Biphasic effect of apomorphine on rat nociception and effect of dopamine D_2 receptor antagonists

Teresa Pelissier [a,*], Claudio Laurido [b], Alejandro Hernandez [b], Luis Constandil [b], Alain Eschalier [c]

[a] *Programa de Biología Molecular y Clínica, Facultad de Medicina, Universidad de Chile, Chile*
[b] *Departamento de Biología, Facultad de Química y Biología, Universidad de Santiago de Chile, Santiago, Chile*
[c] *Equipe Neuro Psycho Pharmacologie, Laboratoire de Pharmacologie Médicale, Faculté de Médecine, Université de Clermont-1, Clermont-Ferrand, France*

Abstract

Studies on the effect of dopaminergic agonists in behavioral measures of nociception have gathered numerous but rather conflicting data. We studied the effects of the D_1/D_2 receptor agonist apomorphine, as well as the modulatory effects of (*S*)-(−)-sulpiride (selective D_2 receptor antagonist) and domperidone (peripheral D_2 receptor antagonist), on thermal, mechanical and chemical nociception on rats. Apomorphine induced a biphasic dose–response relationship, low doses producing hyperalgesia and high doses inducing antinociception. Tonic (chemical) pain was more sensitive to apomorphine than phasic (thermal and mechanical thresholds) pain. (*S*)-(−)-sulpiride, but not domperidone, fully antagonized the antinociceptive effect of apomorphine in all three measures of nociception, pointing to a participation of D_2 dopaminergic receptors for the antinociceptive action of apomorphine. Although spinal sites for dopaminergic ligands mechanistically may account for the effects observed, involvement of dopaminergic receptors of the forebrain could probably explain better the antinociceptive effects of apomorphine, especially in chemical tonic pain.

Keywords: Pain; Dopamine; Apomorphine; (*S*)-(−)-sulpiride; Domperidone; Tail-flick; Paw pressure; Formalin

1. Introduction

Experimental studies on the participation of the central dopamine systems in antinociception have gathered numerous but rather conflicting data. For instance, pharmacological interventions that increased dopaminergic neurotransmission (i.e. administration of L-3,4-dihydroxyphenylalanine (L-DOPA), dopamine receptor agonists with D_1/D_2 selectivity or dopamine reuptake blockers) have demonstrated to produce antinociception (Paalzow and Paalzow, 1975; Michael-Titus et al., 1990; Morgan and Franklin, 1991; Frussa-Filho et al., 1996; Bittencourt and Takahashi, 1997; Gilbert and Franklin, 2001), while other similar studies have reported no effect or even hyperalgesia (Tulunay et al., 1976; Gatch et al., 1998; Malhotra et al., 2000). Contradictory results have also been obtained when studying the modulatory effects of dopamine systems on opioid-induced analgesia, since potentiation (Dunai-Kovacs and Szekely, 1977; Nazarian et al., 1999) as well as inhibition (Zetler, 1983; Kamei and Saitoh, 1996) of the antinociceptive actions of opioids has been found after administration of dopaminergic agonists. Procedures that inhibit dopaminergic transmission in the central nervous system have also led to rather inconclusive results. In fact, administration of both dopamine D_1 and dopamine D_2 receptor antagonists may produce either antinociception (Zarrindast et al., 1999) or hyperalgesia (Paalzow, 1992). In addition, knock-out mice lacking dopamine D_1 (Becker et al., 2001) or dopamine D_2 (King et al., 2001) receptors displayed enhanced opioid analgesia, while rats with chemical lesions of dopaminergic terminals in limbic areas exhibit increased nociceptive reflexes, which may represent a hyperalgesic status (Saade et al., 1997). Taken together, the previous observations indicate that there is a considerable controversy with respect to the conditions under which antinociception induced by activation of central dopamine

* Corresponding author. Tel.: +56 2 678 6768; fax: +56 2 737 2783.
E-mail address: tpelissi@machi.med.uchile.cl (T. Pelissier).

receptors can be demonstrated. These include specificity and dosage of receptor agonists, type of behavioral pain testing and animal species, among other factors.

With regard to the dosage of receptor agonists, it has been suggested that low systemic doses (25–100 μg/kg) of the dopamine D_1/D_2 receptor agonist apomorphine produce hyperalgesia in the rat, whereas higher doses induce antinociception (Paalzow and Paalzow, 1983); a similar concentration-dependent opposing effect in nociception has been shown by utilizing L-DOPA as enhancer of dopamine neurotransmission (Paalzow, 1992). In contrast, other studies have shown that apomorphine significantly increased tail-flick latency only at low doses, while at high doses decreased it (Wesler and Frey, 1985). With respect to the type of behavioral pain testing, it has been reported that systemic apomorphine can induce antinociception in the hot plate test and in phenylbenzoquinone writhing, but not during testing of tail immersion in hot water, tail-flick, tail-clip, or electrical stimulation of the tail in mice (Gonzales-Rios et al., 1986), in the tail-flick and formalin tests but not in hot plate testing in rats (Dennis and Melzack, 1983), as well as in writhing, hot plate, tail-flick and inflamed tail-pinch procedures in rats and mice (Dunai-Kovacs and Szekely, 1977). Finally, with regard to the animal species, antinociceptive and hyperalgesic effects of either agonists or antagonists of dopamine receptors have been found in mice (Tulunay et al., 1976; Dunai-Kovacs and Szekely, 1977; Zetler, 1983; Michael-Titus et al., 1990; Frussa-Filho et al., 1996; Kamei and Saitoh, 1996; Bittencourt and Takahashi, 1997; Zarrindast et al., 1999; Malhotra et al., 2000) and rats (Paalzow and Paalzow, 1975; Dunai-Kovacs and Szekely, 1977; Paalzow and Paalzow, 1983; Morgan and Franklin, 1991; Paalzow, 1992; Gilbert and Franklin, 2001); the only study performed in monkeys revealed that dopamine reuptake inhibitors did not produce antinociception or increase antinociception induced by nalbuphine or morphine (Gatch et al., 1998). As a whole, these later observations show some agreement in that dopamine systems can modulate chemical tonic pain, whereas data concerning to dopaminergic modulation of phasic nociception of thermal and mechanical origin appear to be more inconsistent. Although spinal sites may account for the antinociceptive effects of dopaminergic ligands, it has recently been claimed that dopaminergic neurons of the mesolimbic system (originating from cell bodies within the ventral tegmental area and projecting to the ventral striatum/nucleus accumbens) are mostly involved in the antinociceptive effect of amphetamine and other dopaminergic agonists (see review of Wood, 2006).

In view of the various inconsistencies regarding the nature of pain that may be sensitive to acute administration of dopaminergic agonists and the dosage needed, the present study was aimed to clarify these aspects using a variety of doses of apomorphine as agonist for dopamine D_1/D_2 receptors, on rats submitted to three nociceptive tests: (a) the tail immersion test (phasic thermal nociception); (b) the hindpaw pressure test (phasic mechanical nociception); and (c) the formalin test (tonic chemical nociception). In addition, the antagonistic effects of (*S*)-(−)-sulpiride (a selective dopamine D_2 receptor antagonist) and domperidone (a peripheral dopamine D_2 receptor antagonist) on apomorphine-induced effects were also investigated.

2. Materials and methods

Sprague–Dawley juvenile male rats weighing 220–280 g were used throughout this study. Animals were housed 5 per cage under standard laboratory conditions and were given food and water ad libitum. Experiments were carried out on the afternoon (13:00 to 19:00 h) with a double blind design. The ethical guidelines for investigations of experimental pain in conscious animals recommended by the International Association for the Study of Pain (IASP) were followed (Zimmermann, 1983). In particular, the duration of the experiments was as short as possible, the number of animals involved was kept to a minimum and the animals were killed immediately after termination of each recording session.

2.1. Nociceptive tests

2.1.1. Thermal nociception

The tail immersion test was used, as described by Villanueva et al. (1985). Briefly, the rat tail was immersed into a hot-water bath at 46 °C by immobilizing the animal with both hands. Each rat had been previously adapted to this procedure, so that no fighting or tail movements occurred during 15 s (cut-off limit of hot-water immersion). When the animal reached the threshold of pain sensation, a tail-flick occurred. To repeat the stimulation in order to measure the pain threshold after drug administration, a 15-min period was allowed to elapse between two consecutive tail immersions, since drug-induced changes in tail temperature have been reported to modify tail-flick scores (Juszkiewicz-Donsbach and Levy, 1962). Tail temperature after administration of drugs was measured in a separated group of rats to assess this parameter as a potential factor in the results obtained. This was achieved by means of a thermocouple brought in contact with the dorsal surface of the tail and connected to an electrometer.

2.1.2. Mechanical nociception

The paw pressure test initially described by Randall and Sellito (1957) was used. The test consisted on the progressive application of an increasing point-pressure over the hindpaw, which evokes a pain reaction characterized by a fighting reaction (struggle) and a vocalization as manifestations of the pain sensation. These are integrated reactions with participation of supraspinal structures. To avoid injury, a cut-off value of 750 g was used.

2.1.3. Chemical nociception

The formalin test originally described by Dubuisson and Dennis (1977) was used. The procedure involved subcutaneous injection of dilute formalin (2.5%) into the plantar forepaw, after which the animal response was rated in four pain scores according to the following objective behavioral criteria: (0), the injected paw is not favored with respect to the non-injected paw; (1), the injected paw is favored but still rests in contact with the floor; (2), the injected paw is favored by lifting from the floor; (3), there is a licking, flinching or shaking of the injected paw.

2.2. Drugs administration

Each animal received only one dose of the following drugs: apomorphine hydrochloride (0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, and 6 mg/kg s.c.), (*S*)-(−)-sulpiride (20 and 60 mg/kg s.c.) and domperidone (5 mg/kg s.c.), all from Sigma-Aldrich, St. Louis. The drugs were freshly dissolved in saline and subcutaneously administered in a volume of 0.2 ml/100 g body weight. Additional groups receive saline as controls. The effects produced by the different drug treatments or saline were followed until 120 min (tail immersion and paw pressure tests) or 36 min (formalin test).

2.3. Analysis of results

Results were expressed as the time-course of effects induced by the drugs on tail-flick latency (thermal nociception), on vocalization threshold to paw pressure (mechanical nociception), and on formalin-induced pain scores (chemical nociception). To appreciate the global effect of drug treatments over the total testing period, an estimated area between the curve obtained under drug and the curve obtained under saline was calculated, and expressed as area under curve (AUC). This was calculated as AUC = ∑SUD − ∑SUS, where ∑SUD is the algebraic sum of the scores under drug (SUD).and ∑SUS is the algebraic sum of the scores under saline (SUS) over the total period of testing that followed drug administration.

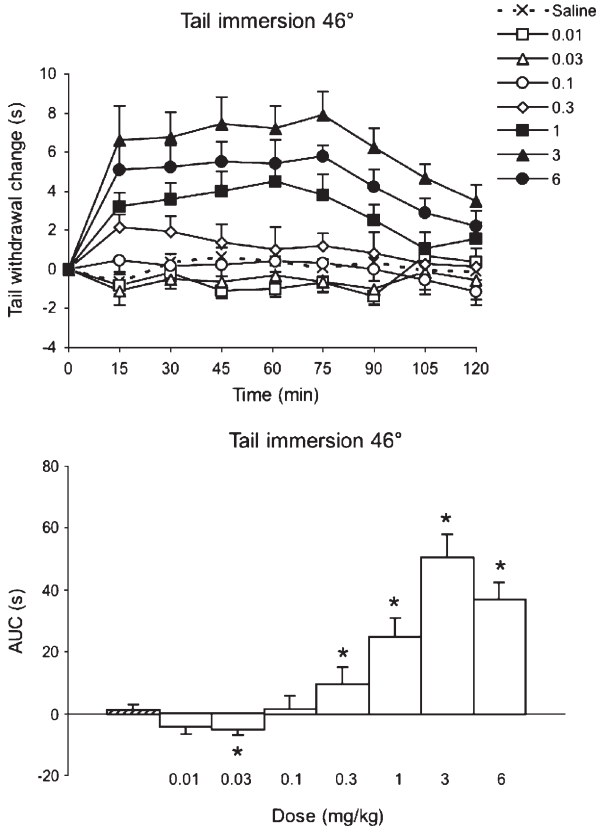

Fig. 1. *Upper panel*: Time-course of changes in tail-flick latency to hot-water immersion after apomorphine (0.01, 0.03, 0.1, 0.3, 1, 3 and 6 mg/kg s.c.) or saline. Apomorphine or saline was injected at 0 min. *Lower panel*: Effect of apomorphine on tail-flick latency to hot-water immersion, as revealed by change of the estimated areas under the curves (AUC). Values are means ± S.E.M. $N=6$ in each group. Asterisks represent a significant change (*$P<0.05$) compared to saline (striped bar) series (one-way ANOVA: P ANOVA <0.0001, $F_{(7,40)}=18.46$, followed by the Student–Newman–Keuls multiple comparisons test).

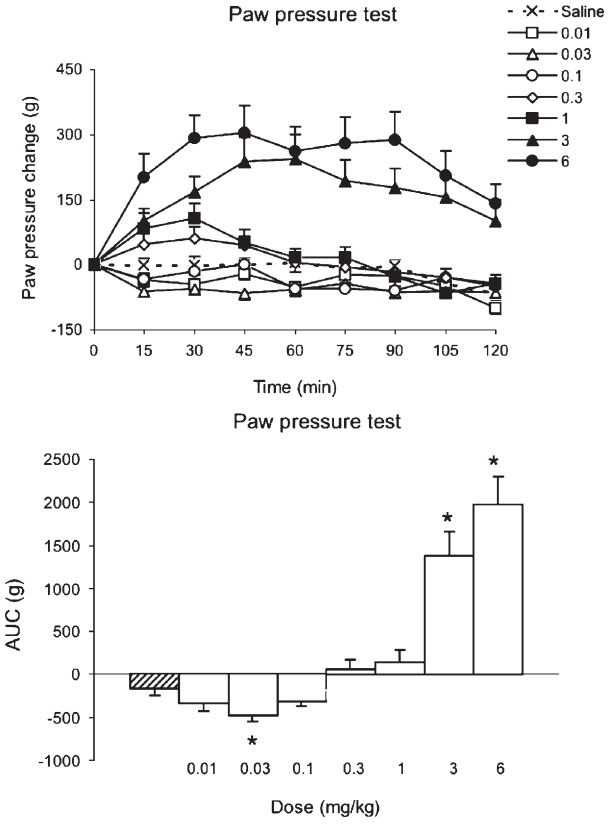

Fig. 2. *Upper panel*: Time-course of changes in vocalization threshold to graded paw pressure after apomorphine (0.01, 0.03, 0.1, 0.3, 1, 3 and 6 mg/kg s.c.) or saline. Apomorphine or saline was injected at 0 min. *Lower panel*: Effect of apomorphine on vocalization threshold to graded paw pressure, as revealed by changes of the estimated areas under the curves (AUC). Values are means ± S.E.M. $N=6$ in each group. Asterisks represent a significant change (*$P<0.05$) compared to saline (striped bar) series (one-way ANOVA: P ANOVA <0.0001, $F_{(7,40)}=25.49$ followed by the Student–Newman–Keuls multiple comparisons test).

Results obtained using apomorphine alone were expressed as means ± S.E.M. and subjected to a one-way analysis of variance (ANOVA) followed by the Student–Newman–Keuls multiple comparisons test to analyze the effects produced by the different doses of each drug or saline (InStat GraphPad 3.0, GraphPad Software Inc., San Diego, CA, USA). In order to analyze the effects of dopaminergic antagonists on apomorphine-treated rats, two-way ANOVA followed by the Bonferroni multiple comparisons test was used. When a P-value in the ANOVAs was less than 0.05, the post-hoc multiple comparisons test was used with a confidence interval of 95%.

3. Results

3.1. Effects of apomorphine

In the tail immersion test, a different response was observed according to the dose of apomorphine administered. Fig. 1

shows that with 0.01 mg/kg of apomorphine no significant change in tail-flick latency was observed, while the dose of 0.03 mg/kg produced a significant decreased latency in tail withdrawal indicating a hyperalgesic effect. Dose of 0.1 mg/kg did not produce any change, but 0.3, 1, 3 and 6 mg/kg of apomorphine increased dose-dependently the latency of the tail withdrawal indicating a hypoalgesic effect (P ANOVA < 0.0001, $F_{(7,40)} = 18.46$). No significant differences were found in the tail temperature of control and apomorphine-treated rats.

A similar biphasic response was also demonstrated using the paw pressure test (Fig. 2): a decreased latency with 0.03 mg/kg (hyperalgesia), no change with 0.1 and 0.3 mg/kg, and an anti-nociceptive effect (hypoalgesia) with the high dose of apomorphine, 3 and 6 mg/kg (P ANOVA < 0.0001, $F_{(7,40)} = 25.49$).

In the formalin test, apomorphine was more active, since the shift of the biphasic effect from hyperalgesia to hypoalgesia was observed with low doses (Fig. 3). The dose of 0.001 mg/kg produced hyperalgesia, as revealed by the significant enhancement of both phases of the formalin-induced painful behavior.

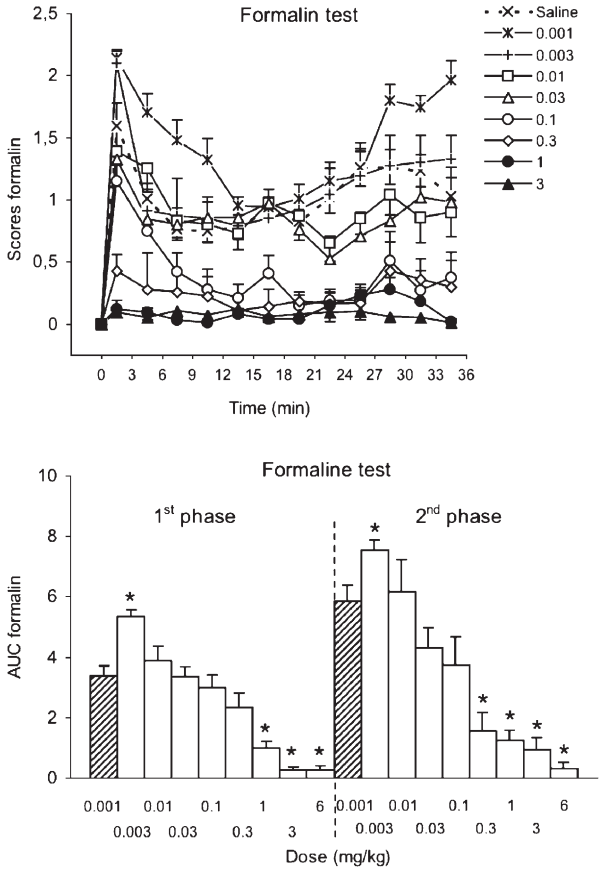

Fig. 3. *Upper panel*: Time-course of changes in formalin-induced pain scores after apomorphine (0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, and 3 mg/kg s.c.) or saline. Apomorphine or saline was injected at 0 min. *Lower panel*: Effect of apomorphine on formalin-induced pain scores phase 1 and phase 2, as revealed by change of the estimated areas under the curves (AUC). Values are means ± S.E.M. $N = 6$ in each group. Asterisks represent a significant change (*$P < 0.05$) compared to saline (striped bar) series (one-way ANOVA: P ANOVA < 0.0001, $F_{(8,45)} = 27.14$ for the first phase and P ANOVA < 0.0001, $F_{(8,45)} = 17.69$ for the second phase, followed by the Student–Newman–Keuls multiple comparisons test).

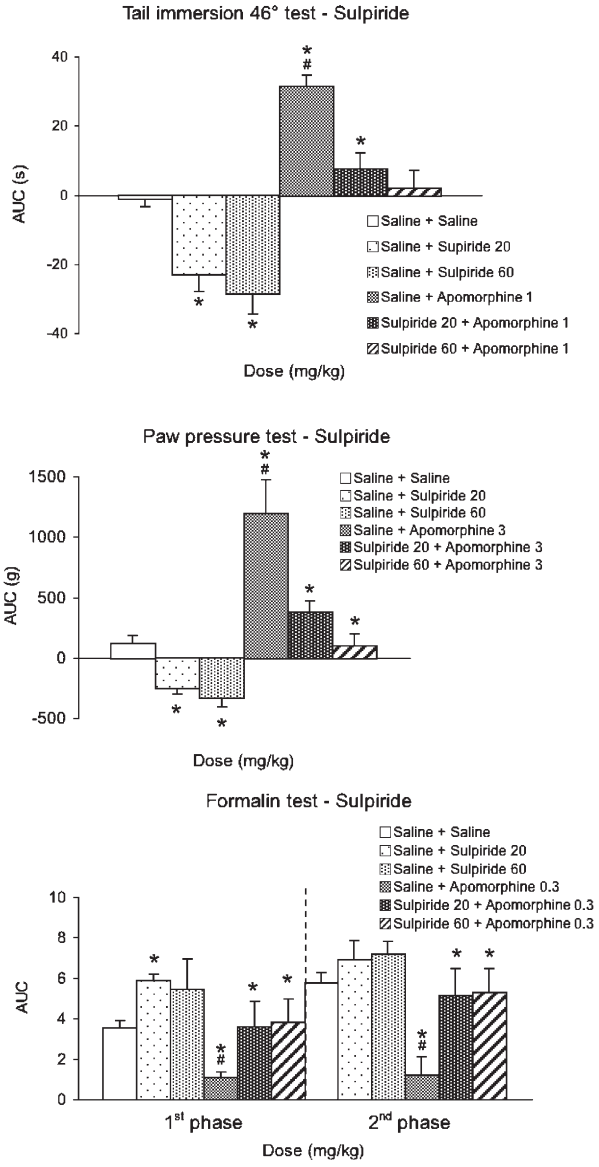

Fig. 4. Antagonistic action of (*S*)-(−)-sulpiride (20 and 60 mg/kg s.c.) on antinociceptive effects induced by apomorphine in the tail immersion (upper panel), paw pressure (middle panel), and formalin (lower panel) tests. (*S*)-(−)-sulpiride or saline was administered 90 min before the administration of apomorphine. Drug-induced effects were expressed as revealed by estimated areas under the curves (AUC). Values are means ± S.E.M. $N = 6$ in each group. Asterisks represent a significant effect of (*S*)-(−)-sulpiride (*$P < 0.05$) compared to saline series. The symbol # represents a significant effect of 1 mg/kg of apomorphine compared to saline (open bar). Two-way ANOVA followed by the Bonferroni multiple comparisons test: tail immersion test (P ANOVA < 0.0001, $F_{(1,10)} = 67.55$), 3 mg/kg of apomorphine in the paw pressure test (P ANOVA < 0.0001, $F_{(1,10)} = 77.94$), and 0.3 mg/kg of apomorphine in the formalin test (P ANOVA = 0.0102, $F_{(1,10)} = 7.524$ for the first phase; P ANOVA = 0.0016, $F_{(1,10)} = 12.07$ for the second phase).

The doses of 0.003, 0.01 and 0.03 mg/kg did not have any effect on both phases. The dose of 0.1 mg/kg significantly diminished the second phase but not the first, and the doses of 0.3, 1 and 4 mg/kg completely suppressed both phases (P ANOVA < 0.0001, $F_{(8,45)} = 27.14$ for the first phase; P ANOVA < 0.0001, $F_{(8,45)} = 17.69$ for the second phase).

3.2. Effects of dopamine receptor antagonists

3.2.1. (S)-(−)-sulpiride

The antagonistic action of (*S*)-(−)-sulpiride on apomorphine-induced effects was tested by using the three nociceptive tests (Fig. 4). (*S*)-(−)-sulpiride was administered 90 min before the administration of apomorphine, at doses of 20 and 60 mg/kg s.c. Both doses of (*S*)-(−)-sulpiride significantly antagonized the antinociceptive effect of 1 mg/kg of apomorphine in the tail immersion test (P ANOVA < 0.0001, $F_{(1,10)}$ = 67.55), 3 mg/kg of apomorphine in the paw pressure test (P ANOVA < 0.0001, $F_{(1,10)}$ = 77.94), and 0.3 mg/kg of apomorphine in the formalin test (P ANOVA = 0.0102, $F_{(1,10)}$ = 7.524 for the first phase; P ANOVA = 0.0016, $F_{(1,10)}$ = 12.07 for the second phase). (*S*)-(−)-sulpiride had a hyperalgesic effect by its own (Fig. 4).

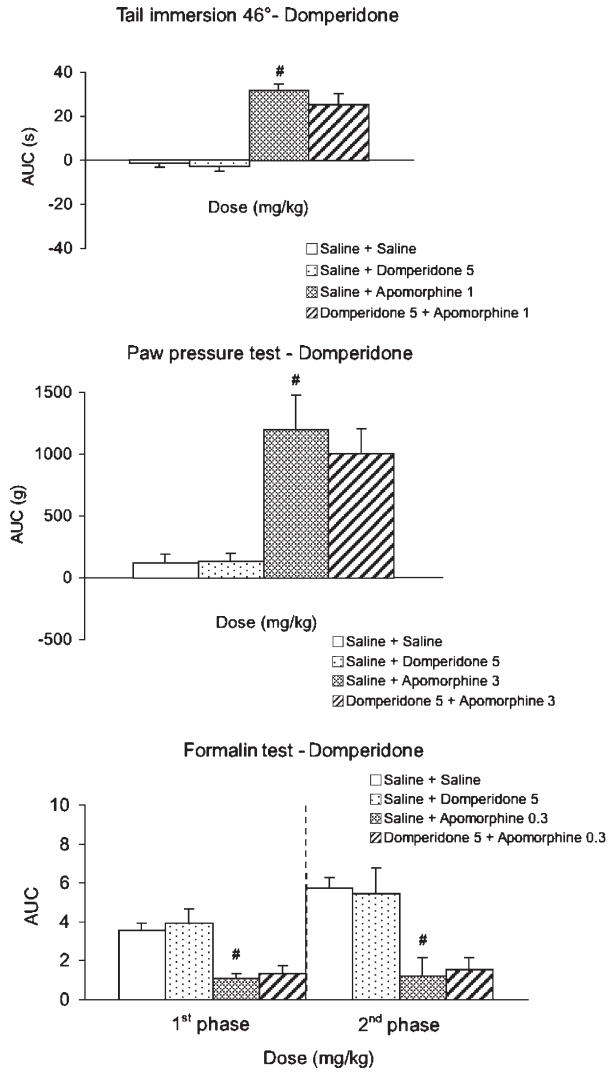

Fig. 5. Effect of domperidone (5 mg/kg s.c.) on the antinociceptive action induced by apomorphine in the tail immersion (upper panel), paw pressure (middle panel), and formalin (lower panel) tests. Domperidone or saline was administered 90 min before the administration of apomorphine. Drug-induced effects were expressed as revealed by estimated areas under the curves (AUC). Values are means ± S.E.M. N = 6 in each group. Domperidone produced no significant effects compared to saline series (P > 0.05). The symbol # represents a significant effect of 1 mg/kg of apomorphine compared to saline (open bar). Two-way ANOVA followed by the Bonferroni multiple comparisons test: P ANOVA = 0.2468, $F_{(1,10)}$ = 1.423 for the tail immersion test; P ANOVA = 0.5231, $F_{(1,10)}$ = 0.420 for the Randall–Selitto test; P ANOVA = 0.5126, $F_{(1,10)}$ = 0.4443 for the formalin test phase 1; P ANOVA = 0.9912, $F_{(1,10)}$ = 0.0001 for the formalin test phase 2.

3.2.2. Effect of domperidone

Domperidone 5 mg/kg s.c., administered 60 min prior to apomorphine, did not significantly antagonize the antinociceptive effect of apomorphine in the three nociceptive tests (P ANOVA = 0.2468, $F_{(1,10)}$ = 1.423 for the tail immersion test; P ANOVA = 0.5231, $F_{(1,10)}$ = 0.420 for the Randall–Selitto test; P ANOVA = 0.5126, $F_{(1,10)}$ = 0.4443 for the formalin test phase 1; P ANOVA = 0.9912, $F_{(1,10)}$ = 0.0001 for the formalin test phase 2). This dose of domperidone had no effect by its own on nociceptive scores (Fig. 5).

4. Discussion

The previous results show that apomorphine administered by subcutaneous route induced a biphasic dose–response relationship in thermal, mechanical and chemical nociception, low doses producing hyperalgesia and high doses inducing hypoalgesia or antinociception. It is known that dopamine and some of its agonists can induce biphasic dose–response curves for a variety of endpoints, such as locomotion, blood pressure, heart rate, memory and adenylate cyclase activity (for review see Calabrese, 2001). The first demonstration that parenteral administration of apomorphine results in a concentration-dependent biphasic effect on nociception was described by Paalzow and Paalzow (1983) using supramaximal electrical stimulation of the tail in rats. Biphasic effects of dopaminergic agonists could possibly be related to concentration-dependent activity of different types of dopamine receptors, autoreceptors being sensitive to low dopamine or dopamine agonist concentration, and postsynaptic dopamine D_1/D_2 receptors being stimulated only by high concentration of these ligands (Calabrese, 2001). This interpretation and the present observations do not support the notion that low doses of apomorphine are related to antinociception and high doses to hyperalgesia, as claimed by Wesler and Frey (1985). Whether the biphasic effect of apomorphine in nociception is also related to effects of the drug in different brain sites playing distinctive (and perhaps opposed) roles in pain modulation is presently unclear. In this regard, it has been reported that rat intrathecal administration of dopamine, apomorphine or selective dopamine D_2 receptor agonists, results in antinociception in the tail-flick test (Barasi and Duggal, 1985; Barasi et al., 1987; Liu et al., 1992), in the hot plate test and acetic acid writhing (Jensen and Yaksh, 1984), as well as in carrageenan hyperalgesia (Gao et al., 2001). Interestingly, none of these reports showed biphasic effects of the dopamine agonists, suggesting that endogenous dopamine has only inhibitory effects in pain transmission at the spinal cord level. However, there are reports claiming that intrathecal administration of apomorphine depressed tail-flick reflex only in spinalized rats, or in rats with lesions of either the dorsal columns or the medioventral parts of the lateral funiculi, but not in intact rats (Jensen and Smith, 1982, 1983; Jensen et al., 1984). The former may suggest that dopamine plays a spinal inhibitory role only in

the absence of descending bulbospinal influences, at least regarding to thermal nociception. On the other hand, unchanged nociception has been observed after intracerebroventricular administration of apomorphine (Jensen and Yaksh, 1984; Barasi and Duggal, 1985), whereas dose-dependent antinociception seems to be produced by injection of dopamine and apomorphine into the nucleus *raphe magnus* (Phillips et al., 1986). More recently, reports on the analgesic properties of infusion of dopamine receptor agonists or dopamine reuptake inhibitors into the nucleus *accumbens septi* (Altier and Stewart, 1993, 1998), into the dorsolateral striatum (Magnusson and Fisher, 2000), or into the rostral agranular insular cortex (Burkey et al., 1999), revealed that these supraspinal regions may be importantly involved in antinociceptive effects of central dopamine systems. Since dopaminergic neurons of the ventral tegmental area are specifically excited by reward but not by aversive stimuli (Ungless et al., 2004), it seems likely that antinociception induced by infusion of dopamine and dopaminergic agonists into the limbic forebrain may represent part of a pain-suppressing system triggered by activation of brain rewarding circuits (Altier and Stewart, 1999).

Interestingly, the present results showed that apomorphine produced antinociception against formalin-induced pain at doses one order of magnitude lower than those required for inhibiting hot water-induced tail-flick and paw pressure-induced vocalization. Thus, it seems apparent that chemical nociception is more sensitive to apomorphine than thermal and mechanical pain. In this regard, differential sensitivity of tonic pain (chemical or inflammatory) versus phasic pain (thermal and mechanical thresholds) to a variety of drugs possessing antinociceptive properties, such as *N*-methy-D-aspartate (NMDA) receptor antagonists (Eisenberg et al., 1993; Vaccarino et al., 1997), opioids (McCormack et al., 1998), monoamine reuptake blockers (Wang et al., 1999), and non-steroidal anti-inflammatory drugs (Hummel et al., 1995) has been reported. The underlying molecular/cellular mechanisms by which tonic chemical nociception would be more sensitive to many antinociceptive drugs than phasic thermal/mechanical nociception are not yet fully understood. They mainly seem to be related to the way of processing the nociceptive signaling (tonic versus phasic) while is being carried to higher brain centers, rather than to the nature of the painful stimulus. For instance, high rate of noxious cutaneous heating is mediated mainly by Aδ nociceptors, while low rate of noxious cutaneous heating is recruited by C polymodal nociceptors (for review see Yeomans and Proudfit, 1996; Yeomans et al., 1996; McCormack et al., 1998), being particularly sensitive to opioids (for review see McCormack et al., 1998), despite the same thermal nature of both stimulating procedures. As pointed out by Altier and Stewart (1999) and Wood (2006), activation of mesolimbic dopamine neurons, arising from cell bodies of the ventral tegmental area and projecting to the *nucleus accumbens*, plays an important role in mediating suppression of tonic pain but is not clearly implicated in modulating phasic nociception.

The present results also show that the selective dopamine D_2 receptor antagonist (*S*)-(−)-sulpiride, but not the peripheral dopamine D_2 receptor antagonist domperidone, fully reversed the antinociceptive effect of apomorphine in the thermal, mechanical and chemical nociception tests utilized. Thus, it is apparent that only central dopaminergic receptors of D_2 type are mostly involved in the effects of apomorphine in nociception. In addition, since the doses of apomorphine to be antagonized were chosen, in some extent, on the basis of producing equianalgesic effects in the different algesimetric tests utilized, it seems not surprising that (*S*)-(−)-sulpiride showed a rather equivalent antagonizing efficacy in all of these tests. Previous studies have shown that administration of (*S*)-(−)-sulpiride antagonized the antinociceptive effect of apomorphine in tail-flick responses elicited in lightly anesthetized rats (Barasi et al., 1987), and induced hyperalgesia in a nociceptive behavioral test involving electric stimulation of the rat tail (Paalzow, 1992), which fully agree with the results reported in the present study. In addition (*S*)-(−)-sulpiride, but not the D_1 dopaminergic receptor antagonist SCH 23390, antagonized antinociception induced in mice by L-DOPA (Shimizu et al., 2004), which further supports the involvement of dopamine D_2 receptors in the antinociceptive mechanisms triggered by endogenous dopamine.

In conclusion, acute administration of parenteral apomorphine induced a biphasic dose–response relationship in thermal, mechanical and chemical nociception, low doses producing hyperalgesia and high doses inducing antinociception. Tonic (chemical) pain was more sensitive to apomorphine than phasic (thermal and mechanical thresholds) pain, the shift of the biphasic effect from hyperalgesia to hypoalgesia being observed with low doses of apomorphine, a feature that could be on the basis of many of the contradictory results reported in the literature regarding to the effects of dopaminergic agonists in various nociceptive behaviors. The biphasic response produced by apomorphine in all the algesimetric tests studied, could perhaps explain the contradictory data found in the literature regarding the effects of dopaminergic antagonists on pain testing, since hypoalgesia or hyperalgesia (or even no effect) can be produced depending on the dose administered. The central D_2 dopaminergic antagonist (*S*)-(−)-sulpiride, but not the peripheral dopamine D_2 antagonist domperidone, fully antagonized the antinociceptive effect of apomorphine in all the three measures of nociception, pointing to a participation of dopamine D_2 receptors at least for the antinociceptive action of dopaminergic agonists. Although spinal sites for dopaminergic ligands mechanistically may account for the effects observed, involvement of dopaminergic receptors of the forebrain could probably explain better the antinociceptive effects of apomorphine, especially in chemical tonic pain.

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