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Antidepressant-like effect of tramadol and its enantiomers in reserpinized mice: comparative study with desipramine, fluvoxamine, venlafaxine and opiates

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Abstract

Tramadol is a centrally acting analgesic that demonstrates opioid and monoaminergic properties. Several studies have suggested that tramadol could play a role in mood improvement. Moreover, it has previously been shown that tramadol is effective in the forced swimming test in mice and the learned helplessness model in rats, two behavioural models predictive of antidepressant activity. The aim of the present study was to test tramadol and its enantiomers in the reserpine test in mice, a classical observational test widely used in the screening of antidepressant drugs. This test is a non-behavioural method where only objective parameters such as rectal temperature and palprebral ptosis are considered. Moreover, we compared the effects of tramadol and its enantiomers with those of antidepressants (desipramine, fluvoxamine and venlafaxine) and opiates [morphine (–)-methadone and levorphanol]. Racemic tramadol, (–)-tramadol, desipramine and venlafaxine reversed the reserpine syndrome (rectal temperature and ptosis), whereas (+)-tramadol and fluvoxamine only antagonized the reserpine-induced ptosis, without any effect on temperature. Opiates did not reverse reserpine-induced hypothermia. (–)-Methadone showed slight effects regarding reserpine-induced ptosis, morphine and levorphanol had no effect. These results show that tramadol has an effect comparable to clinically effective antidepressants in a test predictive of antidepressant activity, without behavioural implications. Together with other clinical and experimental data, this suggests that tramadol has an inherent antidepressant-like (mood improving) activity, and that this effect could have clinical repercussions on the affective component of pain.

Keywords

desipramine, fluvoxamine, levorphanol, methadone, morphine, reserpine test, tramadol, venlafaxine

Introduction

Tramadol (1RS,2RS)-2-(dimethyl-amino)methyl-1-(3-methoxy-phenyl)-cyclohexanol HCL is a centrally acting analgesic (Friderichs *et al*., 1978), and is effective in the treatment of moderate to moderately severe pain (Raffa, 1996). It has a relatively weak opioid receptor affinity with a K_i in the micromolar range (Raffa *et al*., 1992).

Several studies have demonstrated that tramadol is able to inhibit the reuptake of noradrenaline and serotonin in the central nervous system (CNS) (Codd *et al*., 1995; Bamigbade *et al*., 1997), a mechanism similar to that of several antidepressants (Markowitz and Patrick, 1998). This effect on monoamines appears to be involved in the analgesic effect (Raffa *et al*., 1992) of tramadol, as well as in the analgesic effect of certain antidepressants (Valverde *et al*., 1994).

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We have previously demonstrated that, in addition to its analgesic properties, tramadol has an antidepressant effect predictive of antidepressant activity in some behavioural models, such as the forced swimming test in mice (Rojas-Corrales *et al*., 1998) and the learned helplessness model of depression in rats (Rojas-Corrales *et al*., 2002). Several case reports and case series have illustrated a clinically effective antidepressant effect of tramadol in various depressive states (Spencer, 2000), including resistant depression (Shapira *et al*., 2001). Moreover, tramadol has been shown to be effective in neuralgias (Boureau *et al*., 2003), and other clinical data indicate a possible anti-obsessive effect of tramadol (Shapira *et al*., 1997); two clinical conditions particularly responsive to treatment with antidepressants. Thus, it appears probable that tramadol, in addition to its well known analgesic effect, could have a direct action on the emotional component of chronic pain, such as decreased affectivity and helplessness. In all these satisfactory responses to emotional improvement, it is not clear whether the effectiveness of tramadol is due to its opiate or monoaminergic properties, or both. Opioid agonists have shown to induce antidepressant effects in preclinical and clinical conditions (Bodkin *et al*., 1995; Tejedor-Real *et al*., 1995; Stoll and Rueter, 1999)

Tramadol is a racemic 1 : 1 mixture of two enantiomers (+)-tramadol [(+)-tramadol] and (–)-tramadol [(–)-tramadol]. Although the (+)-enantiomer is preferentially an inhibitor of serotonin reuptake (K_i = 0.99 μM), the (–)-enantiomer is a potent inhibitor of noradrenaline reuptake (K_i = 0.79 μM) (Raffa *et al*., 1992). The racemic and (–)-enantiomer have a more evident antidepressant-like effect in the forced swimming test than the (+)-enantiomer (Rojas-Corrales *et al*., 1998).

Opioids have strong influences on behaviour, mainly motor activity and/or analgesia (Ossipov *et al*., 1997; Waddell and Holtzman, 1998). Thus, the antidepressant-like effect of tramadol in the forced swimming test could be influenced by this opioid-mediated behaviour, mainly by increasing motor activity. Nevertheless, in the learned helplessness test, the analgesic effect induced by tramadol might be a confounding factor to be taken in consideration, although this is rather improbable (Rojas-Corrales *et al*., 2002).

In this study, we investigated the possible antidepressant-like effect of tramadol and its two enantiomers in the reserpine test in mice, a classical test predictive of antidepressant activity, without any involvement of a behavioural component. Only objective parameters such as rectal temperature and palpebral ptosis were considered (Askew, 1963; Bourin *et al*., 1983).

Moreover, we compared the effect of tramadol and its two enantiomers with that of several antidepressants and opiates, including those with a different mode of action such as desipramine, a tricyclic antidepressant which preferentially inhibits the reuptake of noradrenaline, fluvoxamine, a selective serotonin reuptake inhibitor, and venlafaxine, a dual non-tricyclic noradrenaline/serotonin reuptake inhibitor. Morphine and other opiates with monoamine inhibitory reuptake properties such as (–)-methadone and levorphanol were also studied. All of these compounds were demonstrated in previous studies to have analgesic (Valverde *et al*., 1994; Schreiber *et al*., 1996, 1999) and antidepressant effects (Tejedor-Real *et al*., 1995; Rojas-Corrales *et al*., 2002).

Methods and materials

Animals

Experiments were performed using male CD1 mice (25–30 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 : 12 h light/dark cycle (lights on at 08.00 h) with food and water available *ad libitum* 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, Madrid, Spain) (+)-tramadol HCl (Grünenthal-Andrómaco) (–)-tramadol HCl (Grünenthal-Andrómaco) (–)-Methadone (RBI, Natick, MA, USA), Levorphanol (RBI), morphine (Servicio de Restricción de Estupefacientes, Ministry of Health, Madrid, Spain), Desipramine (Sigma-Aldrich-Química, Madrid, Spain), Fluvoxamine HCl (Solvay-Duphar, Brussels, Belgium), Venlafaxine (Wyeth, Princetown, NJ, USA) were all dissolved in saline (NaCl 0.9%). Control animals received saline only. Drugs were injected in a volume of 0.1 ml per 100 g body weight, 18 h after reserpine treatment.

Reserpine test

Mice were randomized according to their basal rectal temperature, and thereafter they were treated with reserpine (2 mg/kg s.c.) at 15.00 h and left in the experimental room (21–23 °C). Rectal temperature was measured in degrees centigrade with a rectal probe connected to a thermometer (Panlab, S.L., Barcelona, Spain). Ptosis was scored from 0 (eye open) to 4 (eye completely closed), as described by Rubin *et al*. (1957), in each eye of the mouse (maximum score 8). Eighteen hours after reserpine treatment (09.00 h), rectal temperature and ptosis were measured, and only mice showing severe hypothermia (< 25 °C) and ptosis (> 3 in each eye) were selected for treatment. Reserpinized mice were randomly assigned to experimental groups and rectal temperature and ptosis were recorded 1, 2, 3 and 4 h after drug treatment.

Statistical analysis

Data are expressed as the mean ± SEM of the parameter measured (either rectal temperature in °C or palpebral ptosis scored from 0–8). The data were analysed by using repeated measures analysis of variance (ANOVA) for raw data. Area under the curve ($AUC_{0-4\ h}$) data were calculated by the trapezoidal rule approach, and analysed by one-way ANOVA followed by the Dunnet post-hoc test. $p < 0.05$ was considered to be statistically significant.

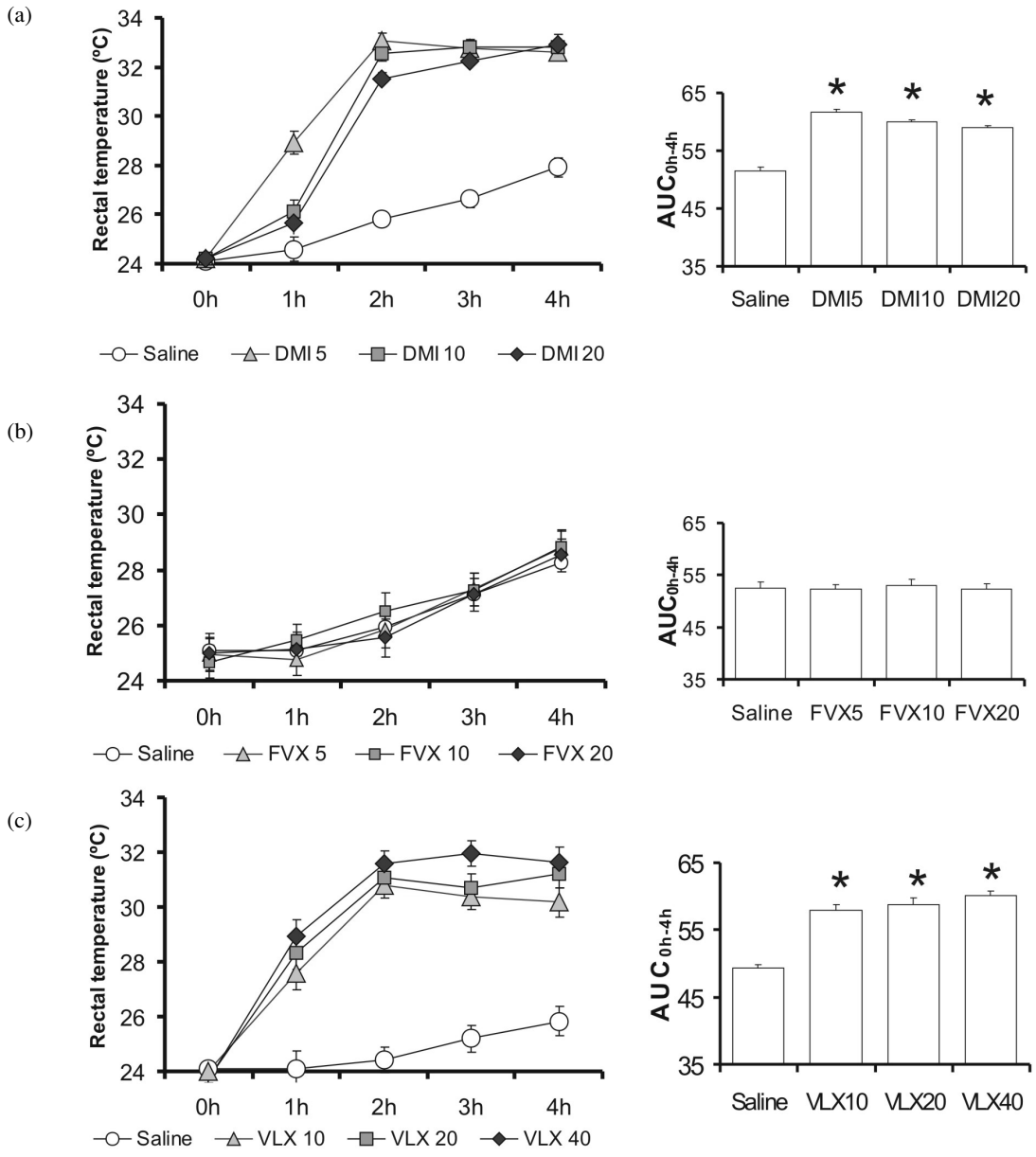

Figure 1 Effects of antidepressants: (a) desipramine (DMI), (b) fluvoxamine (FVX) and (c) venlafaxine (VLX) on reserpine-induced hypothermia in mice. Rectal temperature (°C) was measured 0, 1, 2, 3 and 4 h after drug treatment. Data are expressed as mean ± SE Repeated measures ANOVA showed significant effects of DMI ($P < 0.0001$) and VLX ($p < 0.0001$) but not of FVX ($p = 0{,}9783$) treatments. A *t*-Dunnet post-hoc test showed significant effects ($p < 0.05$) of DMI at 5, 10 and 20 mg/kg and VLX at 10, 20 and 40 mg/kg, respectively, versus saline-treated mice. Bars show the areas under the curve from 0–4 h after drug administration ($AUC_{0-4\ h}$). *$p < 0.05$ versus saline-treated mice

Results

Effect of desipramine, fluvoxamine and venlafaxine on rectal temperature (Fig. 1)

Desipramine (Fig. 1a) Reserpine induced a similar and severe decrease in rectal temperature in all the animals 18 h after administration [24.18 ± 0.05 °C; $F(3,27) = 0.171$, $p = 0.915$]. Rectal temperature measurements after desipramine administration showed effects of time (within-subjects, $p < 0.001$) and treatments (between-subjects, $p < 0.001$). Post-hoc analysis indicated that desipramine reversed hypothermia significantly at 5, 10 and, 20 mg/kg compared to saline-treated mice.

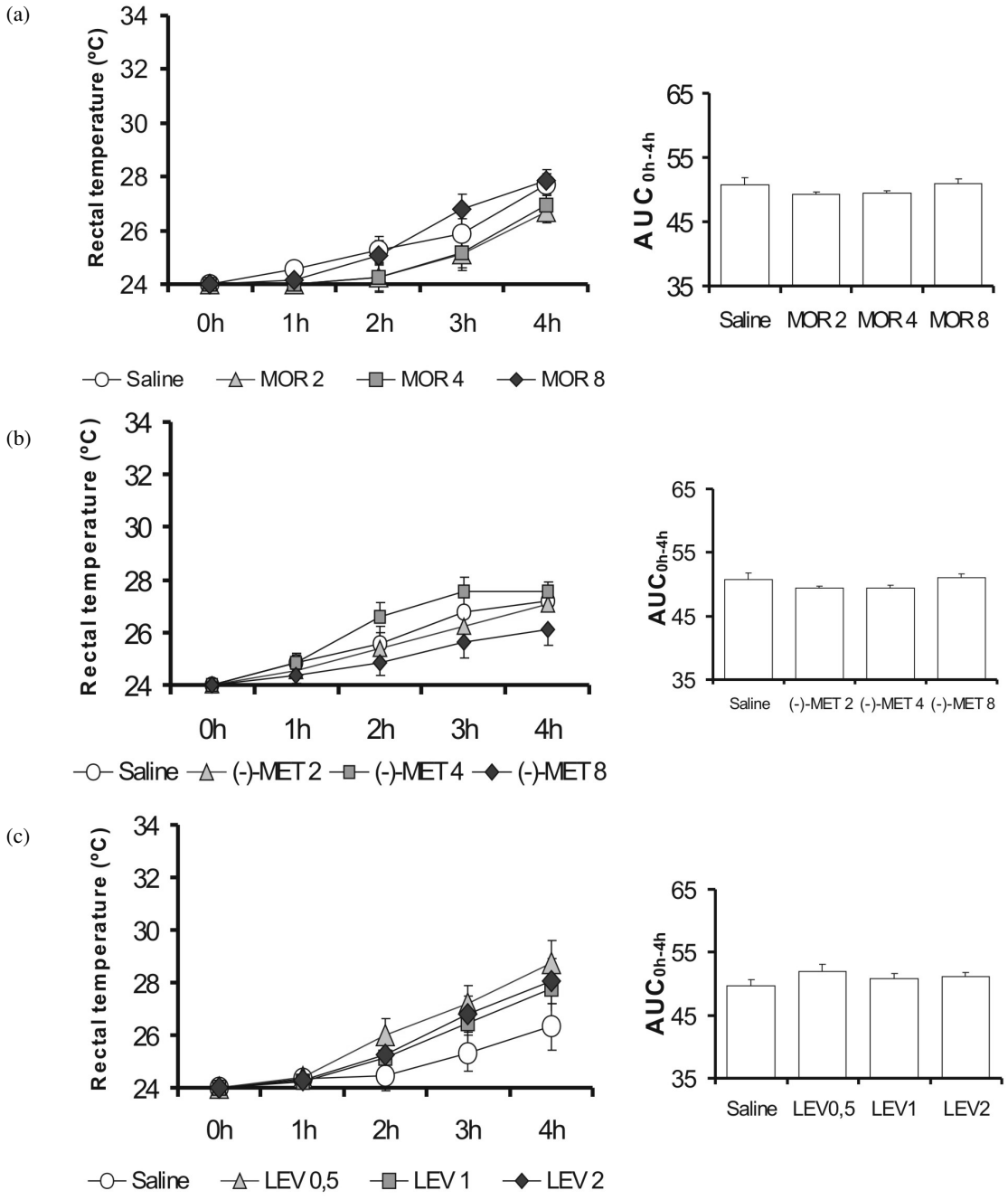

Figure 2 Effects of opiates: (a) morphine (MOR), (b) (−)-methadone [(−)-MET] and (c) levorphanol (LEV) on reserpine-induced hypothermia in mice. Rectal temperature (°C) was measured 0, 1, 2, 3 and 4 h after drug treatment. Data are expressed as mean ± SE Repeated measures ANOVA showed no-significant effects of MOR (p = 0.2006) (−)-MET (p = 0.1970) nor LEV (p = 0.2966) treatments. Bars show the areas under the curve from 0–4 h after drug administration ($AUC_{0-4\ h}$)

Fluvoxamine (Fig. 1b) All animals in the experimental groups were reserpinized to obtain a similar severe hypothermia [24.93 ± 0.29 °C; $F(3,36)$ = 0.088, p = 0.966]. Rectal temperature of mice was slightly enhanced by time course (effect within-subjects, $p < 0.001$) but not by treatment (no effect between-subjects, p = 0.978). Therefore, treatment with 5, 10 and 20 mg/kg of fluvoxamine did not increase temperature significantly compared to saline treatment.

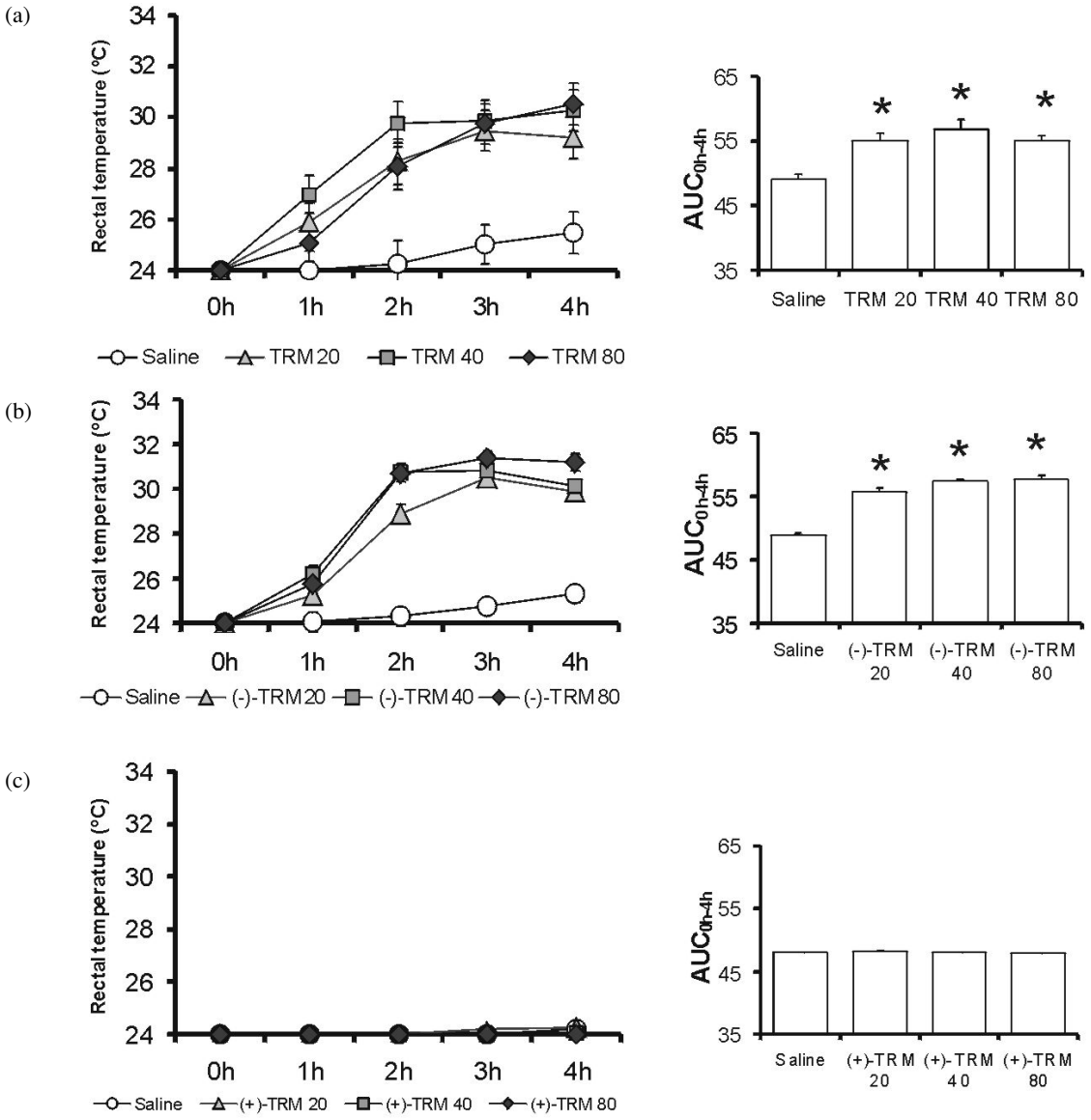

Figure 3 Effects of (a) tramadol (TRM) and its enantiomers, (b) (-)-tramadol [(−)-TRM] and (c) (+)-tramadol [(+)-TRM], on reserpine-induced hypothermia in mice. Rectal temperature (°C) was measured 0, 1, 2, 3 and 4 h after drug treatment. Data are expressed as mean ± SE Repeated measures ANOVA showed significant effects of TRM ($p < 0.0005$) and (−)-TRM ($p < 0.0001$) but not of (+)-TRM ($p = 0.5931$) treatments. A *t*-Dunnet post-hoc test show significant effects ($p < 0.05$) of TRM (20–80 mg/kg) and (−)-TRM (20–80 mg/kg) versus saline-treated mice. Bars show the areas under the curve from 0–4 h after drug administration ($AUC_{0-4\ h}$). *$p < 0.05$ versus saline-treated mice

Venlafaxine (Fig. 1c) The data show effects within- ($p < 0.001$) and between- ($p < 0.001$) subjects along the time. Post-hoc analyses showed that venlafaxine significantly reversed reserpine-induced hypothermia at 10, 20 and 40 mg/kg compared to saline-treated mice.

Effect of morphine (−)-methadone and levorphanol on rectal temperature (Fig. 2)

None of the opioids administered reversed reserpine-induced hypothermia significantly compared with saline treatment. Statistical analyses of morphine, (−)-methadone and levorphanol curves showed effects of time (within-subjects, $p < 0.0001$) but not of treatments (between-subjects, $p > 0.05$).

Effect of (±)-tramadol (−)-tramadol and (+)-tramadol on rectal temperature (Fig. 3)

Rectal temperature rose significantly along time in tramadol and (−)-tramadol-treated mice, but not in (+)-tramadol-treated mice

Table 1 Effects of antidepressants, opiates, tramadol and its enantiomers in palpebral ptosis in reserpinized mice

$AUC_{0-4\ h}$ values of palpebral ptosis time-course in reserpinized mice after drug treatment

Antidepressants			Opiates			Tramadol and enatiomers		
Drug	mg/kg	Mean ± SE	Drug	mg/kg	Mean ± SE	Drug	mg/kg	Mean ± SE
DMI	0	14.57 ± 0.48	MOR	0	15.94 ± 0.06	(±)-TRM	0	15.88 ± 0.13
	5	12.56 ± 0.77		2	15.75 ± 0.18		20	15.25 ± 0.25
	10	12.63 ± 0.59		4	15.06 ± 0.45		40	12.04 ± 1.31*
	20	12.59 ± 0.50		8	15.11 ± 0.41		80	9.96 ± 1.03*
FVX	0	15.75 ± 0.14	(–)-MET	0	16.00 ± 0.00	(+)-TRM	0	15.73 ± 0.21
	5	15.40 ± 0.17		2	15.31 ± 0.44		20	13.80 ± 0.43*
	10	13.73 ± 0.48*		4	15.48 ± 0.21		40	12.38 ± 0.56*
	20	13.75 ± 0.49*		8	13.61 ± 0.50*		80	12.48 ± 0.39*
VLX	0	15.73 ± 0.21	LEV	0	16.00 ± 0.00	(–)-TRM	0	15.67 ± 0.15
	10	12.15 ± 0.69*		0.5	15.46 ± 0.34		20	14.32 ± 0.41
	20	11.08 ± 0.61*		1	15.46 ± 0.45		40	14.12 ± 0.48*
	40	11.25 ± 0.68*		2	14.42 ± 0.78		80	12.21 ± 0.48*

Palpebral ptosis values were expressed as the area under the curve ($AUC_{0-4\ h}$) of time-course evolution, from 0–4 h, of palpebral ptosis score after drug administration. *$p < 0.05$ versus saline-treated mice.

compared to saline-treated mice. Statistical analyses showed effects of tramadol and (–)-tramadol treatments at the three doses tested (20, 40 and 80 mg/kg) ($p < 0.05$). (+)-Tramadol, did not reverse the severe hypothermia induced by reserpine at any of the administered doses.

Effects of antidepressants, opiates, tramadol and its enantiomers on reserpine-induced ptosis.

Antidepressants Repeated measures ANOVA showed that fluvoxamine and venlafaxine treatments significantly reduced palpebral ptosis compared to saline-treated mice, post-hoc analyses showed significant effects of fluvoxamine at 10 and 20 mg/kg and venlafaxine at 10, 20 and 40 mg/kg. Desipramine treatment slightly, but not significantly, diminished reserpine-induced ptosis (no effect between subjects, $p = 0.0841$).

Opiates Morphine (2–8 mg/kg) had no significant effect in reserpine-induced ptosis (no effect between subjects, $p = 0.1438$), nor did levorphanol (0.5–2 mg/kg) (no effect between subjects, $p = 0.1789$). However (–)-methadone reversed reserpine-induced ptosis (effect between subjects, $p < 0.0006$) significantly at 8 mg/kg.

Tramadol and its enantiomers Racemic tramadol decreased palpebral ptosis in reserpinized mice (effect between-subjects, $p < 0.0002$) significantly at 40 and 80 mg/kg versus saline control group. (+)-Tramadol significantly reversed ptosis (effect between-subjects, $p < 0.0001$) at all the doses tested (20–80 mg/kg), and (–)-tramadol reduced it (effect between-subjects, $p < 0.0001$) at 40–80 mg/kg versus saline control group.

Table 1 shows that racemic tramadol and its enantiomers significantly ($p < 0.05$) reduced palpebral $AUC_{0-4\ h}$ values of palpebral ptosis time-course in reserpinized mice as well as fluvoxamine and venlafaxine. (–)-Methadone was the only opiate that significantly reduced $AUC_{0-4\ h}$ values of palpebral ptosis time-course at 8 mg/kg.

Discussion

The reserpine test is a non-behavioural method that is considered as a classical test for the screening of potential antidepressants in mice. It is classified as a 'biochemical test' predictive of antidepressant effects (Askew, 1963; Bourin *et al*., 1983). It is based on early clinical studies demonstrating a tendency for hypertensive patients consuming reserpine to become depressed (Goodwin and Bunney, 1971; Simpson and Waal-Manning, 1971). Moreover, attention was initially drawn to the risk of suicide in some patients (Bunney and Davis, 1965).

Several tricyclics, as well as various atypical antidepressants, are able to inhibit the reserpine syndrome either completely or partially (Millan *et al*., 2001). However, owing to their mode of action, some relevant and clinically effective antidepressants do not produce a consistent effect in this test. Such is the case with clomipramine (Millan *et al*., 2001) despite its clinical efficacy (Lepine *et al*., 2000). Therefore, a negative effect obtained in the reserpine test does not rule out a positive antidepressant effect in man. However, it is well known that, to predict an antidepressant-like effect of a given compound, a battery of tests are required to be performed in mice and rats (Willner, 1990; Geyer and Markou, 1995).

In the case of tramadol, we demonstrate that both the racemic and the levo-enantiomer forms are able to antagonize the behavioural syndrome (rectal temperature and ptosis) induced by reserpine. It has been suggested that tramadol has many of the pre and postsynaptic neurochemical features of a conventional antidepressant (Hopwood *et al*., 2001). In this sense, autoradiographic studies have shown that the effects of chronic tramadol on cortical beta-adrenoceptors and $5\text{-}HT_{2A}$ receptor binding are similar to

those found for most classical antidepressants (Hopwood *et al*., 2001). Because we have previously demonstrated that tramadol elicits an antidepressant-type effect in the forced swimming test in mice (Rojas-Corrales *et al*., 1998) and in the learned helplessness test in rats (Rojas-Corrales *et al*., 2002), all of these data taken together indicate that tramadol, in addition to its analgesic effect, has a clear effect on some factors that may regulate emotionality.

The effects of racemic tramadol (noradrenaline and serotonin reuptake inhibitor) and the levo-enantiomer (noradrenaline reuptake inhibitor) were similar to that produced by venlafaxine, a dual noradrenaline/serotonin reuptake inhibitor, and also to that produced by desipramine, a specific noradrenaline reuptake inhibitor. However, fluvoxamine, a clinically effective antidepressant that selectively inhibits serotonin reuptake, did not show any effect in this test with respect to the reversal of reserpine-induced hypothermia. Interestingly, the (+)-tramadol enantiomer (serotonin reuptake inhibitor) only significantly antagonized reserpine-induced ptosis but had no effect on temperature.

However, and in contrast to some previous results in behavioural models (Tejedor-Real *et al*., 1995; Besson *et al*., 1996; Rojas-Corrales *et al*., 2002), opiates such as morphine, (–)-methadone and levorphanol did not antagonize the reserpine-induced decrease in rectal temperature. Concerning reserpine-induced ptosis, morphine and levorphanol did not have an effect and (–)-methadone was effective only at the highest doses used (8 mg/kg). It is noteworthy that, in addition to being opioid agonists, (–)-methadone and levorpharnol are able to inhibit the reuptake of serotonin and noradrenaline, as are fluvoxamine and (+)-tramadol. Thus, opioid activity plus serotonin-reuptake inhibitory properties is not sufficient to antagonize the reserpine syndrome completely.

Venlafaxine, a dual inhibitor of noradrenaline/serotonin reuptake, inhibits the reserpine-induced syndrome completely, as does the racemic form of tramadol. Some similarities are claimed to exist structurally and pharmacologically between venlafaxine and tramadol (Markowitz and Patrick, 1998). Indeed, both compounds have an analgesic effect on chronic pain (Pernia *et al*., 2000; Schnitzer *et al*., 2000). However, although both inhibit the reuptake of serotonin and noradrenaline at clinically effective doses, the opioid component of venlafaxine still remains a matter of discussion. It has been claimed that the antinociceptive effect of venlafaxine is influenced by the opioid system because naloxone was shown to reverse the antinociceptive effect of venlafaxine in a hot-plate analgesia meter study (Schreiber *et al*., 1999).

Some differences have been observed concerning the ability of the various compounds tested to inhibit reserpine-induced hypothermia or ptosis. It has been suggested that the model includes two bioassays because two parameters are measured (temperature and palpebral ptosis), each responding to different treatments. Therefore, α-adrenergic and serotoninergic agonists are able to reverse palpebral ptosis, and β-adrenergic agonists are able to reverse reserpine-induced hypothermia (Bourin *et al*., 1983).

If tramadol, as demonstrated, has an antidepressant-like effect, the site of action in the CNS seems to be important, because it could open the way for a series of new analgesics combining opioid and monoaminergic activities, thereby having a dual effect on both somatic and emotional aspects of pain. Studies performed *in vitro* show that (+)-tramadol blocks serotonin uptake and increases stimulated serotonin efflux in the nucleus raphe dorsalis, whereas (–)-tramadol increases stimulated norepinephrine efflux and prolongs norepinephrine uptake in the locus coeruleus (Bamigbade *et al*., 1997; Halfpenny *et al*., 1999). These two nuclei are highly involved in pain and depression (Gold *et al*., 1988; Wang and Nakai, 1994) and comprise the main candidates involved in the different dimensions of pain (Price, 2000). Hopwood (2001) showed that chronic tramadol produces an apparent sensitization of 5-HT_{1A} receptors modulating efflux in the nucleus raphe dorsalis, a finding identical to that for the serotonin-selective reuptake inhibitors paroxetine and fluoxetine. Moreover, we have already demonstrated the involvement of 5-HT_{1A} receptors in the analgesic effect of tramadol (Rojas-Corrales *et al*., 2000).

In conclusion, the present study shows that tramadol has a comparable effect to venlafaxine and desipramine, two clinically effective antidepressants, in the reserpine test in mice, which is a test predictive of antidepressant activity. In addition to other preclinical (Rojas-Corrales *et al*., 1998, 2002) and clinical (Shapira *et al*., 2001; Spencer, 2000) studies, our study suggests that tramadol has an inherent activity on emotionality and that this effect could have clinical repercussions on the affective component of pain.

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