ANTIAMNESIC ACTIVITY OF THE NICOTINIC AGONIST DBO-83 IN MICE

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Research Article

Antiamnesic Activity of the Nicotinic Agonist DBO-83 in Mice

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Strategy, Management and Health Policy				
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ABSTRACT The effect of administration of DBO-83 on memory processes was evaluated in the mouse passive avoidance test. DBO-83 (1–5 $mgkg^{-1}$ ip) prevented amnesia induced by scopolamine (1.5 $mgkg^{-1}$ ip), mecamylamine (20 $mgkg^{-1}$ ip) and dihydro-β-erythroidine (10 μg per mouse i.c.v.). In the same experimental conditions, DBO-83 (10 $mgkg^{-1}$ ip) also prevented baclofen (2 $mgkg^{-1}$ ip), clonidine (0.125 $mgkg^{-1}$ ip) and diphenhydramine (20 $mgkg^{-1}$ ip) amnesia in mice. The antiamnesic effect of DBO-83 was comparable to that exerted by nicotine (2 $mgkg^{-1}$ ip), physostigmine (0.2 $mgkg^{-1}$ ip), and the nootropic drug, piracetam (30 $mgkg^{-1}$ ip). In the antiamnesic dose-range, DBO-83 did not impair mouse motor coordination and spontaneous motility, as revealed, respectively, by the Animex apparatus and rotarod test. These results demonstrated the ability of DBO-83 to modulate memory functions and suggest that DBO-83 could be useful in the treatment of cognitive deficits. Drug Dev. Res. 45:45–51, 1998.

Key words: DBO-83; learning; memory; amnesia; nicotinic agonist; passive avoidance

INTRODUCTION

Recently, there has been increased interest in the role of nicotinic neurotransmission in cognitive deficits associated with Alzheimer's disease and in the therapeutic potential of agents that activate neuronal nicotinic receptors. The potential for the development of therapies for Alzheimer's disease that work through the stimulation of nicotinic receptors is suggested by the observation that nicotine improves some aspects of cognitive function in patients affected by Alzheimer's disease [Newhouse et al., 1988; Jones et al., 1992; Wilson et al., 1995]. There is now substantial evidence that nicotinic neurotransmission plays an important role in cognitive function [Levin, 1992]. In rats, nicotine reverses cognitive impairments due to basal forebrain lesions [Hodges et al., 1991; Decker et al., 1992] and age [Arendash et al., 1995; Socci et al., 1995] and in mice prevents mnemonic deficits induced by pharmacological treatments such as mecamylamine [Zarrindast et al., 1996] and scopolamine [Coyle et al., 1987].

The beneficial effects of nicotine have also been exhibited by other nicotinic agonists. (-)-Lobeline [Decker et al., 1993], ABT-418 [Decker et al., 1994], ABT-089 [Decker et al., 1997], AG-4 [Marchese et al., 1997], and GTS-21 [Meyer et al., 1994] have been reported to ameliorate memory impairments in rodents in some experimental paradigms.

Within the framework of the research for new nicotinic agonists potentially useful in the prevention of reduced cognitive performance, it was decided to use DBO-83 (3-[p-Cl-pyridazine-6-yl]-diazabicyclo[3.2.1]-octane). The present work was designed to verify the ability of this new nicotinic agonist [Ghelardini et al.,

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1997; Barlocco et al., 1998] to prevent pharmacologically induced amnesia in the mouse passive-avoidance test.

MATERIALS AND METHODS

Animals

Male Swiss albino mice (23–30 g) from Morini (San Polo d'Enza, Italy) breeding farms were used. Fifteen mice were housed per cage. The cages were placed in the experimental room 24 h before the test for acclimatization. The animals were kept at 23 ± 1°C with a 12-h light/dark cycle, light at 7 AM, with food and water ad libitum. All experiments were carried out according to the guidelines of the European Community Council for experimental animal care.

Passive-Avoidance Test

The test was performed according to the step-through method described by Jarvik and Kopp [1967]. The apparatus consisted of a two-compartment acrylic box with a lighted compartment connected to a darkened one by a guillotine door. Mice, as soon as they entered the dark compartment, received a punishing electrical shock (0.5 mA, 1 sec). The latency times for entering the dark compartment were measured in the training test and after 24 h in the retention test. For memory disruption, animals were injected with amnesic drugs. Scopolamine, mecamylamine, dihydro-β-erythroidine, clonidine, baclofen, diphenhydramine were i.p. injected immediately after the training session. To improve memory animals were treated, 20 min before the training session, with DBO-83, piracetam, nicotine, or physostigmine. The drug administration schedule was chosen on the basis of preliminary experiments in which the time-course for every compound was determined. The maximum entry latency allowed in the training session was 30 sec for mice, whereas in the retention session the entrance latency allowed was 120 sec. The memory degree of received punishment was expressed as latencies recorded in the retention and training sessions.

Spontaneous Activity Meter (Animex)

Locomotor activity in mice was quantified using an Animex activity meter Type S (LKB, Farad, Sweden) set to maximum sensitivity. Every movement of the mice, which were placed on the top of the Animex activity meter, produced a signal due to variation in inductance and capacity of the apparatus resonance circuit. Signals were automatically converted to numbers. On the day of the experiment the mice were treated and then the cage, containing five mice, was put on the measuring platform. Activity counts were made for 5 min at 15-min intervals for 45 min (total of three sessions) starting immediately after injection of the drug. Because of the arbitrary scale adopted to quantify movements, drug-treated mice were always compared with saline-treated ones.

Rotarod Test

The apparatus consisted of a base platform and a rotating rod of 3 cm diameter with a nonslippery surface. This rod was placed at height of 15 cm from the base. The rod, 30 cm in length, was divided into five equal sections by six disks. Thus, up to five mice were tested simultaneously on the apparatus, with a rod-rotating speed of 16 r.p.m. The integrity of motor coordination was assessed on the basis of endurance time of the animals on the rotating rod. One day before the test, the animals were trained twice. On the day of the test only the mice that were able to stay balanced on the rotating rod between 70 and 120 s (cutoff time) were selected for testing. The performance time was measured before and at various times after treatment.

Intracerebroventricular Injection Technique

Intracerebroventricular (icv) administration was performed in mice under ether anesthesia using isotonic saline as solvent, according to the method described by Haley and McCormick [1957]. Briefly, under anesthesia mice were grasped firmly by the loose skin behind the head. A 0.4 mm external diameter hypodermic needle attached to a 10 µl syringe was inserted perpendicularly through the skull to a depth of no more than 2 mm into the brain of the mouse, where 5 µl were then administered. The injection site was 1.5 mm from either side of the midline on a line drawn through to the anterior base of the ears. To ascertain that the drugs were administered exactly into the cerebral ventricle, some mice were icv injected with 5 µl of diluted 1:10 India ink and their brains examined macroscopically after sectioning. The accuracy of the injection technique was evaluated and 95% were correct injections.

Reagents and Compounds

The following compounds were used: DBO-83 (3-[p-Cl-pyridazine-6-yl]-diazabicylo[3.2.1]octane), prepared at the Institute of Pharmaceutical and Toxicological Sciences, University of Milan; diphenhydramine hydrochloride (de Angeli); scopolamine hydrobromide, mecamylamine hydrochloride, clonidine hydrochloride (RBI, Natick, MA), nicotine hydrogentartrate, dihydro-β-erythroidine (Fluxa), baclofen, piracetam, physostigmine hemisulphate (Sigma, St. Louis, MO).

Compounds were dissolved in isotonic (NaCl 0.9%) saline solution and concentrations were prepared in such a way that the necessary dose could be administered in a volume of 5 µl per mouse by intracerebroventricular (icv) injection and 10 ml kg^{-1} by intraperitoneal (ip) injection.

Statistical Analysis

All experimental results are given as the mean ± SEM. Analysis of variance (ANOVA), followed by Fisher's Protected Least Significant Difference (PLSD) procedure for post-hoc comparison was used to verify significance between two means. Data were analyzed with the StatView software for the Macintosh (1992). *P* values of less than 0.05 were considered significant.

RESULTS

Prevention of Amnesia by DBO-83

The nicotinic agonist DBO-83 dose-dependently prevented amnesia induced by the antimuscarinic drug scopolamine (1.5 $mgkg^{-1}$ ip) in the mouse passive-avoidance test (Fig. 1). DBO-83, at the dose of 0.5 $mgkg^{-1}$ ip, was completely ineffective, whereas at the doses of 1 and 5 $mgkg^{-1}$ ip, it prevented antimuscarinic amnesia, reaching entrance latency values comparable to those produced by saline-treated mice.

The maximum antiamnesic effect of DBO-83 (5 $mgkg^{-1}$ ip) was also equal to that produced by the anticholinesterase inhibitor, physostigmine (0.2 $mgkg^{-1}$ ip), and the well-known nootropic drug, piracetam (30 $mgkg^{-1}$ ip) (Fig. 1). However, at active doses DBO-83 it did not enhance the entrance latency in unamnesic mice in comparison with the control group (Fig. 1). There were no differences observed in the various entrance latencies of every group in the training session of the passive-avoidance test (Fig. 1). The administration of DBO-83 (range 1–5 $mgkg^{-1}$ ip) also antagonized the memory disruption produced by the two nicotinic antagonists, mecamylamine (20 $mgkg^{-1}$ ip) and dihydro-β-erythroidine (10 μg per mouse icv), (Fig. 2, 3). Doses of DBO-83 of 5–10 $mgkg^{-1}$ ip were necessary to prevent amnesia induced by the α_2 agonist, clonidine (0.125 $mgkg^{-1}$ ip), the $GABA_B$ agonist, baclofen (2 $mgkg^{-1}$ ip), and the H_1 antagonist, diphenhydramine (20 $mgkg^{-1}$ ip) (Fig. 4) in the mouse passive-avoidance test. The maximum antiamnesic effect was reached at the dose of 10 $mgkg^{-1}$ ip. DBO-83 was active in facilitating memory similar to nicotine in the presence of mecamylamine and dihydro-β-erythroidine-induced amnesia (Figs. 2, 3).

Effect of DBO-83 on Mouse Rotarod Test and Mouse Animex Apparatus

It should be noted that DBO-83 elicited its modulatory effect on cognitive processes without changing the

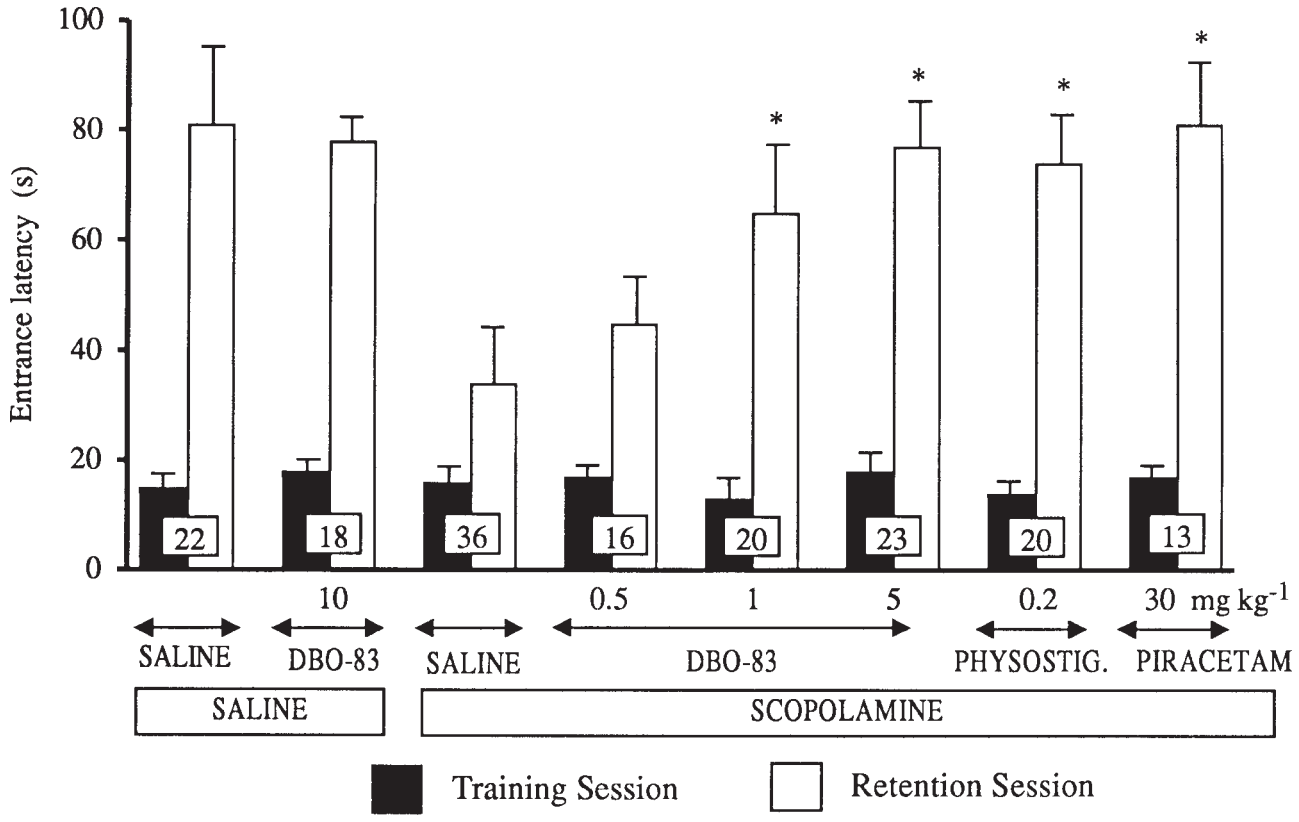

Fig. 1. Dose–response curves of DBO-83 in comparison with piracetam and physostigmine on amnesia induced by scopolamine (1.5 $mgkg^{-1}$ ip) in the mouse passive-avoidance test. DBO-83, piracetam, and physostigmine were administered ip 20 min before the training session while scopolamine was injected immediately afterwards. The number of mice is inside the column. *$P < 0.01$ in comparison with scopolamine-treated mice.

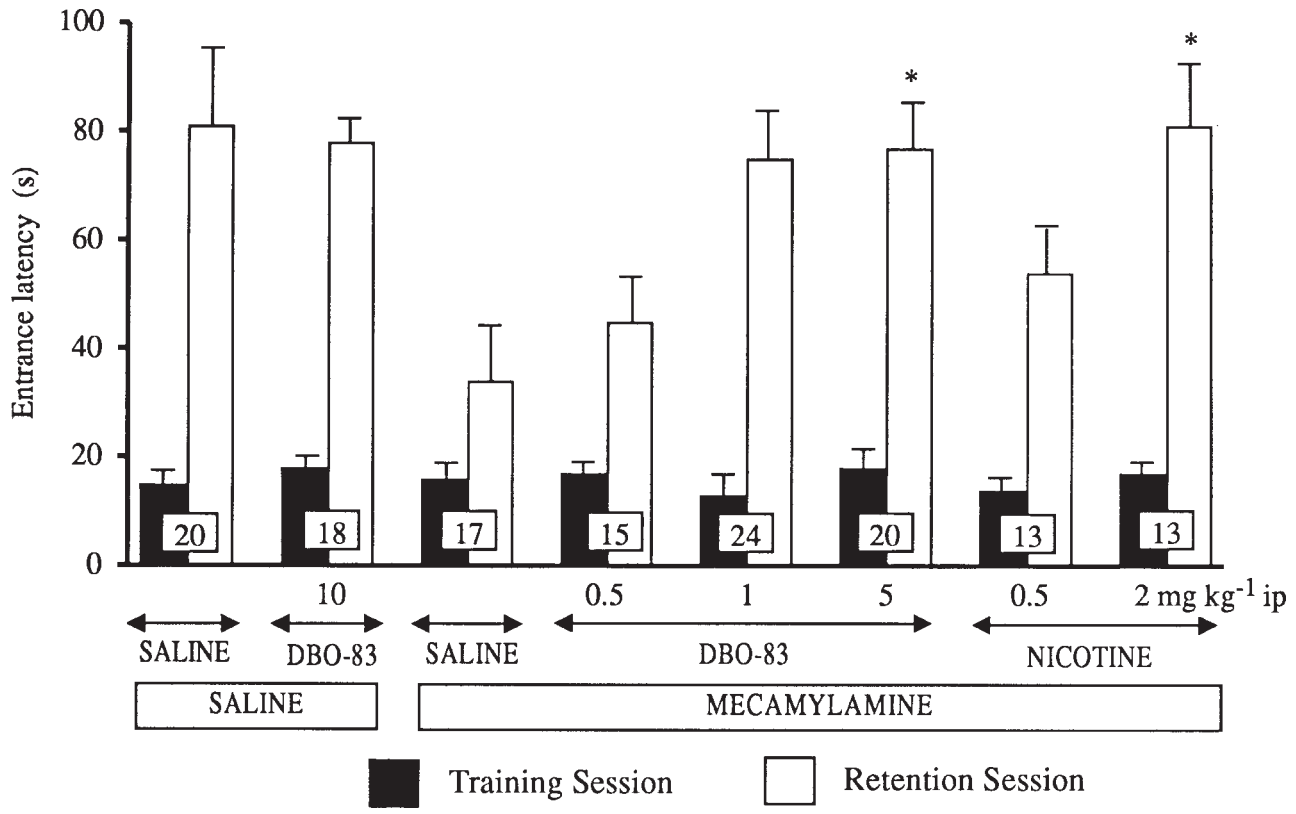

Fig. 2. Dose–response curves of DBO-83 in comparison with nicotine on amnesia induced by mecamylamine (20 $mgkg^{-1}$ ip) in the mouse passive-avoidance test. DBO-83 and nicotine were administered ip 20 min before the training session while mecamylamine was injected immediately afterwards. The number of mice is inside the column. *$P < 0.01$ in comparison with mecamylamine-treated mice.

animal's gross behavior, motor coordination, or spontaneous motility as revealed, respectively, by using the mouse rotarod test (Table 1) and the Animex apparatus (Fig. 5). DBO-83, administered at the highest active doses, did not reduce the endurance time on the rotating rod in comparison with saline-treated mice (Table 1).

The spontaneous motility of mice were unmodified by DBO-83 administration (10 $mgkg^{-1}$ ip) as revealed by the Animex apparatus in comparison with saline-treated mice (Fig. 5).

DISCUSSION

The present results describe acute effects observed with DBO-83 on experimentally impaired memory in mice. DBO-83 has been demonstrated to prevent amnesia induced by pharmacological treatments in the passive-avoidance test.

That stimulation of the nicotinic system improves cognitive processes has long been observed [Tilson et al., 1988; Hodges et al., 1991; Decker et al., 1992; Socci et al., 1995]. On the other hand, the administration of the nicotinic ACh receptor antagonist, mecamylamine, produces a dose-dependent impairment of cognitive performance in mice [Dilts and Berry, 1967; Zarrindast et al., 1996], rats [Elrod and Buccafusco, 1991; Bammer, 1982], monkeys [Elrod et al., 1988], and humans [Newhouse et al., 1992, 1994]. Also, the nicotinic blocker dihydro-β-erythroidine disrupted acquisition in spatial information in the rat Morris water maze [Curzon et al., 1996]. The administration of scopolamine, an unselective muscarinic ACh receptor antagonist, results in impaired learning and memory in humans [Frumier et al., 1976] and animals [Dilts and Berry, 1967; Levin and Bowman, 1986].

Amnesia can also be induced by modulating neurotransmitter systems other than the cholinergic. The α_2 antagonist clonidine is able to induce an amnesic effect in mice and rats in the passive-avoidance test [Coyce et al., 1987]. GABA is the main inhibitory neurotransmitter in the brain and it plays an important role in learning and memory. The activation of $GABA_A$ receptors impairs memory performance [Jerusalinsky et al., 1994] and the stimulation of $GABA_B$ receptors by baclofen disrupts memory after systemic, intra-amygdala or intraseptal administration [Swartzwelder et al., 1987; Castellano et al., 1989; Stackman and Walsh, 1994]. The antihistaminics are known to exert a variety of effects on the central nervous system. Central depression usually accompanies therapeutic doses of the H_1 antagonists, which appears

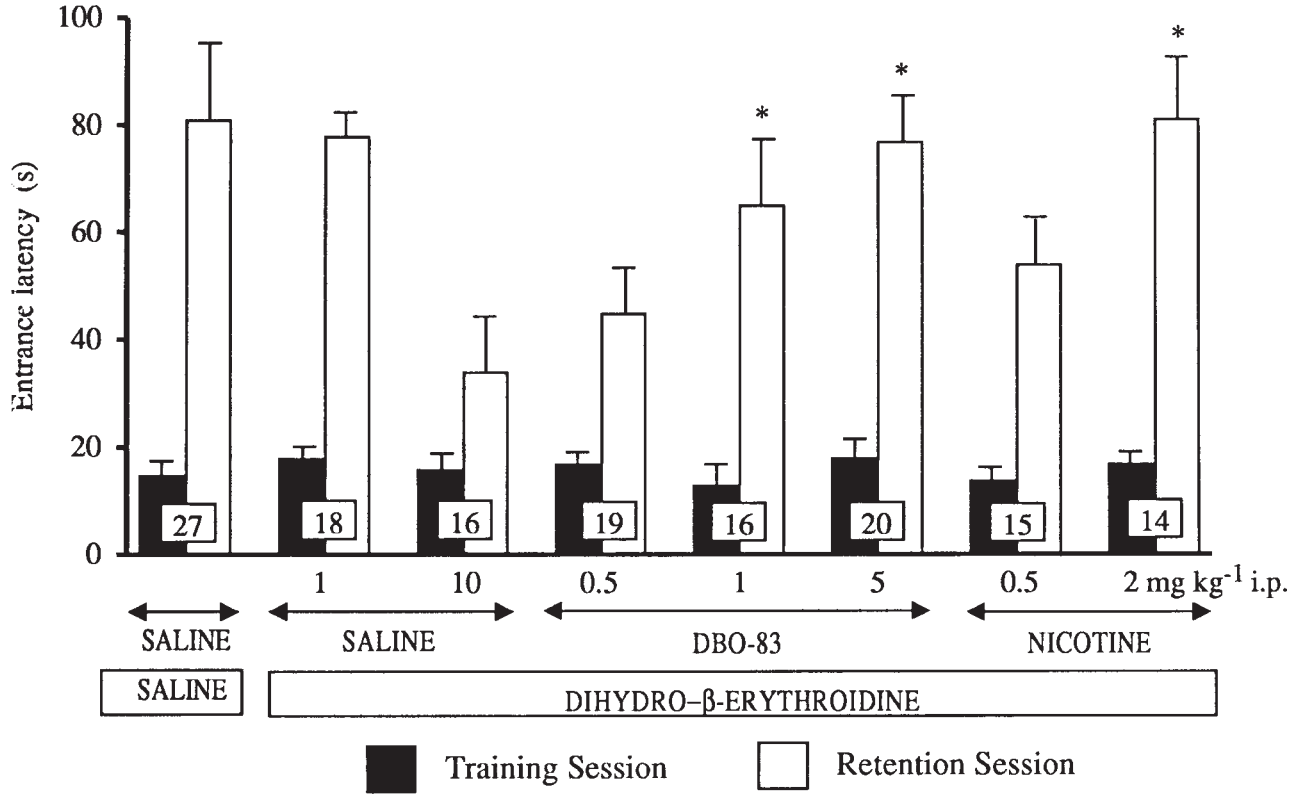

Fig. 3. Dose–response curves of DBO-83 in comparison with nicotine on amnesia induced by dihydro-β-erythroidine (10 μg per mouse icv) in the mouse passive avoidance test. DBO-83 and nicotine were administered ip 20 min before the training session while dihydro-β-erythroidine was injected immediately afterwards. The number of mice is inside the column. *$P < 0.01$ in comparison with dihydro-β-erythroidine-treated mice.

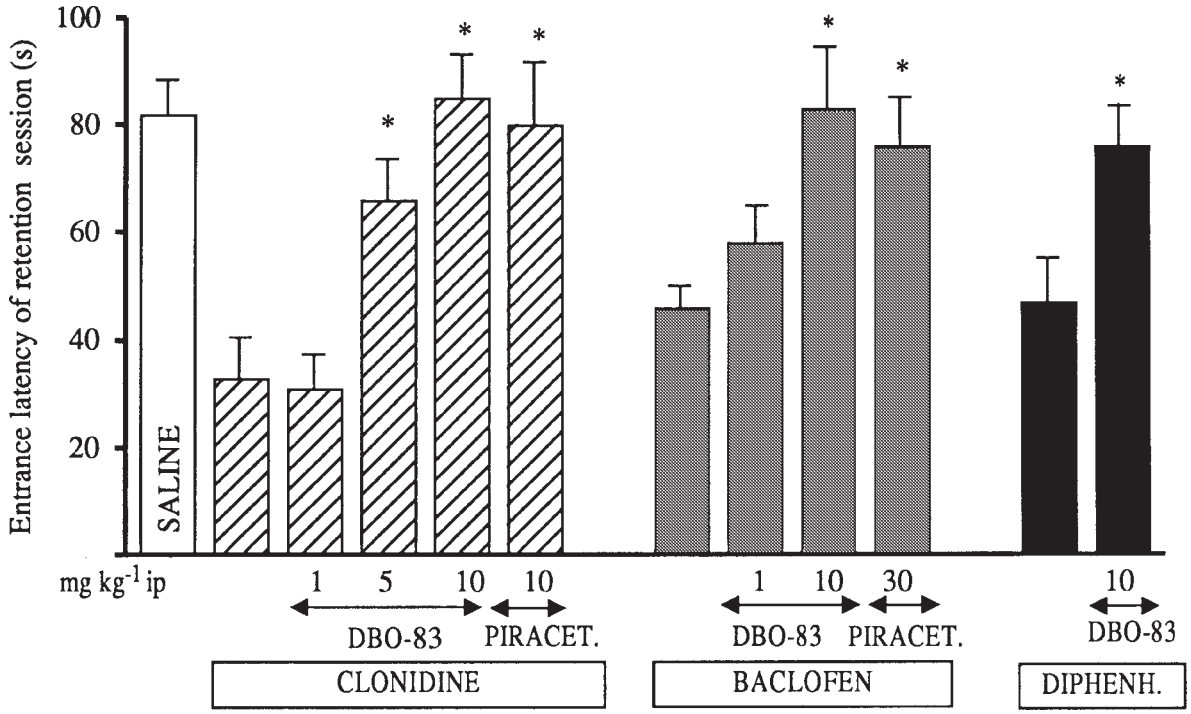

Fig. 4. Dose–response curves of DBO-83 in comparison with piracetam on amnesia induced in the mouse by clonidine (0.125 $mgkg^{-1}$ ip), baclofen (2 $mgkg^{-1}$ ip) and diphenhydramine (20 $mgkg^{-1}$ ip) in the passive-avoidance test. DBO-83 and piracetam were administered ip 20 min before the training session while the other drugs were injected immediately afterwards. Each column represents the mean of at least 15 mice. *$P <$ 0.01 in comparison with amnesic drug-treated animals.

TABLE 1. Effect of DBO-83 in the Rotarod Test

	Endurance time on rotarod(s)			
	Before treatment	After treatment		
		15 min	30 min	45 min
Saline	102.7 ± 5.3 (11)	98.6 ± 7.8 (11)	99.5 ± 6.6 (11)	103.4 ± 5.1 (11)
DBO-83 5 $mgkg^{-1}$ ip	97.1.6 ± 6.2 (10)	101.2 ± 6.9 (10)	97.5 ± 5.9 (10)	103.6 ± 7.4 (10)
DBO-83 10 $mgkg^{-1}$ ip	101.3 ± 7.1 (10)	96.7 ± 8.4 (10)	102.5 ± 9.1 (10)	93.7 ± 6.9 (10)

The number of mice is shown in parentheses.

to be related to occupancy of cerebral H_1 receptors; impairment of cognitive functions is a common manifestation [Simons and Simons, 1994]. Furthermore, the administration of the cerebral H_1 antagonist diphenhydramine also induces amnesia in animals [Kamei et al., 1990; Galeotti et al., 1998].

DBO-83 was able to prevent amnesia induced by the administration of scopolamine, mecamylamine, dihydro-β-erytroidine, clonidine, baclofen, and diphenhydramine. Thus, DBO-83 counteracts amnesia not only induced by nicotinic antagonists, but also that obtained independently from a nicotinic blockade.

DBO-83 is also endowed with antinociceptive properties [Ghelardini et al., 1997; Barlocco et al., 1998] and the time-course of the antiamnesic activity of DBO-83 was equal to that observed for its antinociceptive action, reaching its maximum between 15 and 30 min after injection (data not shown). Therefore, in the learning and memory experiments DBO-83 was administered 20 min before the training session.

In the first session, the latency to enter the dark compartment of the light-dark box in the passive-avoidance test was not modified by the administration of DBO-83. This observation was confirmed by evaluation of the behavioral parameters in mice. DBO-83, at the highest doses used, did not impair motor coordination, as revealed by the rotarod test, or modify spontaneous motility, as indicated by the Animex apparatus. Furthermore, DBO-83 did not elicit the typical tremors produced by injection of nicotine. In other words, DBO-83 is able to counteract amnesia in a physiological manner.

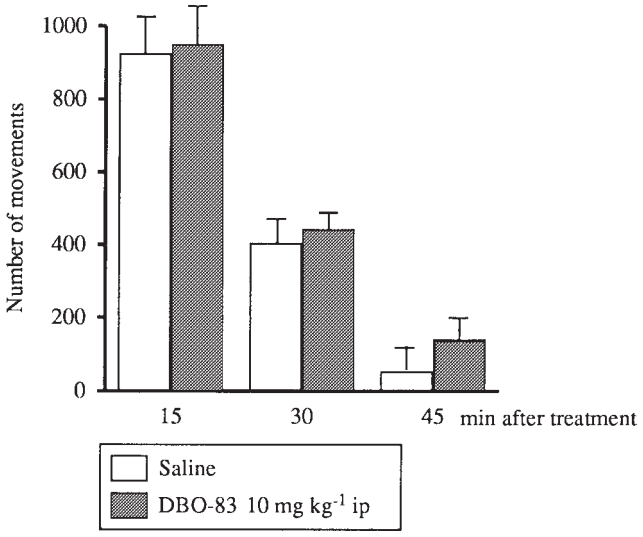

Fig. 5. Lack of effect of DBO-83 on mouse spontaneous motility. Each column represents the mean of 15 mice.

In conclusion, these results indicate the ability of DBO-83 to modulate memory processes. On these bases, DBO-83 could be considered a new potential antiamnesic drug, useful in the treatment of cognitive disorders.

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