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# Characterization of the analgesic properties of nomifensine in rats

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**Abstract**

The analgesic properties of the catecholamine uptake inhibitor nomifensine were investigated in the tail immersion, hot plate and formalin tests. Systemic administration of nomifensine produced analgesia only in the formalin test. The analgesia was dose-dependent (0.625–5 mg/kg), and the highest dose completely abolished nociceptive behaviors induced by 2% formalin. The analgesia was not affected by the opioid antagonist naltrexone (2.5–40 μg sc) but was dose-dependently reversed by the D2 antagonist eticlopride (181.3–270 μg/kg ip). Neither naltrexone nor eticlopride affected formalin pain scores. Nomifensine analgesia appears to be dopamine-mediated but independent of opioid mechanisms. © 2001 Elsevier Science Inc. All rights reserved.

*Keywords:* Dopamine; Formalin test; Tail immersion; Hot plate; Analgesia; Naltrexone; Eticlopride; Nomifensine

## 1. Introduction

Cocaine and amphetamine are known to produce powerful analgesia in animals and humans (Franklin, 1999). In animals, amphetamine and cocaine also enhance morphine analgesia (Kauppila et al., 1992; Sasson et al., 1986) and reduce morphine-induced side effects, such as bradypnoea, bradycardia and hypolocomotion/sedation (Kauppila et al., 1992). Potentiation of morphine analgesia has also been reported with methylphenidate in rats (Dalal and Melzack, 1998) and in humans with advanced cancer pain (Bruera et al., 1992). The analgesic effect of stimulants is different from opioid analgesia. Opioids are antinociceptive for all types of noxious stimuli. Amphetamine and some related compounds attenuate responses to pain originating from injury or disease (Franklin, 1999; Morgan and Franklin, 1990, 1991), but they do not reliably depress brain stem or spinal nociceptive reflexes (Morgan and Franklin, 1990; Pertovaara et al., 1988), though cocaine has been reported to increase tail flick latency (Kiritsy-Roy et al., 1994; Ushijima and Horita, 1993).

Amphetamine and cocaine are indirect monoamine agonists. They increase the synaptic availability of dopamine, noradrenaline and serotonin by blocking their reuptake or stimulating their release (Feldman et al., 1997). Serotonin and noradrenaline participate in inhibition of nociceptive reflexes in the spinal cord (Fields et al., 1991), but the analgesic effect of amphetamine has been attributed to dopamine (Drago et al., 1984; Lin et al., 1989; Morgan and Franklin, 1991). The analgesic activity of more selective monoamine uptake inhibitors has not been documented. Therefore, we have investigated the analgesic effect of the selective catecholamine uptake inhibitor nomifensine in three animal models of pain.

## 2. Methods

This study was approved by the Ethics Subcommittee of the University Animal Care Committee, McGill University, and carried out according to guidelines of the Canadian Council on Animal Care.

### 2.1. Animals

Male Wistar albino rats (Charles River, St. Constant, PQ, Canada, 200–225 g) were housed in groups of two or three in a room maintained at 22±0.5°C with a 12-h light/dark cycle. Food (Purina Rat Chow) and water were freely available.

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### 2.2. Drugs

Nomifensine maleate (Research Biochemical International, Natick, MA, USA) was dissolved in a vehicle of 0.9% saline acidified with 0.1 N HCl, adjusted pH to 7 with NaOH. The opioid antagonist naltrexone hydrochloride (Research Biochemical International) was dissolved in 0.9% saline and solutions were stored at room temperature in light protecting vials. The antagonist of the dopamine D2 receptor, eticlopride hydrochloride (Research Biochemical International) was dissolved in 0.9% saline and solutions were stored at 4°C. For the formalin test, 37% formaldehyde was dissolved in saline for a final concentration of 2% formalin.

### 2.3. Apparatus, testing procedures and injections

Nociception was assessed using the tail immersion version of the tail flick test (Janssen et al., 1963), the hot plate test and the formalin test. For the tail immersion test, rats were brought to the testing room the day prior to testing. Rats were briefly handled and a line was drawn at the distal 5 cm of the tail. The tail immersion test consisted of dipping the tail of the rat into a bath containing water kept at 54°C. The latency for the rat to remove its tail from the hot bath was recorded. A cut-off of 10 s was imposed to avoid tissue damage.

The hot plate apparatus constituted of an aluminum floor ($35 \times 35$ cm) heated to 54°C, surrounded by clear Plexiglas walls (30 cm high). The latency to display either hindpaw licking or flinching/slapping was recorded (Carter, 1991). The animal was removed from the apparatus as soon as a response occurred or after 25 s.

The tail immersion and hot plate tests were carried out in the same session, so that each tail immersion dip was immediately followed by a hot plate test. Baseline latencies were obtained for each rat prior to any drug administration. Then, rats were randomly assigned to a dose of nomifensine. Nomifensine was administered subcutaneously (sc) in a dose of either 0.625, 1.25, 2.5, 5 or 10 mg/kg body weight, 30 min before testing. Tail and paw withdrawal latencies were assessed at 10-min intervals for 1 h starting 30 min after nomifensine administration.

The formalin test was carried out in $30 \times 30 \times 30$ cm clear Plexiglas cubicles with a mirror mounted at 45° beneath the floor to allow unobstructed view of the paws. Animals were habituated to the cubicles for 20–30 min/day, for 4 consecutive days before formalin testing began. Habituation was carried out because stress induced by a novel environment, such as the formalin boxes, decreases pain scores (Abbott et al., 1986). On testing days, nomifensine was administered subcutaneously in a dose of either 0.625, 1.25, 2.5 or 5 mg/kg body weight, 30 min before testing began. Control rats were injected with the vehicle instead of nomifensine. Five minutes after nomifensine injection, 50 μl of 2% formalin was injected subcutaneously into the plantar surface of one hindpaw. For experiments assessing the effects of antagonists, naltrexone was injected subcutaneously in a dose of either 2.5, 5, 10, 20 or 40 μg/kg, 5 min before nomifensine administration. Eticlopride was administered intraperitoneally (ip) in a dose of either 181.3, 221.3 or 270 μg/kg, 30 min before nomifensine (60 min before formalin test). Drug injection times were chosen to ensure testing occurred during the period of optimal drug effect. Naltrexone is rapidly absorbed and has a long duration of action (Verebey and Mule, 1975). The effects of eticlopride are typically observed 1–3 h after its administration, and intraperitoneal administration results in faster absorption of the drug compared to subcutaneous administration. Pilot studies showed the effects of eticlopride were detectable 60 min after intraperitoneal injection.

Only the second phase of formalin-induced behaviours (inflammatory pain) was rated, and animals were observed at the maximum level of formalin pain, from 25 to 50 min after formalin administration (Abbott et al., 1995). Rating of formalin-induced behaviours was performed according to the method of Dubuisson and Dennis (1977). The time spent displaying each of the following behaviours was recorded: normal weight bear on the injected paw (0), favouring (1), lifting (2) and licking and biting (3) the affected paw. A mean pain score with a possible value between 0 (no pain) and 3 (maximum pain) was obtained for each rat (Morgan and Franklin, 1991). This score increases linearly with log formalin concentration (Abbott et al., 1995).

### 2.4. Data analysis

Groups were compared using the analysis of variance (ANOVA) procedure, followed by Scheffe post-hoc tests.

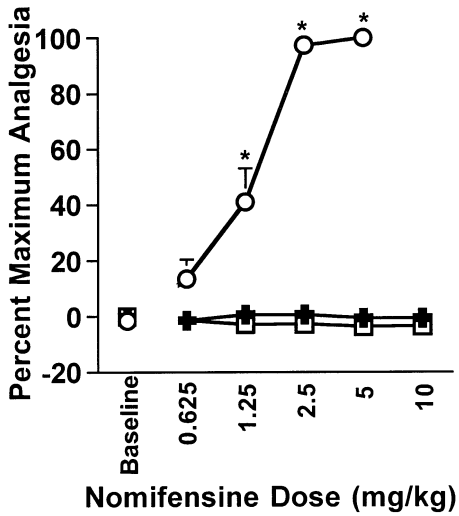


Fig. 1. The effect of nomifensine on nociceptive behavior in the formalin (circle), tail immersion (triangle) and hot plate (square) tests in rats. Baseline refers to pretest for the tail immersion and hot plate tests and to rats treated with 2% formalin and vehicle for the formalin test. Error bars are S.E.M. Asterisks indicate a significant difference from baseline.

The data were transformed to percent maximum analgesia (MPA) by the formula: $(E - E_{min}/E_{max} - E_{min}) \times 100$. For both the tail immersion and hot plate tests, the minimum effect of nomifensine ($E_{min}$) was the average baseline latency of all rats (tail immersion = 2.6 s and hot plate = 5.8 s) and the cut-off imposed was used as $E_{max}$ (tail immersion = 10 s and hot plate = 25 s). In the formalin test, $E_{min}$ was 2.2 (the mean pain score of rats treated with 2% formalin) and $E_{max}$ was 0 (no pain-related behaviors).

## 3. Results

Nomifensine was devoid of analgesic effects in the tail immersion and hot plate tests (Fig. 1). However, nomifensine produced a dose-dependent analgesia in the formalin test [$F(4,21) = 36.4$, $P < .05$]. The doses of 1.25, 2.5 and 5 mg/kg nomifensine produced greater analgesia compared to saline-treated animals (Scheffe critical value 0.7, $P < .05$) (Fig. 1). The dose of 2.5 mg/kg almost completely abolished pain-related behaviors, and all animals treated with 5 mg/kg showed no pain. Fig. 2 shows the effects of naltrexone and eticlopride on nomifensine analgesia and formalin pain. Nomifensine analgesia was not affected by any dose of naltrexone tested. However, the D2 antagonist eticlopride dose-dependently reversed nomifensine analgesia [$F(3,15) = 39.7$, $P < .05$]. The highest dose of eticlopride (270 μg) completely eliminated nomifensine analgesia. To confirm that the antagonism of nomifensine analgesia was not confounded by an effect on formalin pain, the effects of naltrexone and eticlopride on formalin pain were examined. Neither naltrexone nor eticlopride significantly affected formalin pain compared to rats treated with 2% formalin and vehicle systemically (Fig. 2).

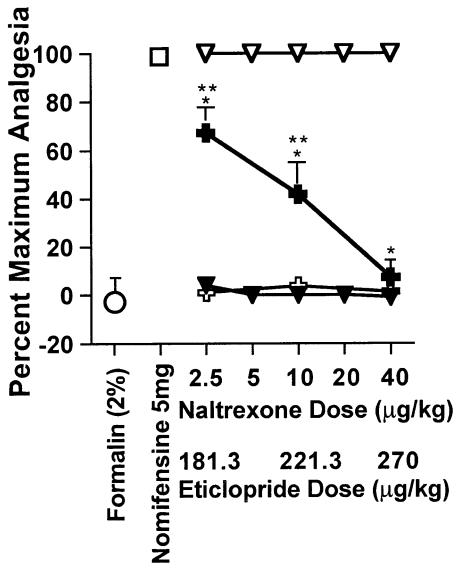


Fig. 2. Dose–effect relations for the influence of naltrexone and eticlopride on formalin pain and on the inhibition of formalin pain by nomifensine. Naltrexone/formalin = filled triangle; eticlopride/formalin = open square; naltrexone/nomifensine = open triangle; eticlopride/nomifensine = filled square. One asterisk indicates MPA significantly lower than MPA induced by nomifensine (5 mg/kg). Two asterisks indicate MPA significantly higher than MPA of rats treated with 2% formalin and vehicle.

## 4. Discussion

Nomifensine produced analgesia in the formalin test, but not in the tail immersion nor in the hot plate tests. These data are consistent with previous evidence that nomifensine is devoid of analgesic activity in the hot plate test (Gonzalez et al., 1980), while hyperalgesic effects have been reported in the tail immersion test (Gonzalez et al., 1980). Our failure to observe hyperalgesic effects in the present study can be explained by the use of an intense thermal noxious stimulation (54°C), which makes it difficult to observe a decrease in baseline latencies.

In the formalin test, the potency and efficacy of nomifensine analgesia were similar to the analgesic effect of morphine after systemic injection in the formalin test (Gilbert and Franklin, 1998). Like opioids (Tjolsen and Hole, 1992), catecholamine agonists can alter skin temperature via an effect on blood flow (Cox et al., 1978) and changes in skin temperature affect nociception (Hole and Tjolsen, 1993). We did not directly assess the effect of nomifensine on skin temperature, but it is unlikely that a change in skin temperature accounts for the analgesic effect of nomifensine in the formalin test. First, the tail flick reflex and the second phase of formalin pain are affected similarly by changes in skin temperature (Hole and Tjolsen, 1993). If the analgesic effect of nomifensine in the formalin test was due to changes in skin temperature, increased latencies in the tail flick test should have been observed. Second, while a decrease in skin temperature can be interpreted as analgesia (Hole and Tjolsen, 1993), dopamine and related agonists such as apomorphine produce an increase in skin temperature, not a decrease (Cox et al., 1978). We did not observed hyperalgesic reactions, but it should be noted that the effects of dopaminergic agents on skin temperature dissipate after 30 min (Kruk, 1972), which is when behavioural testing started in the present experiments. Nomifensine may increase skin temperature through its sympathomimetic effect, but since D2 receptors on sympathetic nerves inhibit catecholamine release, eticlopride should potentiate changes in skin temperature (Friedman et al., 1989).

Naltrexone in doses from 2.5 to 40 μg failed to reverse nomifensine analgesia. By comparison, 2.5 μg naltrexone completely reversed morphine analgesia (5 mg/kg) in the formalin test, and 7 μg is a standard dose used to differentiate between opioid and non-opioid analgesia (Watkins et al., 1992). This result is consistent with the fact that amphetamine analgesia is also not affected by naloxone (Drago et al., 1984). It also consistent with the finding that chronic treatment with nomifensine does not alter naloxone binding to opioid receptors in the rat brain (Christensen et

al., 1986). Naltrexone itself did not affect pain scores in the formalin test. These data extend previous studies using naloxone (Kocher, 1988) and confirm that formalin pain is not affected by opioid antagonists.

The analgesic effect of nomifensine was dose-dependently reversed by the D2 antagonist eticlopride, while formalin pain was not affected by the antagonist. Likewise, the analgesic effect of amphetamine and cocaine are antagonized by haloperidol (Drago et al., 1984), pimozide and *cis*-flupenthixol (Morgan and Franklin, 1991). Like other nomifensine-induced behavioral effects (Gianutsos et al., 1982), nomifensine analgesia appears to be dopamine-mediated. Since nomifensine does not inhibit serotonin uptake (Broch, 1987), the other monoamine candidate would be noradrenaline (Broch, 1987). However, the noradrenaline uptake inhibitor desipramine has only a minor antinociceptive effect in the formalin test (Lund et al., 1991).

The site of action of nomifensine is not known but the analgesic effects of nomifensine are likely to be forebrain-mediated. The analgesic effects of nomifensine and other dopamine agonists are reliably reversed by antagonists of the D2 receptor (Lin et al., 1989; Morgan and Franklin, 1991), a subtype of receptor predominantly located in forebrain areas (Feldman et al., 1997). Microinjection of amphetamine into the ventral striatum produces analgesia (Altier and Stewart, 1993), while 6-hydroxydopamine lesions in the ventral tegmentum (Morgan and Franklin, 1990) or ventral striatum (Clarke and Franklin, 1992) abolish systemic amphetamine analgesia. Moreover, the analgesic activity of dopaminergic drugs is reliably detected in pain tests involving supraspinally mediated behaviors (Franklin, 1999) rather than in pain tests involving a spinal reflex (Morgan and Franklin, 1990; Pertovaara et al., 1988). This observation may suggest that the underlying analgesic mechanism of these drugs relate to an altered perception of the noxious stimulus rather than inhibition of nociceptive transmission at the spinal cord level. The most compelling evidence for a spinal component to dopamine analgesia is that systemic administration of cocaine suppresses dorsal horn unit responses to nociceptive stimulation in lightly anesthetized rats (Kiritsy-Roy et al., 1994). However, cocaine antinociception in the tail flick test is blocked by opioid or NMDA antagonists (Forman et al., 1997; Ushijima and Horita, 1993), suggesting that this effect is not dependent on the dopaminergic systems. The effect of cocaine on spinal reflexes may be due to cocaine's action on the serotoninergic system. Intrathecal injection of serotonin and related serotonin agonists increases tail flick latencies in rats (Reimann et al., 1999; Xu et al., 1994). Further supporting this idea is the finding that the antinociceptive effect of cocaine subcutaneously in the tail immersion test is dose-dependently reversed by pretreatment with the serotonin antagonist mianserin (Gatch et al., 1999). Part of the analgesic effect of cocaine could also be due to blockade of sensory nerve since cocaine can act as a local anesthetic (Bahar et al., 1984). The pharmacological antagonism of cocaine analgesia by opioid, NMDA and serotonin antagonists may explain its efficacy against most types of pain, and suggests that cocaine analgesia is different from the dopaminergic analgesia induced by nomifensine and amphetamine.

Although the analgesic effect of dopamine agents is most likely to be mediated centrally, the presence of inflammation may favor the central analgesic effect of catecholamine uptake inhibitors such as nomifensine. The only other report of the analgesic effect of nomifensine was in the writhing test in mice (Gonzalez et al., 1980). These reports are similar in that formalin and acetic acid are both irritant substances inducing inflammatory responses. Dopaminergic agents do not reliably affect nocifensive reflexes (Morgan and Franklin, 1990), but intracerebroventricular administration of D2 agonists increase hot plate latencies in hyperalgesic rats treated with carrageenan (Gao et al., 2000). Further evidence for an anti-inflammatory effect of dopaminergic agents is that central administration of amphetamine and of the dopamine precursor L-DOPA decreases paw edema in rats treated with Brewer's yeast (Hore et al., 1997). Moreover, it is interesting that nomifensine is reported to be effective in relieving arthritic pain in depressed patients (Wheatley, 1986).

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