



UNIVERSITÀ
DEGLI STUDI
FIRENZE

FLORE

Repository istituzionale dell'Università degli Studi di Firenze

AG-4:A NICOTINIC AGONIST ENDOWED WITH ANTIAMNESIC PROPERTIES

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

Original Citation:

AG-4:A NICOTINIC AGONIST ENDOWED WITH ANTIAMNESIC PROPERTIES / C. GHELARDINI; N. GALEOTTI; L. DI CESARE MANNELLI; S. DEI; F. GUALTIERI; A. BARTOLINI. - In: DRUG DEVELOPMENT RESEARCH. - ISSN 0272-4391. - STAMPA. - 51:(2000), pp. 191-196. [10.1002/1098-2299(200011)51:3191::AID-DDR8>3.0.CO;2-K]

Availability:

The webpage <https://hdl.handle.net/2158/307732> of the repository was last updated on 2017-10-31T11:29:53Z

Published version:

DOI: 10.1002/1098-2299(200011)51:3<191::AID-DDR8>3.0.CO;2-K

Terms of use:

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (<https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf>)

Publisher copyright claim:

La data sopra indicata si riferisce all'ultimo aggiornamento della scheda del Repository FloRe - The above-mentioned date refers to the last update of the record in the Institutional Repository FloRe

(Article begins on next page)

Research Article

AG-4: A Nicotinic Agonist Endowed With Antiamnesic Properties

Carla Ghelardini,^{1*} Nicoletta Galeotti,¹ Lorenzo Di Cesare Mannelli,¹ Silvia Dei,²
Fulvio Gualtieri,² and Alessandro Bartolini¹

¹Department of Pharmacology, University of Florence, Florence, Italy

²Department of Pharmaceutical Sciences, University of Florence, Florence, Italy

Strategy, Management and Health Policy				
Venture Capital Enabling Technology	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT The effect of the nicotinic agonist AG-4 on memory processes was evaluated in the mouse passive avoidance test. AG-4 (100 μg per mouse icv) prevented amnesia induced by scopolamine (1.5 mg kg^{-1} ip), mecamylamine (20 mg kg^{-1} ip), and dihydro- β -erythroidine (10 μg per mouse icv). In the same experimental conditions, AG-4 (100 μg per mouse icv) also prevented baclofen (2 mg kg^{-1} ip), clonidine (0.125 mg kg^{-1} ip), and diphenhydramine (20 mg kg^{-1} ip) amnesia in mice. AG-4 exerted an antiamnesic effect comparable to that produced by nicotine (2 mg kg^{-1} ip), physostigmine (0.2 mg kg^{-1} ip), and the nootropic drug piracetam (30 mg kg^{-1} ip). At the active dose, AG-4 did not impair mice motor coordination and spontaneous motility as revealed, respectively, by Rota-rod test and Animex apparatus. Present results evidence the antiamnesic activity of the nicotinic agonist AG-4 suggesting a potential employment of this compound in the symptomatic treatment of cognitive impairments. *Drug Dev. Res.* 51:191–196, 2000. © 2001 Wiley-Liss, Inc.

Key words: AG-4; amnesia; learning and memory; passive avoidance; nicotinic agonist

INTRODUCTION

Nicotine enhances cognitive function in normal rats [Levine et al., 1990; Levin, 1992] and attenuates memory deficits produced by destruction of cholinergic input to the cortex and hippocampus [Tilson et al., 1988; Decker et al., 1992; Hodges et al., 1992], an effect shared by some other nicotinic acetylcholine receptor (nAChR) agonists [Decker et al., 1993]. In addition, nicotine improves short-term memory performance in both young and aged monkeys [Elrod et al., 1988; Buccafusco and Jackson, 1991]. The involvement of nicotinic neurotransmission in cognitive function processes is further substantiated by observed deficits in cognitive performances following administration of mecamylamine, an nAChR channel blocker, to rodents [Oliverio, 1966; Levine et al., 1987; Riekkinen et al., 1990], monkeys [Elrod et al., 1988], and humans [Newhouse et al., 1992]. Strong evidence for the potential of central nicotinic stimulation to enhance cognitive performance in Alzheimer disease patients derives from the clinical observation that nicotine infused intra-

venously significantly reduced the number of errors in cognitive tests [Newhouse et al., 1988].

The beneficial effect of nicotine was also observed with other agents that act at nAChRs. (-)-Lobeline [Decker et al., 1993] and ABT-418 [Decker et al., 1994] have both been reported to ameliorate spatial learning deficits in rats with septal lesions. Similarly, GTS-21 improved avoidance learning in rats with nucleus basalis magnocellularis lesions and reduced age-related learning deficits in both rats and rabbits [Arendash et al., 1995; Woodruff-Pak et al., 1994]; DBO-83 also prevented pharmacological-induced amnesia in the passive avoidance test [Ghelardini et al., 1998].

Contract grant sponsors: MURST and CNR.

*Correspondence to: Carla Ghelardini, Department of Pharmacology, Viale G. Pieraccini 6, I-50139 Florence, Italy. E-mail: ghelard@server1.pharm.unifi.i

Received 26 June 2000; accepted 7 August 2000

The compound AG-4 (2-methyl-5-N,N-dimethylaminomethyl-cyclopentan-1-one methyl iodide) has been reported by Giannella et al. [1980] to be an agonist selective for the nicotinic receptors. It has also been reported that AG-4 enhanced the pain threshold in rodents without eliciting any side effect [Ghelardini et al., 1997]. Within the framework of research for new nicotinic agonists acting as cognitive enhancers, it was decided to investigate the pharmacological profile of AG-4 as a compound endowed with antiamnesic properties. In order to delineate the AG-4 procognitive action, its potential antiamnesic activity was investigated in the mouse passive avoidance test.

MATERIALS AND METHODS

Animals

Male Swiss albino mice (24–26 g) from Morini (San Polo d'Enza, Italy) 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 fed a standard laboratory diet and tap water *ad libitum* and kept at $23 \pm 1^\circ\text{C}$ on a 12-h light/dark cycle, lights on at 7AM.

Passive Avoidance

The test was performed according to the step-through method described by Jarvik and Kopp [1967]. The apparatus consists of a two-compartment acrylic box with a lighted compartment connected to a darkened one by a guillotine door. As soon as mice entered the dark compartment they received a punishing electrical shock (0.15 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. The maximum entry latency allowed in the training and retention session was 60 and 180 sec, respectively. The memory degree of received punishment was expressed as increase in seconds between the latencies recorded in the training and retention sessions.

Rota-Rod 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 a 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 rpm. The integrity of motor coordination was assessed according to Kuribara et al. [1977] 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 sec (cut-off time) were selected for testing. The performance time was measured before and at various times after treatment.

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 mice, which were placed on top of the Animex activity meter, produced a signal due to variation in inductance and capacity of the apparatus resonance circuit. Then 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 every 15 min for 45 min 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.

ICV Injection Technique

Intracerebroventricular (icv) administration was performed under ether anesthesia with isotonic saline as solvent, according to the method described by Haley and McCormick [1957]. During anesthesia, mice were grasped firmly by the loose skin behind the head. A hypodermic needle (0.4 mm external diameter) attached to a 10 μl syringe was inserted perpendicularly through the skull and no more than 2 mm into the brain of the mouse, where 5 μl of solution was administered. The injection site was 1 mm to the right or left from the midpoint on a line drawn through to the anterior base of the ears. Injections were performed randomly into the right or left ventricle. To ascertain that the drugs were administered exactly into the cerebral ventricle, some mice were 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, with 95% of injections being correct.

Reagents and Compounds

The following compounds were used: AG-4 (2-methyl-5-N,N-dimethylaminomethyl-cyclopentan-1-one methyl iodide) was a kind gift of Prof. Giannella (University of Camerino); diphenhydramine hydrochloride (De Angeli); mecamlamine hydrochloride, clonidine hydrochloride (RBI, Natick, MA), nicotine dihydrogentartrate, dihydro- β -erythroidine (Fluka, Buchs, Switzerland); baclofen, piracetam, physostigmine hemisulphate, scopolamine hydrobromide (Sigma, St. Louis, MO).

Drugs 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 icv injection and 10 ml kg^{-1} by ip injection.

Statistical Analysis

All experimental results are given as the mean \pm SEM. ANOVA, followed by Fisher's Protected Least Significant Difference procedure for post-hoc comparison, were 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

Antiamnesic Activity of AG-4

The nicotinic agonist AG-4 prevented amnesia induced by the antimuscarinic drug scopolamine (1.5 mg kg⁻¹ ip) in the mouse passive avoidance test (Fig. 1). AG-4, at the doses of 10 and 25 µg per mouse icv, was completely ineffective, whereas at the dose of 100 µg per mouse icv it prevented antimuscarinic amnesia, reaching entrance latency values comparable to those produced by saline-treated mice.

The anti-amnesic effect of AG-4 was also equal to that produced by nicotine (2 mg kg⁻¹ ip) and the well-known nootropic drug piracetam (30 mg kg⁻¹ ip) (Fig. 1). However, at the active dose, AG-4 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 AG-4, at the dose of 100 µg per mouse icv, antagonized also the memory disruption produced by the two nicotinic antagonists: mecamylamine (20 mg kg⁻¹ ip; Fig. 2) and dihydro-β-erythroidine (10 µg per mouse icv; Fig. 3). The anti-amnesic effect of AG-4 was comparable to that exerted by nicotine (2–5 mg kg⁻¹ ip; Figs. 2, 3), by the anticholinesterase inhibitor physostigmine (0.2 mg kg⁻¹ ip; Fig. 2) and by the nootropic drug piracetam (30 mg kg⁻¹ ip; Fig. 3).

AG-4, at the dose of 100 µg per mouse icv, was able to prevent amnesia induced by the α₂ agonist clonidine

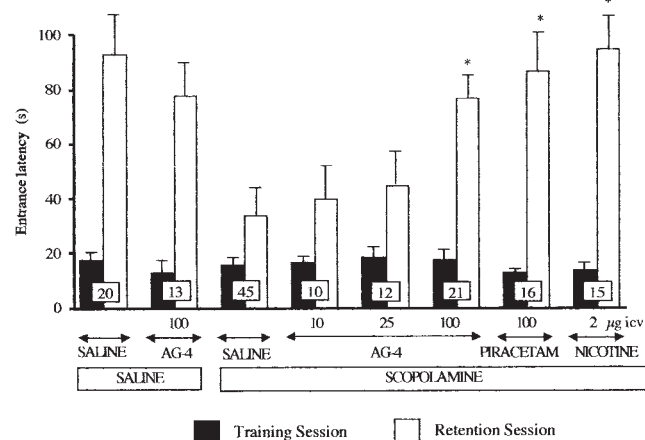


Fig. 1. Dose-response curve of AG-4 in comparison with piracetam and nicotine on amnesia induced by scopolamine (1.5 mg kg⁻¹ ip) in the mouse passive avoidance test. AG-4 (icv), piracetam (icv), and nicotine (icv) were administered 20 min before the training session, while scopolamine was injected immediately afterwards. The number of mice is inside the column. **P* < 0.01 in comparison with scopolamine-treated mice.

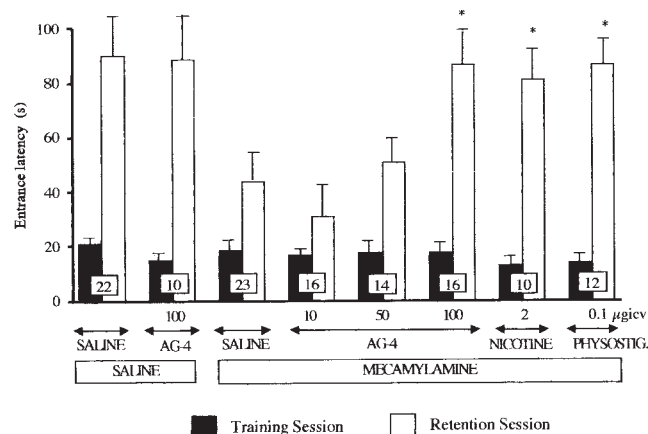


Fig. 2. Dose-response curve of AG-4 in comparison with nicotine and physostigmine on amnesia induced by mecamylamine (20 mg kg⁻¹ ip) in the mouse passive avoidance test. AG-4 (icv), nicotine (icv), and physostigmine (icv) were administered 20 min before the training session, while mecamylamine was injected immediately afterwards. The number of mice is inside the column. **P* < 0.01 in comparison with mecamylamine-treated mice.

(0.125 mg kg⁻¹ ip), the GABA_B agonist baclofen (2 mg kg⁻¹ ip) and the H₁ antagonist diphenhydramine (20 mg kg⁻¹ ip) (Fig. 4) in the mouse passive avoidance test. This anti-amnesic effect was comparable to that exerted by piracetam (30 mg kg⁻¹ ip; Fig. 4).

Effect of AG-4 on Mouse Rota-Rod Test and Mouse Animex Apparatus

It should be noted that AG-4 elicited its modulatory effect on cognitive processes without changing either gross behavior or motor coordination and spontaneous motility

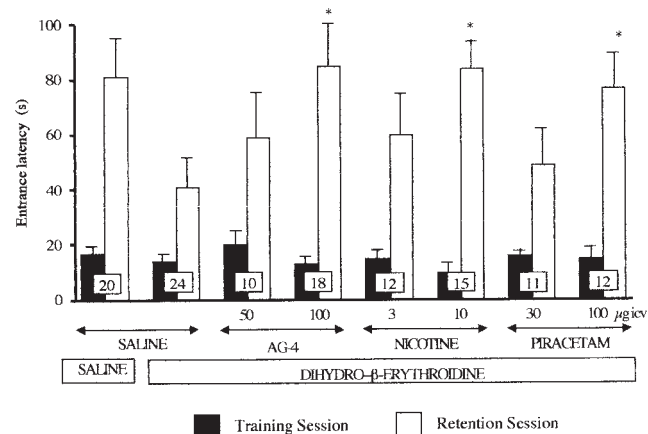


Fig. 3. Dose-response curve of AG-4 in comparison with nicotine and piracetam on amnesia induced by dihydro-β-erythroidine (10 µg per mouse icv) in the mouse passive avoidance test. AG-4 (icv), nicotine (icv), and piracetam (icv) were administered 20 min before the training session, while dihydro-β-erythroidine was injected immediately afterwards. The number of mice is inside the column. **P* < 0.01 in comparison with dihydro-β-erythroidine-treated mice.

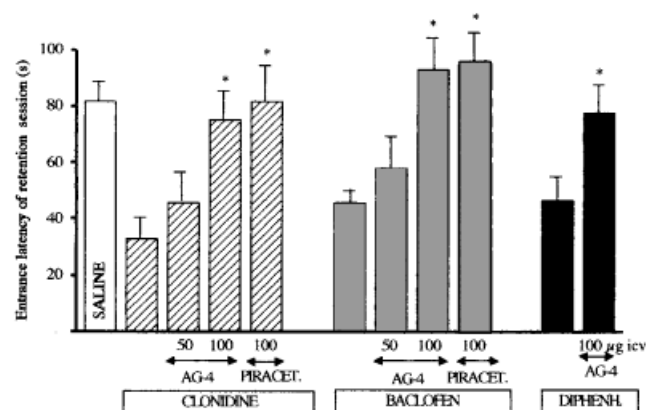


Fig. 4. Dose-response curve of AG-4 in comparison with piracetam on amnesia induced in the mouse by clonidine ($0.125 \text{ mg kg}^{-1} \text{ ip}$), baclofen ($2 \text{ mg kg}^{-1} \text{ ip}$), and diphenhydramine ($20 \text{ mg kg}^{-1} \text{ ip}$) in the passive avoidance test. AG-4 (icv) and piracetam (icv) were administered 20 min before the training session, clonidine 60 min before, baclofen and diphenhydramine immediately afterwards. Each column represents the mean of at least 10 mice. * $P < 0.01$ in comparison with amnesic drug-treated animals.

as revealed, respectively, by the mouse Rota-rod test (Table 1) and the rat Animex apparatus (Fig. 5). AG-4, administered at the active dose, did not reduce the endurance time on the rotating rod in comparison with saline-treated mice (Table 1). The spontaneous motility of mice was unmodified by AG-4 administration ($100 \mu\text{g}$ per mouse icv) as revealed by the Animex apparatus in comparison with saline-treated rats (Fig. 5).

DISCUSSION

The present results describe acute effects observed with AG-4 on experimentally impaired memory in mice. AG-4 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 (see Introduction). On the other hand, the administration of nicotinic ACh receptor antagonists, such as mecamylamine,

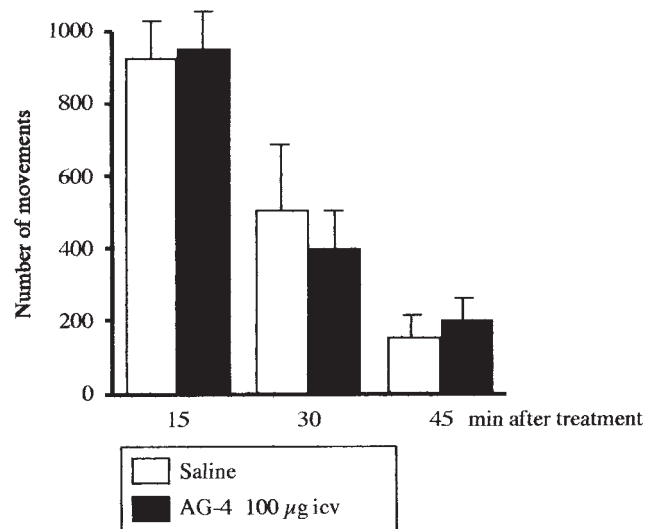


Fig. 5. Lack of effect of AG-4 on mouse spontaneous motility. Each column represents the mean of 15 mice.

produces a dose-dependent impairment of performance in the passive avoidance test [Elrod and Buccafusco, 1991]. 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 obtained by modulating neurotransmitter systems different other than the cholinergic. 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 performances [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 H₁ antagonists, which appears to be related to occupancy of cerebral H₁ receptors; impairment of cognitive functions is a common manifestation [Simons and Simons, 1994]. Furthermore, the administration of the cerebral H₁ antagonist diphenhydramine induces amnesia also in animals [Kamei et al., 1990; Galeotti et al., 1998]. It has also been reported that activation of α_2 receptors modulates memory processes. The administration of the α_2 receptor agonist clonidine induces amnesia [Lazarova-Bakarova et al., 1991; Varonina et al., 1991; Genkova-Papazova et al., 1997].

AG-4 was able to prevent amnesia induced by the administration of scopolamine, mecamylamine, β -eryth-

TABLE 1. Effect of AG-4 in Comparison With Nicotine in the Mouse Rota-rod Test

	Before treatment	Endurance time on Rota-rod (s)		
		15 min	30 min	45 min
Saline	96.5 \pm 7.2 (10)	91.2 \pm 7.9 (10)	102.3 \pm 8.6 (10)	95.4 \pm 7.6 (10)
AG-4	96.8 \pm 7.2 (9)	88.9 \pm 6.7 (9)	94.7 \pm 9.2 (9)	89.5 \pm 8.3 (9)
100 μg icv				
Nicotine	98.7 \pm 8.2 (8)	63.5 \pm 8.1*	75.4 \pm 0.1**	94.3 \pm 8.8 (8)
10 μg icv				

** $P < 0.05$; * $P < 0.01$ in comparison with the corresponding saline controls. The number of mice is shown in parentheses.

roidine, clonidine, baclofen, and diphenhydramine. Thus, AG-4 counteracts amnesia not only induced by nicotinic antagonists, but also that obtained independently from a nicotinic blockade.

AG-4 is also endowed with antinociceptive properties and the time course of the anti-amnesic activity of AG-4 was equal to that observed for its antinociceptive action, reaching its maximum between 15 and 30 min after injection [Ghelardini et al., 1997]. Therefore, in the learning and memory experiments AG-4 was administered 20 min before the training session.

The evaluation of the behavioral parameters in mice indicates that AG-4 exerted its anti-amnesic activity without producing any behavioral side effect. AG-4, at the active dose, nor did impair motor coordination as revealed by the Rota-rod test or modify spontaneous motility, as indicated by the Animex apparatus. Therefore, AG-4 shares many of the positive CNS attributes (e.g., memory-enhancing action, antinociception) of nicotine, but exhibits a reduced propensity to elicit the typical side effects, such as tremors, increase of spontaneous motility produced by injection of nicotine, a limit for its potential use as a safe treatment of cognitive dysfunctions. In other words, AG-4 is able to counteract amnesia in a physiological manner.

In summary, AG-4 appears to have cognitive-enhancing properties in the presence of pharmacologically induced amnesia. On these bases, AG-4 could be considered a new potential anti-amnesic drug useful in the treatment of cognitive disorders.

ACKNOWLEDGMENT

The authors thank Mary Forrest for linguistic revision of the manuscript.

REFERENCES

- Arendash GW, Sengstock GJ, Sanberg PR, Kem WR. 1995. Improved learning and memory in aged rats with chronic administration of the nicotinic receptor agonist GTS-21. *Brain Res* 674:252–259.
- Buccafusco JJ, Jackson WJ. 1991. Beneficial effects of nicotine administered prior to a delayed matching-to-sample task in the young and aged monkeys. *Neurobiol Aging* 12:233–238.
- Castellano C, Brioni JD, Nagahara AH, Mcgaugh JL. 1989. Post-training systemic and intra-amygdala administration of the GABA_B agonist baclofen impairs retention. *Behav Neural Biol* 52:170–179.
- Decker MW, Majchrzak MJ, Anderson DJ. 1992. Effect of nicotine on spatial memory deficits in rats with septal lesions. *Brain Res* 572:281–285.
- Decker MW, Majchrzak MJ, Arneric SP. 1993. Effects of lobeline, a nicotinic receptor agonist, on learning and memory. *Pharmacol Biochem Behav* 45:571–576.
- Decker MW, Brioni J, Sullivan JP, Buckley M, Radek R, Raszkievicz JL, Hughes M, Giardina W, Wasicak JT, Garvey DS, Williams M, Arneric SP. 1994. ABT418: a novel cholinergic ligand with cognition enhancing and anxiolytic activities. II. In vivo characterization. *J Pharmacol Exp Ther* 270:319–328.
- Dilts SL, Berry CA. 1967. Effect of cholinergic drugs on passive avoidance in the mouse. *J Pharmacol Exp Ther* 158:279–285.
- Elrod K, Buccafusco JJ. 1991. Correlation of the amnesic effects of nicotinic antagonists with inhibition of regional brain acetylcholine synthesis in rats. *J Pharmacol Exp Ther* 258:403–409.
- Elrod K, Buccafusco JJ, Jackson WJ. 1988. Nicotine enhances delayed matching-to-sample performance in primates. *Life Sci* 43:277–287.
- Frumier MJ, Herckar VR, Jarvik ME. 1976. Amnesic actions of diazepam and scopolamine in man. *Anesthesiology* 45:406–410.
- Galeotti N, Ghelardini C, Bartolini A. 1998. Effect of pertussis toxin on baclofen- and diphenhydramine-induced amnesia. *Psychopharmacology* 136:328–334.
- Genkova-Papazova M, Petkova BP, Lazarova-Bakarova M, Boyanova E, Staneva-Stoytcheva D. 1997. Effects of flunarizine and nitrendipine on electroconvulsive shock- and clonidine-induced amnesia. *Pharmacol Biochem Behav* 56:583–587.
- Ghelardini C, Galeotti N, Gualtieri F, Bellucci C, Manetti D, Borea PA, Bartolini A. 1997. Antinociceptive property of the nicotinic agonist AG-4 in rodents. *Drug Dev Res* 41:1–9.
- Ghelardini C, Galeotti N, Giuliani F, Barlocco D, Bartolini A. 1998. Anti-amnesic activity of the nicotinic agonist DBO-83 in mice. *Drug Dev Res* 45:45–51.
- Giannella M, Angeli P, Melchiorre C. 1980. Molecular requirements of the active sites of the cholinergic receptors. *Il Farmaco* 35:253–262.
- Haley TJ, McCormick WG. 1957. Pharmacological effects produced by intracerebral injection of drugs in the conscious mouse. *Br J Pharmacol Chemother* 12:12–15.
- Hodges H, Sinden J, Turner JJ, Netto CA, Sowinski P, Gray JA. 1992. Nicotine as a tool to characterize the role of the basal forebrain cholinergic projection system in cognition. In: Lippiello PM, Collins AC, Gray JA, Robinson JH, editors. *The biology of nicotine: current research issues*. New York: Raven Press. p 157–182.
- Jarvik ME, Kopp R. 1967. An improved one-trial passive avoidance learning situation. *Psychol Rep* 21:221–224.
- Jerusalinsky D, Quillfeldt JA, Walz R, Da Silva RC, Silva MB, Bianchin M, Schmitz P, Zanatta MS, Ruschel AC, Paczko N, Medina JH, Izquierdo I. 1994. Effect of the infusion of the GABA_A receptor agonist, muscimol, on the role of the entorhinal cortex, amygdala, and hippocampus in memory processes. *Behav Neural Biol* 61:132–138.
- Kamei C, Chung YH, Tasaka K. 1990. Influence of certain H₁-blockers, on the step-through active avoidance in rats. *Psychopharmacology* 102:312–318.
- Kuribara H, Higuchi Y, Takadoro S. 1977. Effects of central depressants on rota-rod and traction performances in mice. *Jpn J Pharmacol* 27:117–126.
- Lazarova-Bakarova MB, Petkova BP, Todorov IK, Petkov VD. 1991. Memory impairment induced by combined disturbance of noradrenergic and dopaminergic neurotransmissions: effects of nootropic drugs. *Acta Physiol Pharmacol Bulg* 17:29–34.
- Levin ED. 1992. Nicotinic systems in cognitive function. *Psychopharmacology* 108:417–431.
- Levin ED, Bowman RE. 1986. Scopolamine effects on Hamilton search task performance in monkeys. *Pharmacol Biochem Behav* 24:819–821.
- Levine ED, Castonguay M, Ellison GD. 1987. Effects of the nicotinic receptor blocker, mecamylamine, on radial-arm maze performance in rats. *Behav Neural Biol* 48:206–212.

- Levine ED, Lee C, Rose JE, Reyes A, Ellison G, Jaravik M, Gritz E. 1990. Chronic nicotine and withdrawal effects on radial-arm performance in rats. *Behav Neurol Biol* 53:269–276.
- Newhouse PA, Sunderland T, Tariot PN, Blumhardt CL, Weingartner H, Mellow A, Murphy DL. 1988. Intravenous nicotine in Alzheimer's disease: a pilot study. *Psychopharmacology* 95:171–175.
- Newhouse PA, Potter A, Corwin J, Lenox R. 1992. Acute nicotinic blockade produces cognitive impairment in normal humans. *Psychopharmacology* 108:480–484.
- Oliverio A. 1966. Effects of mecamylamine on avoidance conditioning and maze learning of mice. *J Pharmacol Exp Ther* 154:350–356.
- Riekkinen P Jr, Sirvi J, Aaltonen M, Riekkinen P. 1990. The effects of concurrent manipulations of nicotinic and muscarinic receptors on spatial and passive avoidance learning. *Pharmacol Biochem Behav* 37:405–410.
- Simons FER, Simons KJ. 1994. The pharmacology and use of H₁-receptor-antagonist drugs. *N Engl J Med* 330:1663–1670.
- Stackman RW, Walsh TJ. 1994. Baclofen produces dose-related working memory impairments after intraseptal injection. *Behav Neural Biol* 61:181–185.
- Swartzwelder HS, Tilson HA, McLamb RL, Wilson WA. 1987. Baclofen disrupts passive avoidance retention in rats. *Psychopharmacology* 92:398–401.
- Tilson HA, McLamb RL, Shaw S, Rodgers BC, Pediaditakis P, Cook L. 1988. Radial-arm maze deficits produced by colchicine administered into the area of nucleus basalis are ameliorated by cholinergic agents. *Brain Res* 438:83–94.
- Varonina TA, Garibova TL, Trofimov SS, Sopyev ZhA, Petkov VD, Lazarova MB. 1991. Comparative studies on the influence of ONK (N(5-hydroxynicotinoil) glutamic acid), piracetam and meclofenoxate on the learning- and memory-impairing effect of scopolamine, clonidine, and methergoline. *Acta Physiol Pharmacol Bulg* 17:8–16.
- Woodruff-Pak DS, Li Y-T, Kem WR. 1994. A nicotinic agonist (GTS-21), eyeblink classical conditioning, and nicotinic receptor binding in rabbit brain. *Brain Res* 645:309–317.