reduced the number of escape failures to 5.11 ± 1.86 (n = 9, $p < 0.05$ *vs* 15.10 ± 1.86 in controls, n = 10) and 6.89 ± 3.03 (n = 9, $p < 0.05$ *vs* 16.10 ± 2.47 in controls, n = 10) in the second and third sessions respectively. Administration of (−)methadone at 4 mg/Kg significantly reduced the number of failures to 5.56 ± 2.98 (n = 9, $p < 0.05$ *vs* 15.10 ± 1.86 in controls, n = 10) and 6.44 ± 2.17 (n = 9, $p < 0.05$ *vs* 16.10 ± 2.47 in controls, n = 10) respectively, in the two sessions.

(−)Methadone did not induce any significant change in the inter-trial activity compared with the saline-treated control group, in any of the three daily shuttle box sessions (1st session: $F = 0.865$, $p = 0.433$; 2nd session: $F = 3.385$, $p = 0.050$; 3rd session: $F = 2.931$, $p = 0.072$).

Effects induced by levorphanol in the learned helplessness model

Levorphanol administered at 0.5 and 1 mg/Kg induced a significant effect in this model (Fig. 3). Compared with the controls, the number of escape failures was reduced by levorphanol at both doses

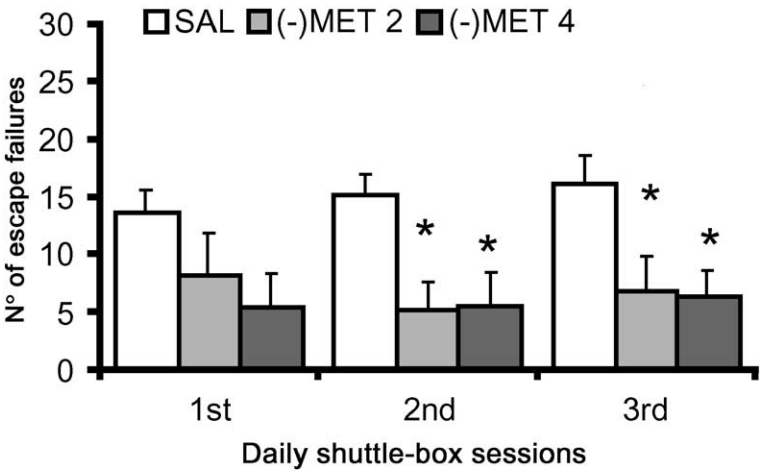

Fig. 2. Effect of *(−)*methadone, MET, in the learned helplessness model in rats. Bars show the mean ± S.E.M. of the number of escape failures in the 30 trials performed in each of the 3 daily shuttle-box sessions. *(−)*Methadone or saline were i.p. administered 20 minutes before each daily shuttle-box session (started 48 hours after inescapable, unpredictable foot-shock pretreatment). *(−)*Methadone significantly reduced the number of escape failures at 2 (grey bars) and 4 (black bars) mg/Kg in the second and third shuttle-box sessions. * $p < 0.05$ vs saline treated control animals (white bars) (Student Newman-Keuls *post hoc* test, after significant ANOVA analysis).

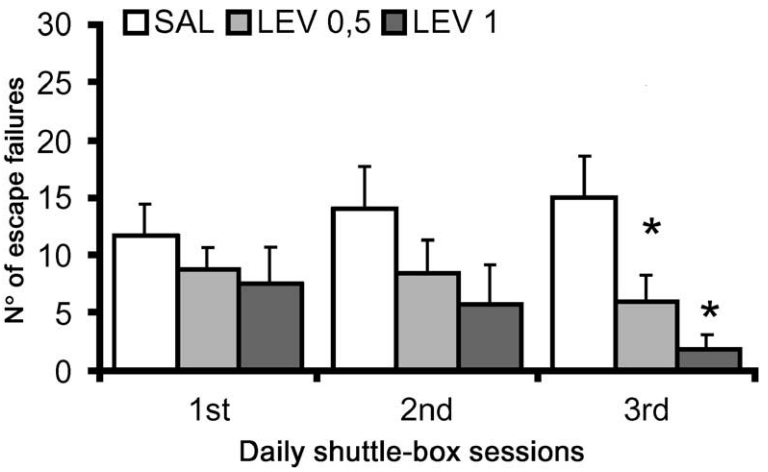

Fig. 3. Levorphanol administered at 0.5 and 1 mg/Kg induced a significant effect in this model (Fig. 3). Compared with the controls, the number of escape failures was reduced by levorphanol at both doses tested in the three daily shuttle-box sessions, but these reductions did not reach statistical significance in either the first (F = 0.5804; $p = 0.5667$) or the second (F = 1.6763 $p = 0.2067$) daily sessions. Only in the third session did levorphanol induce a significant effect (F = 6.846; $p = 0.004$) reducing the number of failures from 14.90 ± 3.61 (n = 10) in the controls to 6.00 ± 2.29 (n = 9, $p < 0.05$) and 1.80 ± 1.26 (n = 10, $p < 0.05$) induced by 0.5 and 1 mg/Kg of levorphanol, respectively.

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Conversely to the other analgesics, levorphanol significantly increased the number of inter-trial crossings in the first ($F = 4.439$, $p = 0.022$), the second ($F = 3.984$, $p = 0.031$) and the third ($F = 5.586$, $p = 0.010$) daily sessions. This enhancement of the ITI activity was induced by 1 mg/Kg in the first (24.4 ± 6.45, n = 10, $p < 0.05$ *vs* 9.4 ± 2.35 in controls, n = 10), the second (64.2 ± 21.41, n = 10, $p < 0.05$ *vs* 10.4 ± 3.43 in controls, n = 10), and the third (85.5 ± 24.41, n = 10, $p < 0.05$ *vs* 12.6 ± 2.96 in controls, n = 10) sessions.

Discussion

This study shows that three opiate analgesics capable of inhibiting the reuptake of noradrenaline and serotonin: tramadol, *(−)*methadone and levorphanol, induce antidepressant-like effects in helpless rats. Learned helplessness is a model of depression and PTSD in animals that has been showed to have high construct, face and predictive validity [35]. Neurobiologically, it has been demonstrated that opioids, as well as noradrenaline and serotonin, play an important role in this experimental model [9,36].

Taking into account that tramadol, *(−)*methadone and levorphanol are effective analgesics, one caveat to consider in this result is that alterations in nociceptive thresholds could interfere with the test. However, several points argue against the interference of analgesia in the present study. First, reduced

pain sensitivity would be predicted to decrease rather than to increase the number of escapes from noxious stimuli such as shocks in the learned helplessness test. However, rats receiving tramadol, *(−)*methadone or levorphanol make a greater number of crossings to avoid or escape from the shock, compared with the controls. Secondly, all the animals were exposed to inescapable shock pre-treatment prior to drug or saline administration, therefore the induction of learned helplessness takes place under non-analgesic control conditions. Thirdly, analgesia should be evident from the first session, but in rats treated with tramadol, the antidepressant-like effect is evident only at the second and the third sessions and, in the cases of methadone and levorphanol, only in the third session. Finally, at least in the case of tramadol, the effect induced in the forced swimming test [31] completely circumvents this problem. The fact that similar antidepressant-like effects are obtained (with tramadol) in both animal models argues against the interference of analgesia in the results.

On the other hand, one could think that the decreased number of escape failures (rats avoiding or escaping the shocks) is due to a greater number of indiscriminate crossings (which would occur during both the trials and the inter-trial intervals) induced by the opiate agonists. However, the results show that the number of ITI crossings was not significantly increased by tramadol or (−)methadone, compared with saline-treated controls. Levorphanol increased the number of ITI crossings at 1 mg/Kg, nevertheless the reduced number of escape failures was significant from 0.5 mg/Kg.

These results confirm and extend previous studies showing that tramadol has potential antidepressant-like effects in rodents [31] and that opiates play a role in the learned helplessness model of depression [37]. In fact, previous research in our laboratory has shown that the opioid peptides, met-enkephalin and leu-enkephalin, and the opiate analgesic, morphine, induce an antidepressant-like effect in this model. In addition, naloxone was able to antagonize the antidepressant-like effect of imipramine, a mixed inhibitor of noradrenaline and serotonin reuptake, under the same conditions [9]. We have previously demonstrated that mixed and selective inhibitors of enkephalin-degrading enzymes and delta-opioid agonists also showed an antidepressant-like effect in the learned helplessness model in rats [38,39]. In addition, Besson et al have proposed the hypothesis that dopamine mediates the effect of morphine and imipramine (a mixed noradrenaline-serotonin reuptake inhibitor) but not that of desipramine (a selective noradrenaline reuptake inhibitor) in the learned helplessness paradigm [40,41]. Interestingly, tramadol enhances dopamine turnover via an opioid mechanism [42]. More recently, [43] it has been demonstrated that different antidepressants reduce learned helplessness in rats by activating the dopaminergic system. In this sense, it would be of interest to determine in further studies the specific mechanisms, either monoaminergic or opioid, which were predominantly involved in the effects induced by tramadol, (−)methadone and levophanol in this model.

Several clinical reports have pointed to the possibility of an antidepressive effect of tramadol. Shapira et al. [44] very recently reported the efficacy of tramadol monotherapy in a case of refractory major depression, and Spencer [45] describes a case of severe suicidal ideation rapidly resolved with intramuscular tramadol. These are isolated case studies, but an open label study [46] showed the improvement of obsessive-compulsive symptoms with tramadol. It should be noted that obsessive-compulsive disorders have been successfully treated with antidepressants [47–49]. Moreover, some reports describe the treatment of patients with refractory major depression using augmentation with the μ-opiate agonists, oxycodone and oxymorphone, and the partial agonist, buprenorphine [50,51]. In the case of tramadol, it has been reported effective in augmenting treatment in patients with major depressive disorder who showed a partial response to selective serotonin reuptake inhibitors [52].

Conclusion

All these clinical data, together with previous experimental studies and the results reported in this work, suggest that tramadol, and probably also other analgesics with monoaminergic properties, improve mood, experimentally as well as clinically. Consequently, the basis for this observed effect could be the regulation of the affective dimension of pain by these compounds.

Acknowledgements

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