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Nicotine potentiation of morphine-induced catalepsy in mice

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Abstract

In the present study, effects of nicotine on catalepsy induced by morphine in mice have been investigated. Morphine but not nicotine induced a dose-dependent catalepsy. The response of morphine was potentiated by nicotine. Intraperitoneal administration of atropine, naloxone, mecamylamine, and hexamethonium to mice reduced catalepsy induced by a combination of morphine with nicotine. Intracerebroventricular injection of atropine, hexamethonium, and naloxone also decreased catalepsy induced by morphine plus nicotine. Intraperitoneal administration of atropine, but not intraperitoneal or intracerebroventricular injection of hexamethonium, decreased the effect of a single dose of morphine. It was concluded that morphine catalepsy can be elicited by opioid and cholinergic receptors, and the potentiation of morphine induced by nicotine may also be mediated through cholinergic receptor mechanisms.

Keywords: Nicotine; Nicotinic antagonists; Morphine; Naloxone; Atropine; Catalepsy; Mice

1. Introduction

Nicotine is one of the most widely used psychoactive drugs, which has a long history in human psychopharmacology. Despite the well-known health hazards of nicotine, little is known about the mechanisms of the drug in the central nervous system. The drug is a lipophilic compound that rapidly enters and accumulates in the central nervous system after systemic injection. It exerts a wide range of pharmacological effects in both the central and the peripheral nervous system (Clarke and Kumar, 1983a,b). Many of its effects are associated with the ability of nicotine to release various neurotransmitters (Balfour, 1982; Wonnacott et al., 1989). In the central nervous system, it was found that nicotinic receptor stimulation enhances the release of acetylcholine from the striatal cholinergic interneurons (Sandor et al., 1991) and cortex (Rowell and Winkler, 1984) and that of noradrenaline (Hall and Turner, 1972) and serotonin (Hery et al., 1977) from the hippocampus, and that it also increases the resting release of dopamine from striatal preparations (Rapier et al., 1988).

Nicotine is also involved in activating opioid system(s) (Balfour, 1982; Davenport et al., 1990). Nicotinic receptor stimulation activates enkephalin release and biosynthesis in discrete brain nuclei and adrenal chromaffin cells (Eiden et al., 1984; Houdi et al., 1991). Previous investigations have shown that nicotine is able to alter some effects of morphine. The drug attenuates naloxone-induced jumping in morphine-dependent mice (Zarrindast and Farzin, 1996). Development of cross-tolerance between anitinociception induced by morphine and nicotine in mice has also been shown (Zarrindast et al., 1999). Nicotine also potentiates morphine antinociception through possible cholinergic mechanism (Zarrindast et al., 1996). Moreover, cholinergic and opioid receptor mechanisms may be involved in nicotine-induced antinociception (Zarrindast et al., 1997).

Catalepsy is an abnormal motor state which is characterized by muscular rigidity (Turski et al., 1980). The inhibition of striatal dopamine receptor sites induces cata-

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lepsy in rodents (Van Rossum, 1966). The catalepsy induced by neuroleptics can be potentiated by nicotine (Dunstan et al., 1981; McConville et al., 1991; Zarrindast et al., 1999). It can be induced by many opioid agonists, including morphine (Muley et al., 1982). Peripheral administration of morphine (Vanderwende and Spoerlein, 1979) or injection of the drug into the nucleus accumbens (Winkler et al., 1982), the striatum (Havemann et al., 1980), the reticular formation (Dunstan et al., 1981), or the periaqueductal gray (Pert, 1977) of rodents also induces catalepsy. However, it has been shown that morphine, unlike dopamine receptor antagonists, does not induce catalepsy through the inhibition of postsynaptic striatal dopamine receptors (Nordberg et al., 1989). The opioid neither changes the basal activity of the dopamine-sensitive adenylyl cyclase nor antagonizes the stimulation of the enzyme in striatal homogenates of mouse brain (Racagni et al., 1979). Since nicotine and morphine showed interactions in many ways, in the present study, potentiation of catalepsy due to a combination of nicotine with morphine has been investigated. Moreover, the effects of the central nicotinic receptor antagonist mecamylamine, the peripheral nicotinic receptor antagonist hexamethonium, the muscarinic receptor antagonist antagonist atropine, and the opioid receptor antagonist naloxone on this interaction were examined to assess possible involvement of nicotinic, muscarinic, or opioid receptor mechanisms in this phenomenon.

2. Method

2.1. Animals

Male albino NMRI mice, weighing between 20 and 25 g were used in these experiments. The animals were housed in plastic cages in groups of up to 10 in a room maintained at 22 ± 2 °C on a 12-h dark cycle. Food and water were freely available except during the experiments. Each animal was used once.

2.2. Drugs

The following drugs were used: atropine sulfate (Merck, Germany), hexamethonium bromide (Sigma, England), mecamylamine HCl (Merck, Germany), nicotine hydrogen (+)-tartrate (BDH Chemicals, England), morphine sulfate (MacFarlan, Smith, England), naloxone HCl (Sigma). The drugs were dissolved in saline. Nicotine solution was prepared in saline and the pH was adjusted to 7.2 ± 0.1 with sodium hydroxide. The drugs were given in a volume of 10 ml/kg peripherally or intracerebroventricularly in a volume of μl/mouse and were prepared immediately before use. Nicotine and mecamylamine were injected intraperitoneally, morphine was administered subcutaneously, and hexamethonium, atropine, and naloxone were injected intraperitoneally or intracerebroventricularly. The doses of antagonists and pretreatment time were those used previously and were shown to be pharmacologically active (Zarrindast and Farzin, 1996; Zarrindast et al., 1997).

2.3. Chronic guide cannula implantation

Stainless-steel guide cannulae (23 gauge) were stereotaxically (David Koft Instruments, USA) implanted under anesthesia with pentobarbital (60 mg/kg ip), 5–7 days before the experiments. The guide cannulae were implanted in the lateral ventricle at the following coordinates based on the method of Jiang et al. (1990) (Izenwasser et al., 1991) with a minor modification: 2 mm lateral and 0.9 mm caudal to the bregma at the depth of 3 mm. The drugs were injected in a volume of 2 μl in a period of 2 min, by means of an internal cannula (30 gauge) connected by polyethylene tubing to a 10-μl Hamilton syringe and the injection cannula was left in place for a further 1 min before being slowly withdrawn.

2.4. Assessment of catalepsy

Catalepsy was measured based on the method of Morelli and Di Chiara (1985) (Mopurgo, 1962), by the "bar test" in mice. The forepaws of the animals were gently placed on a bar 0.3 cm in diameter and 20 cm long, which was fixed at a height of 5.5 cm above the working surface.

The length of time that the animals maintained this position was recorded. A cut-off time of 180 s was introduced after which observation was stopped if no displacement had occurred within that time (Tzschentke and Schmidt, 1996). Catalepsy was quantified as the area under the curve (AUC) of (s) on 15, 30, 45, 60 min after drug administration for each animal. AUC [time (min)× latency (s)] was calculated as drug response (s) plotted against time (min) using the trapezoidal rule (Coutinho et al., 1998).

2.5. Statistical analysis

Analysis of variance (ANOVA) followed by the Newman–Keuls test was performed. $P < .05$ was considered significant.

3. Results

3.1. Catalepsy induced by morphine or nicotine in mice

Subcutaneous injection of different doses of morphine (10, 20, 40, 60, and 80 mg/kg) to mice induced a bell-shaped cataleptogenic response [one-way ANOVA; $F(5,54) = 7.96$, $P < .0001$]. The maximum effect was achieved with 40 mg/kg of morphine administration. The highest dose of morphine (80 mg/kg) showed no catalepsy (Fig. 1A). However, one-way ANOVA showed a significant difference between

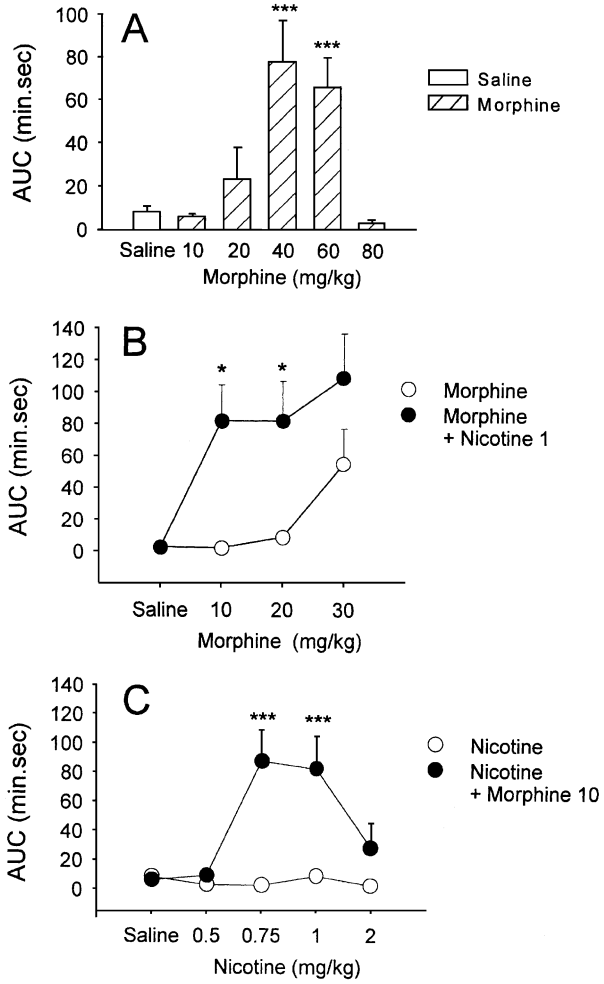

Fig. 1. Cataleptogenic effect of morphine (10, 20, 40, 60 and 80 mg/kg) (A), nicotine (1 mg/kg) plus different doses of morphine (B) and morphine (10 mg/kg) plus different doses of nicotine (0.5, 0.75, 1, and 2 mg/kg) (C) in mice. Morphine was administered subcutaneously and nicotine was injected intraperitoneally. Catalepsy (s) was measured every 15 min for a period of 1 h (15, 30, 45, and 60 min) after morphine injection. Nicotine was injected 5 min before morphine. Each point is the mean ± S.E.M. of the AUC of catalepsy in 10 experiments. *$P<.05$, ***$P<.001$ different from saline control group.

the response of intraperitoneal injection of different doses of nicotine (0.5, 0.75, 1, and 2 mg/kg) to mice, with that of saline [$F(4,45)=3.1$, $P<.05$], but further analysis did not indicate any effect for nicotine (Fig. 1C).

3.2. The effect of nicotine on the morphine-induced catalepsy

Effects of a single dose of nicotine on catalepsy induced by different doses of morphine are in Fig. 1B. Animals were treated with nicotine (1 mg/kg ip) 5 min before saline or different doses of morphine (10, 20, 30 mg/kg). Two-way ANOVA showed a significant difference between the response induced by morphine (Factor A) and that induced by nicotine (Factor B) plus morphine

Table 1
Effects of intraperitoneal injection of antagonists on morphine- and/or nicotine-induced catalepsy in mice

Drug (mg/kg)	AUC (mean±S.E.M.)
Saline	7.3 ± 1.2
Mor 10	8.5 ± 1.3
Nic 0.75	2.3 ± 0.6
Mor 10 + Nic 0.75	87.5 ± 4.5***
Mor 10 + Nic 0.75 + Atr 5	7.0 ± 3.9***
Mor 10 + Nic 0.75 + Atr 10	2.4 ± 1.1***
Mor 10 + Nic 0.75 + Hexa 2.5	21.5 ± 11.5***
Mor 10 + Nic 0.75 +Hexa 5	16.3 ± 7.0***
Mor 10 + Nic 0.75 + Hexa 10	4.0 ± 1.2***
Mor 10 + Nic 0.75 + Nal 0.5	82.0 ± 22.0
Mor 10 + Nic 0.75 + Nal 1	15.5 ± 5.5***
Mor 10 + Nic 0.75 + Nal 2	4.9 ± 0.7***
Mor 20 + Nic 1	62.5 ± 18.5
Mor 20 + Nic 1 + Mec 0.5	7.8 ± 2.8**
Mor 20 + Nic 1 + Mec 1	4.1 ± 1.6**

Animals were treated with saline (10 ml/kg ip), morphine (Mor; sc), nicotine (Nic; ip), morphine plus nicotine or atropine (Atr; ip) 15 min; hexamethonium (Hexa; ip) 30 min; naloxone (Nal; ip) 2 min; and mecamylamine (Mec; ip) 15 min before nicotine injection. Nicotine was injected 20 min and morphine 15 min prior to catalepsy measurement. Each point is the mean ± S.E.M. of the AUC of 10 experiments.

** $P<.01$ different from respective (saline or morphine+nicotine) control groups.

*** $P<.001$ different from respective (saline or morphine+nicotine) control groups.

[Factor A, $F(3,72)=6.3$, $P<.001$; Factor B, $F(1,72)=16.1$, $P<.0001$; Factor A×B, $F(3,72)=2.8$, $P<.05$]. Further analysis indicated that nicotine potentiated the catalepsy induced by morphine.

Fig. 1C shows the effect of different doses of nicotine on the catalepsy induced by morphine. Two-way ANOVA

Table 2
Effects of intracerebroventricular injection of antagonists on the response of morphine+nicotine in mice

Treatment 1 (mg/kg ip)	Treatment 2 (μg/mice icv)	AUC (mean±S.E.M.)
Mor 10 + Nic 0.75	Saline	131 ± 15.5
Mor 10 + Nic 0.75	Atr 5	7.0 ± 3.4***
Mor 10 + Nic 0.75	Atr 10	10.0 ± 2.4***
Mor 10 + Nic 0.75	Atr 20	2.2 ± 1.0***
Mor 10 + Nic 0.75	Hexa 5	24.9 ± 9.4***
Mor 10 + Nic 0.75	Hexa 7.5	13.7 ± 3.3***
Mor 10 + Nic 0.75	Hexa 10	5.5 ± 2.1***
Mor 10 + Nic 0.75	Nal 2	23.8 ± 5.9***
Mor 10 + Nic 0.75	Nal 4	21.2 ± 8.0***
Mor 10 + Nic 0.75	Nal 6	7.7 ± 4.0***

Animals were treated with morphine (Mor; 10 mg/kg sc) plus nicotine (Nic; 0.75 mg/kg ip), or intracerebroventricular injection of atropine (Atr; 5, 10, and 20 μg/mice), hexamethonium (Hexa; 5, 7.5, and 10 μg/mice), and naloxone (Nal; 2, 4, and 6 μg/mice) 2 min prior to morphine administration. Nicotine was injected 20 min and morphine 15 min prior to catalepsy measurement. Each point is the mean ± S.E.M. of the AUC of 10 experiments.

*** $P<.001$ different from saline or morphine+nicotine control group.

Table 3
Effect of intracerebroventricular or intraperitoneal dose of hexamethonium on morphine-induced catalepsy

Treatment 1 (μg/mice icv)	Treatment 2 (mg/kg sc)	AUC (mean ± S.E.M.)
Saline	Morphine 40	77.2 ±14.5
Hexamethonium 5	Morphine 40	45.4 ± 12.3
Hexamethonium 7.5	Morphine 40	82.0 ± 13.5
Hexamethonium 10	Morphine 40	54.4 ± 10.3
ip (mg/kg):	sc:	
Saline	Morphine 40	64.5 ± 17.8
Hexamethonium 2.5	Morphine 40	75.9 ± 17.5
Hexamethonium 5	Morphine 40	87.5 ± 19.3
Hexamethonium 10	Morphine 40	90.4 ± 19
Saline	Morphine 40	82.5 ± 9.2
Atropine 2.5	Morphine 40	32.8 ± 23.7*
Atropine 5	Morphine 40	22.5 ± 9.4*

Animals were treated with morphine (40 mg/kg sc) or centrally with different doses of hexamethonium (Hexa; 5, 7.5, and 10 μg/mice) 2 min or intraperitoneally with different doses of hexamethonium (2.5, 5, and 10 mg/kg ip) 35 min before morphine administration. Each point is mean ± S.E.M. of the AUC of 10 experiments.

* $P < .05$ different from morphine control group.

indicated a significant difference between animals injected with morphine (Factor A, 10 mg/kg sc) and those that received morphine plus different doses of nicotine (Factor B, 0.5, 0.75, 1, and 2 mg/kg ip) [Factor A, $F(1,90) = 23.8$, $P < .0001$; Factor B, $F(4,90) = 4.6$, $P < .01$; Factor A×B, $F(4,90) = 5.3$, $P < .001$]. Further analysis showed that the doses of 0.75 and 1 mg/kg of nicotine can increase the catalepsy induced by morphine.

3.3. The effects of opioid or cholinergic receptor antagonists on catalepsy induced by morphine or morphine+nicotine

Table 1 shows the effects of atropine, hexamethonium, mecamylamine, or naloxone on catalepsy induced by morphine plus nicotine. One-way ANOVA indicates a significant difference between the animals which received lower doses of morphine (10 mg/kg sc) plus nicotine (0.75 mg/kg ip) with those which were injected with morphine + nicotine in the presence of atropine, hexamethonium, or naloxone [$F(11,108) = 14.8$, $P < .0001$]. Further analysis showed that morphine+nicotine induced catalepsy whereas neither morphine nor nicotine alone induced any response. Pretreatment of animals with atropine, hexamethonium, or naloxone reduced the response induced by morphine plus nicotine. One-way ANOVA also indicates a significant difference between animals treated with a combination of a higher dose of morphine (20 mg/kg sc) with nicotine in the presence or absence of mecamylamine (0.5 and 1 mg/kg ip) [$F(2,27) = 9.1$, $P < .001$]. Post hoc analysis showed that mecamylamine decreased the effect of morphine plus nicotine.

The effect of intracerebroventricular administration of antagonists on catalepsy induced by morphine plus nicotine is shown in Table 2. Intracerebroventricular injection of different doses of atropine (5, 10, and 20 μg/mice), hexamethonium (5, 7.5, and 1 μg/mice), or naloxone (2, 4, and 6 μg/mice) reduced the catalepsy induced by morphine plus nicotine [one-way ANOVA, $F(9,90) = 30.6$, $P < .000$].

The effect of intracerebroventricular injection of hexamethonium or intraperitoneal administration of hexamethonium and atropine is shown in Table 3. One-way ANOVA indicates no effect for intracerebroventricular [$F(3,36) = 1.9$, $P > .0$] or intraperitoneal [$F(3,36) = 1.14$, $P > .05$] injection of hexamethonium. However, intraperitoneal administration of atropine reduced morphine response [$F(2,27) = 4.2$, $P < .05$].

4. Discussion

Nicotine may alter some effects of morphine (see Introduction). In the present study, the influence of nicotine on morphine-induced catalepsy has been investigated.

The present results show that morphine induces catalepsy in mice. Other studies have also shown that the drug also induced catalepsy in rat (Brown et al., 1983) and mice (Muley et al., 1982; Vanderwende and Spoerlein, 1979). The higher dose of morphine (80 mg/kg), which showed hyperactivity, did not induce catalepsy. Previously, we have shown that high doses of morphine induce locomotion through dopaminergic mechanism (Zarrindast and Zarghi, 1992), which may account for the decrease in cataleptogenic response with high doses of the drug in the present study. Our present data indicate that nicotine increases catalepsy induced by morphine. The results show that central or peripheral administration of the opioid receptor antagonist, naloxone, reduced the catalepsy induced by a combination of nicotine and morphine. This is in agreement with other investigators indicating that naloxone blocked morphine-induced catalepsy (Brown et al., 1983; Winkler et al., 1982). Since peripheral (ip) or central (icv) injection of hexamethonium decreased the response of morphine plus nicotine but not that induced by morphine alone, potentiation of morphine's catalepsy by nicotine may be mediated through nicotinic receptor mechanism(s) whereas that of morphine was not.

There is widespread clinical and experimental evidence that the dopaminergic system modulates cholinergic neurotransmission in different areas of the brain. Thus, the hypothesis of a reciprocal dopamine–acetylcholine balance (Lloyd et al., 1973) has for long been suggested. It has been proposed that neuronal impulses, which mediate the neuroleptic catalepsy, are conveyed from the striatum to the substantia nigra pars reticulata and further on to the ventromedial thalamic nucleus (Kolasiewicz et al., 1988; Wolfarth et al., 1985). Therefore, increase in cholinergic tone may be implicated in catalepsy induced by the drugs in the present work.

Several investigators have shown that nicotine increases release of acetylcholine in the brain (Balfour, 1982; Nord-

berg et al., 1989; Sandor et al., 1991). Since central cholinergic mechanism may induce catalepsy (Klemm, 1983a,b), nicotine may elicit potentiation of morphine-induced catalepsy through acetylcholine release, independent of the dopamine system. The hypothesis may be emphasized by the present data showing that atropine used peripherally or centrally reduces the response induced by the combination of nicotine with morphine. Peripheral injection of atropine also reduced the morphine response. This can be supported by the results indicated by others that neuroleptic catalepsy can be enhanced or reduced by cholinergic or anticholinergic agents, respectively (Costall and Olley, 1971). The present data indicate that intracerebroventricular and intraperitoneal injection of the nicotinic receptor antagonist hexmethonium and peripheral injection of the nicotinic receptor antagonist mecamylamine (Martin et al., 1989) decreased the potentiation of morphine-induced catalepsy by nicotine. It seems likely that the response of the nicotine is mediated through nicotinic mechanism(s). The potentiation of morphine catalepsy by mecamylamine has been previously shown (Bronson and Sparber, 1989). It may be postulated that either the inhibition of tonic activity of nicotinic receptors or the increased activity of these receptors by exogenous nicotine contributes to the enhancement of morphine catalepsy. However, it has also been proposed that the dopaminergic system is involved in the nicotine effect (Rapier et al., 1988).

There is evidence that nicotine induces ataxia and typically depresses locomotor activity for several minutes, after which a locomotor stimulant effect may emerge, lasting 1 h or more (Clarke and Kumar, 1983a). Whether the depressant response of nicotine accounts for the potentiation of morphine's effect should be considered. However, we did not observe a decrease in locomotor activity with the doses used.

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