ELSEVIER

European Journal of Pharmacology 298 (1996) 1–6

ejp

Nicotine attenuates naloxone-induced jumping behaviour in morphine-dependent mice

Mohammad-Reza Zarrindast *, Davood Farzin

Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Received 22 May 1995; revised 25 October 1995; accepted 7 November 1995

Abstract

In the present study the effect of nicotine on naloxone-induced jumping behaviour in morphine-dependent mice was examined. In addition, the modulatory role of dopaminergic, adrenergic and cholinergic mechanisms upon the effect of nicotine were investigated. Animals were rendered dependent on morphine by subcutaneous (s.c.) injections of morphine sulfate 3 times a day for 3 days, and jumping behaviour was induced by intraperitoneal (i.p.) administration of naloxone 2 h after the tenth injection of morphine sulfate on day 4. Nicotine (0.001–2 mg/kg s.c.) caused a significant decrease in withdrawal jumping behaviour in morphine-dependent mice. The effect of nicotine was blocked by the central nicotinic antagonist mecamylamine (0.01–0.1 mg/kg i.p.) but not by the peripheral nicotinic antagonist hexamethonium (0.01 and 0.1 mg/kg i.p.) nor the muscarinic receptor antagonist atropine (2.5–10 mg/kg i.p.). The dopamine receptor antagonist SCH 23390 (*R*-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-ol maleate) (0.01–0.5 mg/kg s.c.) reduced the response induced by nicotine. The dopamine receptor antagonist sulpiride (25 and 50 mg/kg s.c.) and the adrenoceptor antagonists phenoxybenzamine (5 and 10 mg/kg i.p.) and propranolol (5 and 10 mg/kg i.p.) were without an effect. The results indicate that the effect of nicotine on naloxone-induced jumping is mediated by central nicotinic receptors.

Keywords: Nicotine; Morphine; Naloxone; Acetylcholine receptor antagonist; Jumping; (Mouse)

1. Introduction

Nicotine is the most pharmacologically active component of tobacco products (Benowitz, 1988; Henningfield and Goldberg, 1988; Stolerman, 1988). It exhibits widespread pharmacological effects in the central and peripheral nervous system. Many of these effects are possibly due to the ability of nicotine to release various neurotransmitters (Balfour, 1982). In the central nervous system, nicotinic receptor stimulation enhances the release of acetylcholine from the cortex (Chiou et al., 1970; Nordberg et al., 1989), and noradrenaline (Hall and Turner, 1972; Goodman, 1974) and serotonin (Balfour, 1982) from the hippocampus. It also increases the release of dopamine from the limbic system (Imperato et al., 1986) and from striatal slices (Goodman, 1974; Giorguieff et al., 1979). There is also good evidence that nicotine is 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). These findings may have some bearing on the observation that opiate addicts and cigarette smokers display parallel emotional profiles during abstinence from their habits (Gossop et al., 1990). This hypothesis would predict that nicotine should alleviate at least some of the signs of morphine abstinence. There is a report that nicotine suppresses naloxone-induced jumping in morphine-dependent mice (Brase et al., 1974). The purpose of the present study was to determine the possible mechanism(s) of the suppressive action of nicotine on the jumping behaviour induced by the opiate antagonist naloxone as an index of withdrawal in mice treated chronically with morphine and injected with naloxone (Way et al., 1969; Saelens et al., 1971).

* Corresponding author. Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, P.O. Box 13145-784, Tehran, Iran.

SSDI 0014-2999(95)00761-X

2. Materials and methods

2.1. Animals

Male albino mice (20–25 g) were housed in plastic cages in an animal room maintained at 21 ± 2°C on a 12-h dark cycle. Food and water were available at all times except during the experiments. Each animal was used once only and was killed immediately after the experiment.

2.2. Induction of dependence

The mice were rendered dependent on morphine using the method previously described by Marshall and Grahame-Smith (1971). Morphine sulfate was injected subcutaneously (s.c.) 3 times daily at 9:30, 13:30 and 17:30 h on the following dosage schedule. The first three doses were 50, 50 and 75 mg/kg, respectively. The higher dose at the third daily injection was aimed to minimize any overnight withdrawal. Each of the doses was then increased by 25 mg/kg/day. Morphine administration was carried out over a maximum of 3 days for all groups of mice. A dose of 50 mg/kg of morphine sulfate also was injected on the 4th day (2 h before naloxone injection). Hyperactivity and the Straub tail effect were seen after morphine injections. With chronic administration of morphine sulfate, loss of weight (8–12%) and death (5–10%) also were observed.

2.3. Jumping

Groups of mice were tested for the occurrence of jumping after their tenth injection of morphine on day 4. Two hours after the last dose of morphine (50 mg/kg), abstinence was precipitated by an intraperitoneal (i.p.) injection of naloxone; then animals were placed individually on filter paper in a cylindrical glass (25 cm in diameter, 40 cm height) and the number of jumps was recorded over a 30 min period.

2.4. Drugs

The following drugs were used: atropine sulfate (Merck, Germany), domperidone (Research Biochemicals, USA), hexamethonium bromide (Sigma, UK), mecamylamine HCl (Merck, Germany), morphine sulfate (MacFarlan Smith, UK), naloxone HCl (Sigma, UK), nicotine hydrogen (+)-tartrate (BDH Chemicals, UK), phenoxybenzamine HCl (SK&F, USA), propranolol (ICI, UK), SCH 23390 (*R*-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-ol maleate; Research Biochemical, USA) and sulpiride (Sigma, UK). Nicotine solutions were prepared in saline and the pH was adjusted to 7.2 ± 0.1 with sodium hydroxide. In all cases, the drug doses reported are for the base, except for morphine sulfate. The drugs were dissolved in saline, except for sulpiride and domperidone, which were dissolved in a drop of acetic acid and diluted with saline. SCH 23390 was dissolved in a drop of lactic acid and diluted with saline. The vehicle control in respective cases was acetic acid or lactic acid in saline. The drugs were given in a volume of 10 ml/kg and were prepared immediately before use. The doses of antagonists and pretreatment time were usually those used previously and shown to be pharmacologically active (Zarrindast and Abolfathi-Araghi, 1992; Zarrindast and Tabatabai, 1992; Zarrindast and Heidari, 1994).

2.5. Statistical analysis

Comparisons between groups were made with a Newman-Keuls test following ANOVA. Differences with $P \leq 0.05$ between experimental groups at each point were considered statistically significant.

3. Results

3.1. Naloxone-induced withdrawal jumping in morphine-dependent mice

Fig. 1 shows the number of jumps per mouse during the abstinence syndrome elicited by different doses of naloxone. Naloxone produced significant withdrawal jumping in morphine-dependent mice [$F(7,64) = 82.3$, $P < 0.01$]. The maximum response was obtained with 20 mg/kg of the drug. The dose of 5 mg/kg of naloxone was chosen for morphine withdrawal-induced jumping in subsequent experiments.

3.2. Effects of nicotine on naloxone-induced jumping

Nicotine, when administered 15 min before naloxone (5 mg/kg, i.p.), significantly decreased the jumping response

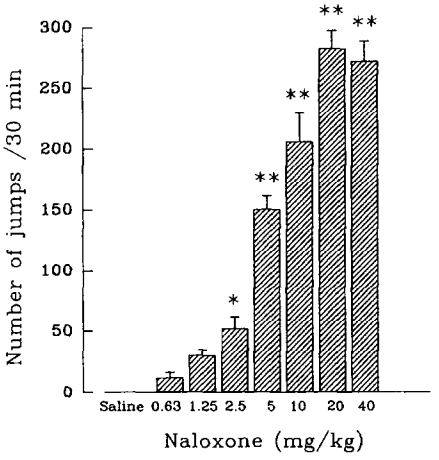

Fig. 1. Dose-related induction of jumping behaviour by injection of naloxone into morphine-treated mice. Each group had 9 mice. Data are means + S.E.M. * $P < 0.05$, ** $P < 0.01$ different from the control group (saline-treated animals).

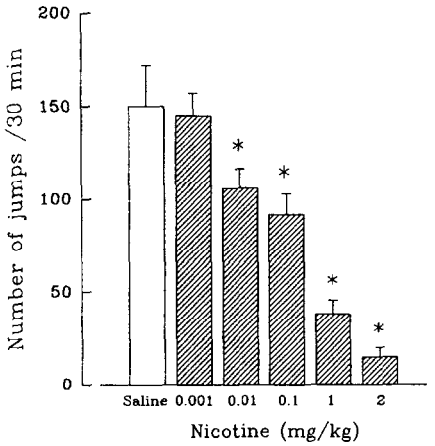

Fig. 2. Effects of different doses of nicotine on jumping induced by naloxone (5 mg/kg, i.p.) in morphine-dependent mice. Each group had 9 mice. Data are means + S.E.M. * $P < 0.01$, different from the control group.

induced by naloxone in morphine-dependent animals [$F(5,48) = 32.8$, $P < 0.01$]. The nicotine response was dose-dependent, with an ED_{50} of 0.1 mg/kg (obtained by regression analysis) (Fig. 2).

3.3. Effects of mecamylamine on the suppressive action of nicotine

Pretreament of animals with different doses of mecamylamine 5 min prior to nicotine (0.1 mg/kg, s.c., 15 min before naloxone) produced a statistically significant reduction [$F(3,32) = 11.2$, $P < 0.01$] of the inhibitory response induced by nicotine (Fig. 3A). However, administration of mecamylamine alone, 20 min before naloxone, did not alter the withdrawal jumping induced by the opioid antagonist [$F(3,32) = 1.42$, $P > 0.05$] (Fig. 3B).

3.4. Effects of hexamethonium and atropine on the suppressive action of nicotine

Naloxone-induced jumping in morphine-dependent mice in the presence of nicotine (0.1 mg/kg s.c., 15 min before naloxone) + either hexamethonium (0.01 and 0.1 mg/kg i.p., 15 min before nicotine, 96 ± 15 and 97 ± 11, respectively) or atropine (2.5, 5 and 10 mg/kg i.p., 15 min before nicotine, 107 ± 8, 112 ± 15 and 105 ± 11, respectively) was not significantly different from that induced when nicotine (0.1 mg/kg s.c., 92 ± 11) was injected [$F(5,48) = 0.4$, $P > 0.05$].

Jumping induced by naloxone in animals treated with either hexamethonium (0.01 and 0.1 mg/kg i.p., 30 min before naloxone, 142 ± 9 and 149 ± 27, respectively) or atropine (2.5, 5 and 10 mg/kg i.p., 30 min before naloxone, 176 ± 26, 184 ± 27 and 166 ± 14, respectively) alone also was not significantly different from that of the saline controls (10 ml/kg i.p., 150 ± 11) [$F(5,48) = 0.67$, $P > 0.05$].

3.5. Effects of dopamine D_1 and D_2 receptor antagonists on the suppressive action of nicotine

Pretreatment of animals with SCH 23390, 15 min before nicotine (0.1 mg/kg, s.c.), dose relatedly antagonized

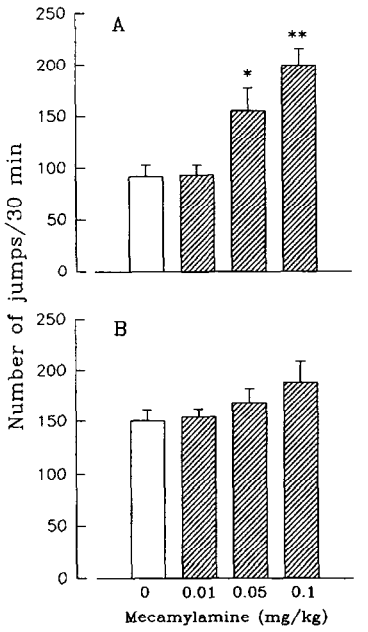

Fig. 3. (A,B) Effects of mecamylamine on jumping induced by naloxone (5 mg/kg i.p.) in morphine-dependent mice, in the presence (A) or the absence (B) of nicotine (0.1 mg/kg, s.c.). Results are expressed as means + S.E.M. for 9 mice. * $P < 0.05$, ** $P < 0.01$, different from the control group.

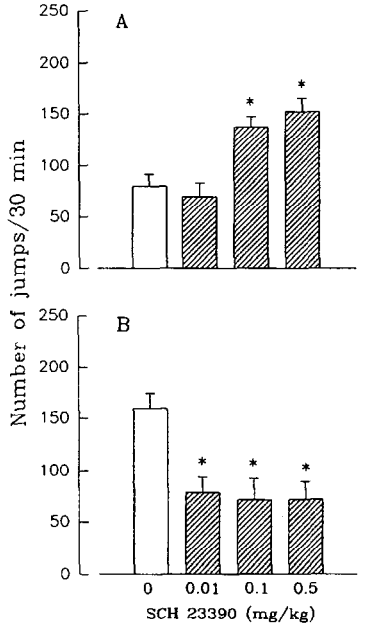

Fig. 4. (A,B Effects of SCH 23390 on jumping induced by naloxone (5 mg/kg i.p.) in morphine-dependent mice, in the presence (A) or the absence (B) of nicotine (0.1 mg/kg, s.c.). Each group had at least 9 mice. Results are expressed as means + S.E.M. * $P < 0.01$, different from the control group.

the reduction of jumping induced by nicotine [$F(3,57) = 10.2$, $P < 0.01$] (Fig. 4A). Pretreatment of animals with SCH 23390 alone significantly decreased the jumping response induced by naloxone in morphine-dependent mice [$F(3,32) = 6.1$, $P < 0.01$]. The lowest dose of SCH 23390 (0.01 mg/kg) was able to maximally suppress withdrawal-induced jumping, although it was ineffective in altering the action of nicotine (Fig. 4B).

Jumping induced by naloxone in animals treated with nicotine (0.1 mg/kg s.c., 15 min before naloxone) + sulpiride (25 and 50 mg/kg s.c., 90 min before naloxone, 98 ± 12 and 88 ± 11, respectively) was not significantly different from jumping induced in animals treated with vehicle (10 ml/kg s.c.) + nicotine (0.1 mg/kg s.c., 87 ± 20) [$F(2,24) = 0.2$, $P > 0.05$]. The response induced in the presence of nicotine (0.1 mg/kg s.c., 15 min before naloxone) + domperidone (5 and 10 mg/kg s.c., 20 min before naloxone, 92 ± 20 and 107 ± 11, respectively) also was not significantly different from that of mice given the vehicle (10 ml/kg s.c.) + nicotine (0.1 mg/kg s.c., 84 ± 8) [$F(2,24) = 0.8$, $P > 0.05$].

Treatment of animals with sulpiride (25 and 50 mg/kg s.c., 164 ± 22 and 166 ± 24, respectively) itself did not have any significant effects on the jumping induced by naloxone in morphine-dependent mice as compared with vehicle controls (10 ml/kg s.c., 154 ± 18) [$F(2,24) = 0.01$, $P > 0.05$]. Domperidone itself (5 and 10 mg/kg s.c., 147 ± 25 and 141 ± 23, respectively) likewise was devoid of activity in this regard, as compared with vehicle controls (10 ml/kg s.c., 152 ± 11) [$F(2,24) = 0.08$, $P > 0.05$].

3.6. Effects of propranolol and phenoxybenzamine on the suppressive action of nicotine

Jumping induced by naloxone in morphine-dependent mice treated with either nicotine (0.1 mg/kg s.c., 15 min before naloxone) + propranolol (5 and 10 mg/kg i.p., 60 min before naloxone, 95 ± 20 and 87 ± 9, respectively) or nicotine (0.1 mg/kg s.c., 15 min before naloxone) + phenoxybenzamine (2.5 and 5 mg/kg i.p., 60 min before naloxone, 93 ± 8 and 97 ± 13, respectively) was not significantly different from that induced in animals treated with saline (10 ml/kg i.p.) + nicotine (0.1 mg/kg s.c., 85 ± 12) [$F(4,40) = 0.16$, $P > 0.05$].

Jumping induced by naloxone in morphine-dependent mice was not altered in animals treated with propranolol (5 and 10 mg/kg i.p., 60 min before naloxone, 132 ± 24 and 125 ± 12, respectively) or phenoxybenzamine (5 and 10 mg/kg i.p., 60 min before naloxone, 133 ± 14 and 130 ± 11, respectively) as compared with that of saline controls (141 ± 13) [$F(4,40) = 0.14$, $P > 0.05$].

4. Discussion

In the present experiment nicotine was remarkably effective in reducing the incidence of withdrawal jumping in morphine-dependent mice. The results indicate that nicotinic receptor mechanism(s) may be involved in the suppressive action of nicotine. Interactions between nicotinic receptors and opioid systems were observed in relation to the release of endogenous opioid peptides, including enkephalins (Eiden et al., 1984; Davenport et al., 1990; Houdi et al., 1991) and β-endorphin (Rosecrans et al., 1985). This leads to the hypothesis that nicotine may stimulate the release of endogenous opioid peptides, with overactivation of opioid receptors as a result (Malin et al., 1993, 1994). It may be that nicotine suppresses withdrawal jumping by such a mechanism.

The present data demonstrate that the central nicotinic receptor antagonist mecamylamine (Martin et al., 1989), but not the peripheral nicotinic receptor antagonist hexamethonium, antagonized the suppression of withdrawal jumping produced by nicotine in a dose-related manner. Since the muscarinic receptor antagonist atropine did not alter the effect of nicotine, both peripheral and central muscarinic receptor involvement may be excluded. Several investigations have indicated that nicotine increases acetylcholine release in brain (Balfour, 1982; Nordberg et al., 1989), suggesting that nicotine can directly and indirectly stimulate nicotinic receptors. Other authors have also pointed out that withdrawal jumping in morphine-dependent mice can be inhibited by acetylcholine receptor agonists and potentiated by acetylcholine receptor antagonists (Jhamandas and Dickinson, 1973; Jhamandas et al., 1973; Brase et al., 1974).

It has also been reported that morphine inhibits the release of substance P from the spinal cord and that substance P accumulates during the development of morphine dependence, possibly due to chronic inhibition of substance P release (Bergstrom et al., 1984). There is a report showing that the opioid receptor antagonist naloxone is able to release substance P and that substance P receptor antagonists inhibit naloxone-induced withdrawal jumping (Ueda et al., 1987). Since nicotine has been proposed to inhibit substance P release through a presynaptic nicotinic receptor mechanism (Torrens et al., 1981), it may be that nicotine suppresses withdrawal jumping by such a mechanism.

The selective dopamine D_1 receptor antagonist SCH 23390, which has more than 500 times greater affinity for the dopamine D_1 than for the dopamine D_2 receptor (Hyttel, 1983; Christensen et al., 1984), decreased the effect of nicotine on withdrawal jumping behaviour induced by naloxone. Therefore, nicotine may also elicit its effect upon withdrawal jumping through a dopamine D_1 receptor mechanism. Nicotinic receptors are located in the striatum and the mesolimbic system at the levels of cell bodies and terminals (Giorguieff et al., 1979; Clarke and Pert, 1985). Activation of nicotinic receptors has been shown to be effective in stimulating the release of dopamine from the striatum and the limbic system (Goodman, 1974; Balfour, 1982; Imperato et al., 1986). One may speculate

that nicotine indirectly causes the inhibition of jumping through dopamine D_1 receptor stimulation. It has also been reported that the dopamine D_2 receptor agonist bromocriptine may potentiate morphine withdrawal signs (Gomaa et al., 1989), and that the dopamine D_1 and D_2 receptors exert opposite influences on morphine antinociception (Zarrindast and Moghadampour, 1989).

Adminstration of the dopamine D_2 receptor antagonist sulpiride (Di Chiara et al., 1976; Stoof and Kebabian, 1984) did not alter the effect of nicotine. Sulpiride itself also did not affect withdrawal jumping. These data indicate that the dopamine D_2 receptor is not involved in the attenuation of withdrawal jumping induced by nicotine.

The present data show that administration of the dopamine D_1 receptor antagonist SCH 23390 itself reduced withdrawal jumping. Although SCH 23390 is thought to be a selective dopamine D_1 receptor antagonist, it binds with high affinity to 5-HT_2 receptors in the brain (Bischoff et al., 1986) and antagonizes 5-HT_2 receptor activation both centrally and peripherally (Bijak and Smialowski, 1989; Hicks et al., 1984). The administration of 5-HT_2 receptor antagonists attenuates naloxone-precipitated withdrawal and quasi-morphine withdrawal (Kleven and Sparber, 1989; Neal and Sparber, 1986; Neal and Sparber, 1990). This may account for the reduction of withdrawal jumping by SCH 23390.

The α- or β-adrenoceptor antagonists phenoxybenzamine and propranolol did not alter the effect of nicotine. Therefore, the involvement of adrenergic mechanism(s) in this action of nicotine is unlikely.

References

Balfour, D.J.K., 1982, The effects of nicotine on brain neurotransmitter systems, Pharmacol. Ther. 16, 269.

Benowitz, N.L., 1988, Pharmacologic aspects of cigarette smoking and nicotine addiction, New Engl. J. Med. 319, 1318.

Bergstrom, L., T. Sakurada and L. Terenius, 1984, Substance P levels in various regions of the rat central nervous system after acute and chronic morphine treatment, Life Sci. 35, 2375.

Bijak, M. and A. Smialowski, 1989, Serotonin receptor blocking effect of SCH 23390, Pharmacol. Biochem. Behav. 32, 585.

Bischoff, S., M. Heinnch, J.M. Soontag and J. Krauss, 1986, The D-1 dopamine receptor antagonist SCH 23390 also interacts potently with brain serotonin (5-HT_2) receptors, Eur. J. Pharmacol. 129, 367.

Brase, D.A., L.F. Tseng, H.H. Loh and E.L. Way, 1974, Cholinergic modification of naloxone-induced jumping in morphine dependent mice, Eur. J. Pharmacol. 26, 1.

Chiou, C.Y., J.P. Long, R. Potrepka and J.L. Spratt, 1970, The ability of various nicotinic agent to release acetylcholine from synaptic vesicles, Arch. Int. Pharmacodyn. Ther. 187, 88.

Christensen, A.V., J. Arnt, J. Hyttel, J.J. Larsen and O. Svensen,1984, Pharmacological effects of a specific dopamine D-1 antagonist SCH 23390 in comparison with neuroleptics, Life Sci. 34, 1529.

Clarke, P.B.S. and A. Pert, 1985, Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons, Brain Res. 348, 355.

Davenport, K.E., A.A. Houdi and G.R. Van Loon, 1990, Nicotine protects against μ-opioid receptor antagonism by β-funaltrexamine: evidence for nicotine-induced release of endogenous opioids in brain, Neurosci. Lett. 113, 40.

Di Chiara, G., M.L. Porceddu, L. Vargiu, A. Argiolas and G.L. Gessa, 1976, Evidence for dopamine receptors in the mouse brain mediating sedation, Nature 264, 564.

Eiden, L.E., P. Giraud, J.T. Dave, A.J. Hotchkiss and H. Affolter, 1984, Nicotinic receptor stimulation activates enkephalin release and biosynthesis in adrenal chromaffin cell, Nature 312, 661.

Giorguieff, M.F., M.L. Kemel, D. Wandscheer and J. Glowinski, 1979, Regulation of dopamine release by presynaptic nicotinic receptors in rat striatal slices: effect of nicotine in a low concentration, Life Sci. 25, 1257.

Gomaa, A., L.H. Mohamed and H.N. Ahmed, 1989, Modification of morphine-induced analgesia, tolerance and dependence by bromocriptine, Eur. J. Pharmacol. 170, 129.

Goodman, F.R., 1974, Effects of nicotine on distribution and release of ^{14}C-norepinephrine and ^{14}C-dopamine in rat brain striatum and hypothalamus slices, Neuropharmacology 13, 1025.

Gossop, M., J. Powell, S. Grey and P. Hajek, 1990, What do opiate addicts and cigarette smokers mean by "craving"? A pilot study, Drug Alcohol Depend. 26, 85.

Hall, G.H. and D.M. Turner, 1972, Effects of nicotine on the release of [^{3}H]-noradrenaline from the hypothalamus, Biochem. Pharmacol. 21, 1829.

Henningfield, J.E. and S.R. Goldberg, 1988, Pharmacologic determinants of tobacco self-administration by humans, Pharmacol. Biochem. Behav. 30, 221.

Hicks, P.E., H. Schoemaker and S.Z. Langer, 1984, 5-HT receptor antagonist properties of SCH 23390 in vascular smooth muscle and brain, Eur. J. Pharmacol. 105, 339.

Houdi, A.A., K. Pierzchala, L. Marson, M. Palkovits and G.R. Van Loon, 1991, Nicotine-induced alteration in Tyr-Gly-Gly and Met-enkephalin in discrete brain nuclei reflects altered enkephalin neuron activity, Peptides 12, 161.

Hyttel, J., 1983, SCH 23390 the first selective dopamine antagonist, Eur. J. Pharmacol. 91, 153.

Imperato, A., A. Mulas and G. Di Chiara, 1986, Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats, Eur. J. Pharmacol. 132, 337.

Jhamandas, K. and G. Dickinson, 1973, Modification of precipitated morphine and methadone abstinence in mice by acetylcholine antagonists, Nature New Biol. 245, 219.

Jhamandas, K., M. Sutak and S. Bell, 1973, Modification of precipitated morphine withdrawal syndrome by drugs affecting cholinergic mechanisms, Eur. J. Pharmacol. 24, 296.

Kleven, M.S. and S.B. Sparber, 1989, Modification of the behavioral effects of 3-isobutyl-1-methylxanthine by serotonin agonists and antagonist: evidence for a role of serotonin in the expression of opiate withdrawal, Psychopharmacology 98, 231.

Malin, D.H., J.R. Lake, V.A. Carter, J.S. Cunningham and Wilson O.B., 1993, Naloxone precipitates nicotine abstinence syndrome in the rat, Psychopharmacology 112, 339.

Malin, D.H., J.R. Lake, V.A. Carter, J.S. Cunningham, K.M. Hebert, D.L. Conrad and O.B. Wilson, 1994, The nicotinic antagonist mecamylamine precipitates nicotine abstinence syndrome in the rat, Psychopharmacology 115, 180.

Marshall, I. and D.G. Grahame-Smith, 1971, Evidence against a role of brain 5-hydroxytryptamine in the development of physical dependence upon morphine in mice, J. Pharmacol. Exp. Ther. 179, 634.

Martin, B.R., E.S. Onaivi and T.J. Martin, 1989, What is the nature of mecamylamine's antagonism of the central effects of nicotine, Biochem. Pharmacol. 38, 3391.

Neal, B.S. and S.B. Sparber, 1986, Mianserin attenuates naloxone-precipitated withdrawal in rats acutely or chronically dependent upon morphine, J. Pharmacol. Exp. Ther. 236, 157.

Neal, B.S. and S.B. Sparber, 1990, The serotonin$_2$ antagonist ritanserin

blocks quasi-morphine withdrawal at a time when mianserin in no longer effective, Psychopharmacology 100, 258.

Nordberg, A., L. Romanelli, A. Sundwall, C. Bianchi and L. Beani, 1989, Effect of acute and subchronic nicotine treatment on cortical acetylcholine release and on nicotinic receptors in rats and guinea-pigs, Br. J. Pharmacol. 98, 71.

Rosecrans, J.A., J.S. Hendry and J.S. Hong, 1985, Biphasic effects of chronic nicotine treatment on hypothalamic immunnoreactive beta-endorphin in the mouse, Pharmacol. Biochem. Behav. 23, 141.

Saelens, J.K., F.R. Granat and W.K. Sawyer, 1971, The mouse jumping test. A simple screening method to estimate the physical dependence capacity of analgesics, Arch. Int. Pharmacodyn. Ther. 190, 213.

Stolerman, I.P., 1988, Characterization of central nicotinic receptors by studies on the nicotine cue and conditioned taste aversion in rats, Pharmacol. Biochem. Behav. 30, 235.

Stoof, J.C. and J.W. Kebabian, 1984, Two dopamine receptors: biochemistry, physiology and pharmacology, Life Sci. 35, 2281.

Torrens, Y., J.C. Beaujouan, M.J. Besson, R. Michelot and J. Glowinski, 1981, Inhibitory effects of GABA, L-glutamic acid and nicotine on the potassium-evoked release of substance P in substantia slice of the rat, Eur. J. Pharmacol. 71, 383.

Ueda, H., S. Tamura, M. Satoh and H. Takagi, 1987, Excess release of substance P from the spinal cord of mice during morphine withdrawal and involvement of the enhancement of presynaptic Ca^{2+} entry, Brain Res. 425, 101.

Way, E.L., H.H. Loh and F.H. Shen, 1969, Stimultaneous quantitative assessment of morphine tolernce and physical dependence, J. Pharmacol. Exp. Ther. 167, 1.

Zarrindast, M.R. and F. Abolfathi-Araghi, 1992, Effects of bupropion on core body temperature of mice, Psychopharmacology 106, 248.

Zarrindast, M.R. and M.R. Heidari, 1994, On the mechanisms by which theophylline changes core body temperature in mice, Eur. J. Pharmacol. 257, 13.

Zarrindast, M.R. and E. Moghadampour, 1989, Opposing influences of D-1 and D-2 dopamine receptor activation on morphine-induced antinociception, Arch. Int. Pharmacodyn. Ther. 300, 37.

Zarrindast, M.R. and S.A. Tabatabai, 1992, Involvement of dopamine receptor subtypes in mouse thermoregulation, Psychopharmacology 107, 341.