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Effects of nicotine on memory retrieval in mice

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Abstract

The effect of nicotine was tested on retrieval 24 h after training on a passive avoidance task. Intraperitoneal (i.p.) injection of nicotine (0.25–1.5 mg/kg) increased the step-down latency in mice dose dependently. Pretreatment with the nicotinic receptor antagonist mecamylamine (0.5–1 mg/kg) decreased, whereas pretreatment with the dopamine D_1 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, 0.05 and 0.1 mg/kg) and the β-adrenoreceptor antagonist propranolol (10 mg/kg) increased the nicotine response. The dopamine receptor D_2 receptor antagonist sulpiride (5–10 mg/kg), the anti-muscarinic agent atropine (2.5–10 mg/kg), the peripheral nicotinic receptor antagonist hexamethonium (0.01–0.5 mg/kg), the α-adrenoceptor antagonist phenoxybenzamine (1 and 10 mg/kg) and the peripheral dopamine D_2 receptor antagonist domperidone (5 and 10 mg/kg) did not change the response induced by nicotine. Single administration of the antagonists did not cause response; however, a high dose of domperidone (10 mg/kg) and propranolol alone increased the step-down latencies. It may be concluded that a nicotinic receptor mechanism is involved in the nicotine-induced improvement of memory retrieval.

Keywords: Nicotine; Retrieval; Passive avoidance; (Mouse)

1. Introduction

Nicotine is the only chemical available in a biologically significant quantity in tobacco that has been shown to meet criteria for an abusable drug. Nicotine has wide-ranging effects on the performance of behavioural tasks by animals and humans. The drug may affect the acquisition (Bovet et al., 1966; Balfour and Morrison, 1975; Bovet-Nitti, 1969; Evangelista et al., 1970; Morrison, 1974) and retention (Bättig, 1970; Castellano, 1976; Erikson, 1971) of a learning task. Other nicotine effects in animals include increases in locomotion (Clarke and Kumar, 1983; Cronan et al., 1985), tail tremors (Gomita et al., 1989), antinociception (Aceto et al., 1983) and responding for intracranial self-stimulation (Schaefer and Michael, 1986) or food reinforcement (White, 1989). Similar behaviours can be observed in humans (Perkins et al., 1990). The cholinergic system has been proposed to modulate memory (Haroutunian et al., 1985; Brioni and Izquierdo, 1988). Nicotine has also been shown to have both facilitating and impairing effects on learning and memory in animals. The dose of nicotine used may play an important role in the drug effect. The drug has been shown to improve recall in humans (Peeke and Peeke, 1984) and to produce a retrieval deficit in mice (Gillian and Schlessinger, 1985). The interaction of nicotine with postsynaptic nicotine receptors should play an important part in the production of its effects. However, many central effects of the drug have been shown to be attributed to changes in the release of a number of neurotransmitters (Balfour, 1982). Although the effect of nicotine in the central nervous system has been the subject of many experimental studies, the precise mechanisms involved in the behavioural and centrally mediated responses to the drug are not clear. In the present study, the effect of nicotine on retrieval from memory was investigated.

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2. Materials and methods

2.1. Animals

Male albino mice weighing 20–30 g body weight were used. The animals were housed 10 per cage at room temperature (22–24°C) and a 12-h light/12-h dark cycle, with food and water ad libitum.

2.2. Passive avoidance task

2.2.1. Apparatus

The method used in this experiment is based on the method we used in our previous study (Zarrindast and Shafaghi, 1994). The passive avoidance apparatus consisted of a wooden box (30 × 30 × 40 cm high) with a steel-rod grid floor (29 parallel steel rods, 0.3 cm in diameter set 1 cm apart). A wooden platform (4 × 4 × 4 cm) was set in the centre of the grid floor. Intermittent electric shocks (1 Hz, 0.5 s, 60 V DC) were delivered to the grid floor by an isolated stimulator.

2.2.2. Training

Each mouse was gently placed on the wooden platform. When the animal stepped down from the platform and placed all its paws on the grid floor, intermittent electric shocks were delivered continuously for 4 s.

2.2.3. Retrieval testing

24 h after training, each mouse was placed on the platform again, and the step-down latency was measured with a stop watch as passive avoidance behaviour. The latencies (s) indicated the level of retrieval. An upper cut-off time of 300 s was set.

2.3. Locomotion

The locomotor activity of each animal was measured individually with an activity meter, Animex, type S (LKB Farad). The locomotor activity of the animals was measured 30 min after propranolol or domperidone and 15 min after nicotine administration for 5 min.

2.4. Drugs

Nicotine (B.D.H. Chemicals, UK) and hexamethonium bromide (Sigma, UK), atropine sulfate (E. Merck, Germany), sulpiride, SCH 23390 (*R*-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-ol maleate), mecamylamine and domperidone (Research Biochemical, USA), propranolol (ICI, UK) phenoxybenzamine (Smith Kline and French, USA). The drugs were dissolved in saline, except for SCH 23390, which was dissolved in a drop of lactic acid and sulpiride and domperidone, which were dissolved in a drop of acetic acid and then diluted with saline. Nicotine was administered 15 min prior to the retrieval test. Atropine, domperidone, hexamethonium and propranolol were administered 15 min, mecamylamine and SCH 23390 30 min, phenoxybenzamine 60 min, and sulpiride 90 min before nicotine injection. The doses of the drugs were adopted from our previous works (Zarrindast et al., 1994, 1995).

2.5. Data analysis

The step-down latencies(s) are expressed as the median and interquartile ranges. The latencies indicated the level of retrieval. The data were analysed by Kruskal-Wallis non-parametric one-way analysis of variance (ANOVA) followed by Mann-Whitney's U-test. The locomotor activity of animals (counts/5 min) was analysed by Student's *t*-test. The criterion for statistical significance for all the tests was $P < 0.05$.

3. Results

3.1. Effect of nicotine on retrieval in trained mice

Fig. 1 shows the effect of nicotine administration on step-down latencies. Different doses of nicotine (0.1, 0.25, 0.5, 1 and 1.5 mg/kg) were administered interaperitoneally (i.p.) 24 h after training and 15 min before testing. Kruskal-Wallis one-way ANOVA revealed a significant drug effect, $H(5) = 39.2$, $P < 0.001$. Further statistical analysis with the Mann-Whitney U-test showed that different doses of nicotine (0.5, 1 and 1.5 mg/kg) caused a statistically significant increase in

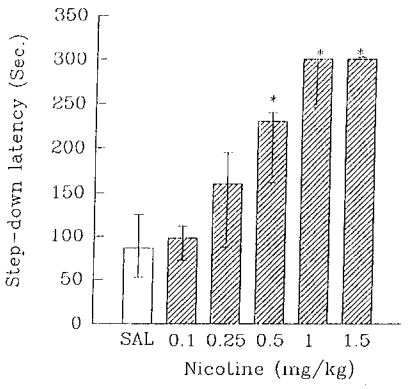

Fig. 1. Effect of nicotine on the step-down latencies in the retrieval test. Different doses of nicotine were administered intraperitoneally (i.p.) 24 h after training and 15 before the retrieval test. Each point is the median and interquartile ranges for 10 mice. $^{*}P < 0.001$ compared to the saline-treated group.

step-down latencies on retrieval of passive avoidance learning.

3.2. Effect of nicotinic and muscarinic receptor antagonists in the presence or absence of nicotine on the step-down latency

Animals were treated with saline (10 ml/kg) or mecamylamine (0.5 mg/kg,i.p.) 30 min before different doses of nicotine (0.1, 0.5 and 1 mg/kg) and were tested 15 min after nicotine injection. There was a significant difference between groups of animals which had been treated with mecamylamine alone or nicotine plus mecamylamine [$H(3) = 13.54$, $P < 0.01$, Kruskal-Wallis one-way ANOVA]. Statistical analysis showed that mecamylamine decreased the effect of nicotine (0.5 and 1.0 mg/kg) significantly (Mann-Whitney's U-test). There was no significant difference between groups of animals which received mecamylamine alone or saline (Mann-Whitney's U-test) (Fig. 2).

Table 1 shows the effect of different doses of mecamylamine, hexamethonium and atropine on the nicotine response. A significant difference was found between the animals pretreated with different doses of mecamylamine (0.1, 0.25, 0.5 and 1 mg/kg) or nicotine (0.5 mg/kg) [$H(4) = 23.6$, $P < 0.001$, Kruskal-Wallis one-way ANOVA]. Further analysis showed that a significant reduction in the nicotine-induced improvement of retrieval was obtained in animals treated with doses of 0.25, 0.5 and 1 mg/kg of mecamylamine. Mecamylamine alone did not change the step-down latencies at the doses used [$H(4) = 1.088$, $P > 0.05$, Kruskal-Wallis one-way ANOVA].

The step-down latencies of trained mice, that received either saline, atropine (2.5, 5 and 10 mg/kg, i.p.) or hexamethonium (0.01, 0.1 and 0.5 mg/kg) 15 min prior to nicotine and nicotine (0.5 mg/kg) 15 min before the retrieval test are also presented in Table 1. Analysis of the responses shows that atropine $H(3) = 0.58$, $P > 0.05$ or hexamethonium $H(3) = 2.04$, $P > 0.05$ (Kruskal-Wallis one-way ANOVA) alone or in combination with nicotine (atropine: $H(3) = 2.55$, $P > 0.05$; hexamethonium: $H(3) = 0.66$, $P > 0.05$) did not alter the step-down latencies significantly (Kruskal-Wallis one way ANOVA) compared with the those of saline or the saline-nicotine-treated group.

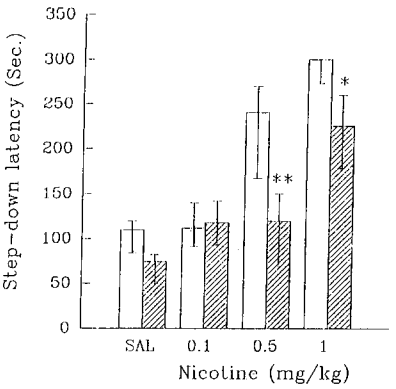

Fig. 2. Effect of mecamylamine on the nicotine-induced improvement of retrieval. Different doses of nicotine (0.1–1 mg/kg, i.p.) were administered 24 h after training session. Saline (10 ml/kg, i.p.) or mecamylamine (0.5 mg/kg, i.p.) was administered 30 min before nicotine and step-down latencies were recorded 15 min after nicotine injection. Each value represents the median and interquartile ranges ($n = 8$). $^{*}P < 0.05$, $^{**}P < 0.01$ different from saline + nicotine control group.

Table 1
Effects of nicotinic antagonist or antimuscarinic agents on the nicotine-induced improvement of retrieval

Treatment	Dose (mg/kg)	Latency to step-down (s)	
		After saline	After nicotine (0.5 mg/kg)
Saline	10 ml/kg	80 (76– 84)	150 (131–178)
Mecamylamine	0.1	64 (45– 83)	140 (80–150)
Mecamylamine	0.25	54 (40– 80)	110 (61–115) [a]
Mecamylamine	0.5	74 (47– 82)	60 (45– 77) [a]
Mecamylamine	1.0	78 (45– 85)	44 (25– 50) [a]
Saline	10 ml/kg	110 (75–165)	205 (122–246)
Hexametonium	0.01	103 (84–120)	225 (150–250)
Hexametonium	0.1	98 (90–120)	230 (155–300)
Hexametonium	0.5	81 (60–115)	175 (155–223)
Saline	10 ml/kg	85 (80– 95)	135 (115–205)
Atropine	2.5	46 (27– 65)	188 (135–240)
Atropine	5.0	90 (45–100)	150 (70–240)
Atropine	10	56 (45– 98)	170 (80–132)

Mice were administered nicotine (0.5 mg/kg, i.p.) or saline (10 ml/kg, i.p.) 24 h after the training session. Different doses of mecamylamine were administered 30 min and hexamethonium or atropine was injected 15 min before saline or nicotine injection. The step-down latencies were recorded 15 min after nicotine or saline injection. Each point represents the median and interquartile ranges for seven mice. [a] $P < 0.01$ different from nicotine control group.

3.3. Effects of dopamine receptor antagonists alone or in the presence of nicotine on step-down latencies of passive avoidance learning

Table 2 indicates the effect of SCH 23390, sulpiride and domperidone on the step-down latency of the passive avoidance response and the effect of these agents on the improvement of retrieval induced by nicotine. ANOVA showed a significant difference between the response induced by nicotine plus SCH 23390 and that induced by nicotine alone, $H(3) = 8.51$, $P < 0.05$. Analysis of the response to the drugs showed that SCH 23390 (0.01, 0.05 and 0.1 mg/kg) increased the response to nicotine in the step-down passive avoidance test (Mann-Whitney U-test). Single administration of SCH 23390 did not elicit any response $H(3) = 0.3$, $P > 0.05$. No differences were found between groups of animal which received sulpiride alone $H(3) = 0.42$, $P > 0.05$ or in combination with nicotine $H(3) = 3.3$, $P > 0.05$. However, there was a significant difference seen between animals administered domperidone or saline $H(2) = 7.6$, $P < 0.05$. Whitney's U-test showed that domperidone (10 mg/kg) increased the step-down latencies. Administration of domperidone before nicotine did not alter the response induced by nicotine $H(2) = 3.67$, $P > 0.05$ (Kruskal-Wallis one-way ANOVA).

3.4. Effects of adrenoceptor antagonists alone or in the presence of nicotine on retrieval of the passive avoidance task

Table 3 presents the effects of propranolol and phenoxybenzamine on passive avoidance and also the effects of these drugs on the retrieval improvement induced by nicotine. Analysis of the effects of propranolol with Kruskal-Wallis one-way ANOVA showed

Table 2
Effects of dopamine receptor antagonists on the nicotine-induced improvement of retrieval

Treatment	Dose (mg/kg)	Latency to step down(s)	
		After saline	After nicotine (0.5 mg/kg)
Saline	10 ml/kg	110 (75–165)	178 (140–260)
SCH 23390	0.01	122 (60–155)	300 (160–300) [b]
SCH 23390	0.05	89 (69–130)	300 (203–300) [b]
SCH 23390	0.1	95 (60–105)	300 (210–300) [b]
Saline	10 ml/kg	110 (75–140)	160 (135–195)
Sulpiride	5	105 (82–125)	158 (105–160)
Sulpiride	7.5	96 (75–120)	180 (110–185)
Sulpiride	10	97 (55–125)	210 (150–250)
Saline	10 ml/kg	90 (50–120)	164 (118–222)
Domperidone	5	102 (50–113)	178 (115–180)
Domperidone	10	220 (120–255) [a]	278 (187–280)

Mice were administered nicotine (0.5 mg/kg, i.p.) or saline (10 ml/kg, i.p.) 24 h after the training session. Different doses of SCH 23390 were administered 30 min, sulpiride 90 min and domperidone 15 min prior to nicotine or saline administration. The step-down latencies were recorded 15 min after nicotine or saline injection. Each point represents the median and interquartile ranges for seven mice. [a] $P < 0.05$ different from respective saline control group. [b] $P < 0.05$ different from nicotine + saline control group.

Table 3
Effects of α- and β-adrenoceptors on the improvement of retrieval induced by nicotine

Treatment	Dose (mg/kg)	Latency to step down(s)	
		After saline	After nicotine (0.5 mg/kg)
Saline	10 ml/kg	88 (68–125)	182 (165–230)
Propranolol	5	175 (85–180)	202 (127–240)
Propranolol	7.5	164 (102–185)	163 (123–265)
Propranolol	10	300 (180–300) [a]	300 (270–300) [a]
Saline	10 ml/kg	110 (75–165)	240 (142–265)
Phenoxybenzamine	1	105 (70–140)	210 (180–230)
Phenoxybenzamine	5	110 (83–150)	220 (170–240)
Phenoxybenzamine	10	230 (210–270)	200 (140–220)

Mice were administered nicotine (0.5 mg/kg, i.p.) or saline (10 ml/kg, i.p.) 24 h after the training session. Different doses of phenoxybenzamine were administered 60 min and propranolol 15 min before saline or nicotine injection. The step-down latencies were recorded 15 min after nicotine or saline injection. Each point represents the median and interquartile ranges for seven mice. [a] $P < 0.01$ different from respective control group.

that there was a significant drug effect between animal groups $H(3) = 12.22$, $P < 0.01$. Further statistical analysis by Mann-Whitney U-test revealed that the high dose of propranolol alone (10 mg/kg) significally increased the step-down latencies.

However, no difference was found in animals treated with phenoxybenzamine alone $H(3) = 4.3$, $P > 0.05$. Administration of propranolol 15 min before nicotine injection significantly altered the response induced by nicotine $H(3) = 9.47$, $P < 0.05$. Further analysis showed that propranolol 10 mg/kg increased the response induced by nicotine. Pretreatment with the α-adrenoceptor antagonist phenoxybenzamine did not change the nicotine response significantly $H(3) = 0.66$, $P > 0.05$ (Kruskal-Wallis one-way ANOVA).

4. Discussion

Nicotine was shown in this study to increase step-down latencies in a passive avoidance learning task in mice. The present data show that nicotine increased step-down latencies in a dose-dependent manner. Low doses of nicotine have been shown to increase locomotor activity (Clarke and Kumar, 1983; Cronan et al., 1985). Locomotor activity is a major problem in testing the effect of different agents on learning and memory and it has been suggested that this task is more reliable than other methods of memory and learning assessment in this respect (Ichihara et al., 1988). Nicotine in the dose used (0.5 mg/kg) did not alter locomotion in our present study, and therefore the increase in step-down latencies induced by the drug is not due to a decrease in locomotion. However, a higher dose of the drug (1 mg/kg; 40.7 ± 10.8; $P < 0.05$) decreased the locomotor activity significantly as compared with saline (155 ± 19.5) (Student's t-test). The other drugs used in this study had no effect on locomotor activity (data not shown). The response obtained is not in agreement with the results of other authors showing that nicotine produces a retrieval deficit in mice (Gillian and Schlessinger, 1985).

The improvement of retrieval induced by nicotine was decreased by the nicotinic receptor antagonist mecamylamine (Martin et al., 1989), which may indicate that the nicotine response is mediated by nicotinic receptor mechanism(s). The results obtained by some investigators (Quartermain et al., 1988; Gozzani and Izquierdo, 1976) show that both peripheral and central mechanisms are involved in learning and memory processes. Since the peripheral nicotinic receptor antagonist hexamethonium did not decrease the nicotine effect, central nicotinic receptor sites may be involved.

Nicotine has been shown to release a number of neurotransmitters (Balfour, 1982) including acetylcholine (Chiou et al., 1970). A cholinergic mechanism has been proposed to be involved in memory (Haroutunian et al., 1985). Since the antimuscarinic cholinergic agent atropine failed to alter the nicotine-induced improvement of retrieval, the involvement of muscarinic receptors in the response seems unlikely.

There is evidence that dopaminergic neurons possess nicotinic receptors, and nicotine enhances dopamine release by increasing neuronal firing and via a direct presynaptic action on terminals (Clarke, 1990). The present data indicate that the dopamine D_1 receptor antagonist SCH 23390 (Hyttel, 1984) increased the effect of nicotine. It is possible that dopaminergic mechanisms exert a negative influence on the improvement of retrieval induced by nicotine. However, the antagonist alone did not elicit any response. SCH 23390 may also bind with high affinity to 5-HT_2 receptors in the brain (Bischoff et al., 1986) and antagonize 5-HT_2 receptor activation both centrally and peripherally (Bijak and Smialowski, 1989; Hicks et al., 1984). Therefore, to evaluate the present results, more studies may be required. Dopaminergic mechanisms have been shown to affect learning (Zarrindast et al., 1992; Bracs et al., 1984). The D_2 dopamine receptor antagonist sulpiride (Stoof and Kebabian, 1984) did not change the nicotine effect. Thus, the involvement of D_2 dopamine receptor mechanism(s) seems unlikely. Single administration of domperidone improved recall. This may reflect the involvement of a peripheral dopamine mechanism in the task, although the antagonist did not alter the nicotine effect.

Although nicotine has been proposed to release catecholamines (Balfour, 1982) and adrenergic mechanisms have been shown to effect learning and memory processes (Quartermain et al., 1988), the α-adrenoceptor antagonist phenoxybenzamine did not change the step-down latencies, thus α-adrenoceptor mechanisms appear not to be involved in the nicotine-induced improvement of retrieval.

The β-adrenoceptor antagonist propranolol increased the nicotine response. The antagonist alone also increased the retrieval of the learned task, which may not be in agreement with the report (McGaugh et al., 1988) showing that β-adrenergic activation enhances memory. It seems unlikely that propranolol actually potentiated the effect of nicotine, and thus further studies are needed to elucidate the precise mechanism involved in the interaction between β-adrenoceptor and nicotinic mechanisms in the process of learning and memory.

References

Aceto, M.D., H. Awaya, B.R. Martin and E.L. May, 1983, Antinociceptive action of nicotine and its methiodide derivatives in mice and rats, Br. J. Pharmacol. 79, 869.

Bättig, K., 1970, The effect of pre-and post-trial application of nicotine on the 12 problems of the Hebb-Williams Test in the rat, Psychopharmacology 18, 68.

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

Balfour, D.J.K., C.T., Morrison, 1975, A possible role for the pituitary-adrenal system in the effects of nicotine on avoidance behaviour, Pharmacol. Biochem. Behav. 3, 349.

Bijak, M. and A. Smialowski, 1989, Serotonin receptor blocking effect of SCH23390, Pharmacol. Biochem. Behav. 32, 585.

Bischoff, S., M. Heinnch, J.M. Soontag and J. Krauss, 1986, The D-1 dopamine receptor antagonist SCH23390 also interacts potently with brain serotonin (5-HT_2) receptors, Eur. J. Pharmacol. 129, 367.

Bovet, D., F. Bovet-Nitti, A. Oliverio, 1966, Effects of nicotine on avoidance conditioning of inbred strians of mice, Psychopharmacology 10, 1.

Bovet-Nitti, F., 1969, Facilitation of simultaneous visual discrimination by nicotine in four 'inbred' strains of mice, Psychopharmacologia 14, 193.

Bracs, P.U., P. Gregory and D.M. Jackson, 1984, Passive avoidance in rats: disruption by dopamine applied to the nucleus accumbens, Psychopharmacology 83, 70.

Brioni, J.D. and I. Izquierdo, 1988, Retention enhancement by pre-test B-endorphin and oxotremorine and its reversal by scopolamine, Behav. Neural. Biol. 50, 251.

Castellano, C., 1976, Effects of nicotine on discrimination learning, consolidation and learned behaviour in two inbred strains of mice, Psychopharmacology 48, 37.

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.

Clarke, P.B.S., 1990, Dopaminergic mechanisms in locomotor stimulant effects of nicotine, Biochem. Pharmacol. 40, 1423.

Clarke, P.B.S. and R. Kumar, 1983, The effects of nicotine on locomotor activity in non-tolerant and tolerant rats, Br. J. Pharmacol., 78, 329.

Cronan, T., J. Conrad and R. Bryson, 1985, Effects of chronically administrated nicotine and saline on motor activity in rats, Pharmacol. Biochem. Behav. 22, 897.

Erikson, C.K., 1971, Studies on the mechanism of avoidance facilitation by nicotine, Psychopharmacologia 22, 357.

Evangelista, A.M., R.C. Gattoni and I. Izquierdo, 1970, Effect of amphetamine, nicotine and hexamethonium on performance of a conditioned response during acquisition and retention trials, Pharmacology 3, 91.

Gillian, D.M. and K. Schlessinger, 1985, Nicotine-produced relearning deficit in C57BL/6J and DBA/2J mice, Psychopharmacology 86, 291.

Gomita, Y., K. Suermani, K. Furuno and Y. Araki, 1989, Nicotine-induced tail-tremor and drug effects, Pharmacol. Biochem. Behav. 34, 817.

Gozzani, J.L. and I. Izquierdo, 1976, Possible peripheral adrenergic and central dopaminergic influences in memory consolidation. Psychopharmacology 49, 109.

Haroutunian, V., E. Barnes and K.L. Davis, 1985, Cholinergic modulation of memory in rats, Psychopharmacology 87, 266.

Hicks, P.E., H. Schoemaker and S.Z. Langer, 1984, 5-HT receptor antagonist properties of SCH23390 in vascular smooth muscle and brain, Eur. J. Pharmacol. 105, 339.

Hyttel, J., 1984, Functional evidence for selective dopamine D_1 receptor blockade by SCH 23390, Neuropharmacology 23, 1395.

Ichihara, K., T. Nabeshima and T. Kameyama, 1988, Effect of haloperidol, sulpiride and SCH 23390 on passive avoidance learning in mice, Eur. J. Pharmacol. 151, 435.

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.

McGaugh, J.L., I.B. Introini and A.H. Nagahara, 1988, Memory-enhancing effects of posttraining naloxone: involvement of β-noradrenergic influences in the amygdaloid complex, Brain Res. 446, 37.

Morrison, C.F., 1974, Effects of nicotine and its withdrawal on the performance of rats on signalled and unsignalled avoidance schedulles, Psychopharmacology 38, 25.

Peeke, S.C. and Peeke, H.V.S., 1984, Attention, memory, and cigarette smoking, Psychopharmacology 84, 205.

Perkins, K.A., L.H. Epstein, R.L. Stiller, J.E. Sexton, T.D. Debski and R.G. Jacob, 1990, Behavioral performance effects of nicotine smokers and nonsmokers, Pharmacol. Biochem. Behav. 37, 11.

Quartermain, D., M.E. Judge and P. Leo, 1988, Attenuation of forgetting by pharmacological stimulation of aminergic neurotransmitter systems, Pharmacol. Biochem. Behav. 30, 77.

Schaefer, G.J. and R.P. Michael, 1986, Task-specific effects of nicotine in rats: intracranial self-stimulation and locomotor activity, Neuropharmacology 25, 125.

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

White, J.M., 1989, Behavioural interactions between nicotine and diazepam, Pharmacol. Biochem. Behav. 32, 497.

Zarrindast, M.R. and B. Shafaghi, 1994, Effects of adenosine agoinst and antagonists on acquisition of passive avoidance learning, Eur. J. Pharmacol. 256, 233.

Zarrindast, M.R., M. Satari-Naeini and F. Motamedi, 1992, Effect of D-1 or D-2 receptor stimulation on memory retrieval in mice, J. Psychopharmacol. 6, 526.

Zarrindast, M.R., A. Vahedy, M.R. Heidari and M. Ghazi Khansari, 1994, On the mechanism(s) of morphine-induced hypothermia, J. Psychopharmacol. 8, 222.

Zarrindast, M.R., A. Zarghi and A. Amiri, 1995, Nicotine induced hypothermia through indirect dopaminergic mechanisms, J. Psyschpharmacol. 9, 20.