DDR

Research Article

Antiamnesic Effect of the Two Novel κ-Opioid Agonists, VA-100 and VA-101, in the Mouse Passive Avoidance Test

Carla Ghelardini,[1]* Nicoletta Galeotti,[1] Lorenzo Di Cesare Mannelli,[1] Andrea Cappelli,[2] Maurizio Anzini,[3] and Alessandro Bartolini[1]

[1]Dipartimento di Farmacologia, Università di Florence, Florence, Italy
[2]Dipartimento Farmaco Chimico Tecnologico, Siena, Italy
[3]Dipartimento di Scienze Farmacobiologiche, Università di Catanzaro "Magna Grecia," Catanzaro, 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 effects of the administration of the two novel κ-opioid agonists (VA-100, VA-101) on memory processes were evaluated with the mouse passive avoidance test. The administration of VA-100 (50–100 mg kg^{-1} p.o.) and VA-101 (100 mg kg^{-1} p.o.) administered 20 min before the training session prevented nor-binaltorphimine (4.9 μg per mouse i.c.v.), scopolamine (1.5 mg kg^{-1} i.p.), mecamylamine (20 mg kg^{-1} i.p.), diphenhydramine (20 mg kg^{-1} i.p.), and baclofen (2 mg kg^{-1} i.p.) amnesia. At the highest effective doses, none of the drugs impaired motor coordination, as revealed by the rota-rod test, nor modified spontaneous motility and inspection activity, as revealed by the hole board test. The antiamnesic effect induced by VA-100 and VA-101 was comparable to that exerted by the κ-opioid agonist U-50,488H, as well as that induced by the nootropic drug piracetam and the cholinesterase inhibitor physostigmine. These results suggest that the activation of κ-opioid receptors plays an important role in the prevention of memory impairment. On these bases, κ-opioid receptor agonists could represent a useful symptomatic treatment for cognitive deficits. Drug Dev. Res. 54:12–18, 2001.   © 2001 Wiley-Liss, Inc.

Key words: κ-opioid receptor agonist; κ-opioid receptor antagonist; VA-100; VA-101; U-50,488H; n-BNI; learning and memory; passive avoidance

INTRODUCTION

Opioids produce their principal effects by binding to at least three different types of receptors, the μ, δ, and κ opioid receptors [Raynor et al., 1994]. In general, the μ and δ agonists interfere with learning and memory and produce retrograde amnesia [Castellano, 1975; Ukai et al., 1997a]. Alternatively, the antagonists naloxone and ICI 174,864 facilitate them, increase retention of recently learned tasks, and alleviate amnesia [Flood et al., 1987; Izquierdo and Netto, 1990; Schultieis and Martinez, 1990]. By contrast, activation of κ-opioid receptors appears to produce opposite effects. The function of dynorphin, an endogenous κ-opioid ligand, as well as other κ-opioid agonists in the CNS has been found to include modulation of memory processes. In particular,

activation of κ-opioid receptors prevents amnesia in laboratory animals. Dynorphin A-(1-13) and the κ-opioid agonist U-50,488H improves the scopolamine- and pirenzepine-induced impairment of step-down type passive avoidance response and spontaneous alternation performance [Ukai et al., 1995, 1997b]. Dynorphin A-(1-13) also attenuates basal forebrain-lesion-induced amnesia in rats obtained by the injection of the cholinergic neurotoxin ibotenic acid [Ukai et al., 1993]. Furthermore, stimula-

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

tion of κ-opioid receptors markedly prevents memory dysfunctions induced by transient cerebral ischemia [Itoh et al., 1993a,b] and improves carbon monoxide-induced delayed amnesia in mice [Hiramatsu et al., 1995, 1996]. However, studies of the effects of κ-selective agonists on memory have yielded highly conflicting results. Izquierdo et al. [1985] reported that posttraining administration of dynorphin did not affect retention on either active or passive avoidance tasks. Intracerobroventricular injection of dynorphin impairs retention of an inhibitory avoidance task, but not of Y-maze discrimination [Tilson et al., 1986; Introini-Collison et al., 1987]. Colombo et al. [1992] reported that dynorphin A-(1-13) impaired memory in a dose-dependent manner and that U-50,488H produced a biphasic dose-dependent effect on cognitive function: low doses caused a trend toward enhanced memory and high doses caused significant impairment. Therefore, the role of κ-opioid receptor on memory processes may depend on the concentrations and the experimental paradigm used. VA-100 (2,3-dihydro-2-[[(4-fluorobenzoyl)-amino]ethyl]-1-methyl-5-phenyl-1H-1,4-benzodiazepine) and VA-101 (2,3-dihydro-2[[(2-thienylcarbonyl)amino]-ethyl]-1-methyl-5-phenyl-1H-1,4-benzodiazepine) are two tifluadom analogs with high affinity and selectivity for κ-opioid receptors in comparison with μ and δ receptors [Cappelli et al., 1996]. By using both the above-mentioned κ-opioid receptor agonists (VA-100 and VA-101) and the selective antagonist nor-BNI, the role of κ-opioid receptors in the modulation of learning and memory processes was further investigated in a passive avoidance paradigm.

MATERIALS AND METHODS
Animals

Male Swiss albino mice (23–30 g) from Morini (San Polo d'Enza, Italy) were used. The mice were housed 15 per cage. The cages were placed in the experimental room 24 h before the test for adaptation. The animals were fed a standard laboratory diet and tap water ad libitum and kept at $23 \pm 1°C$ with a 12-h light/dark cycle, lights on at 7 AM. 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 consists of a two-compartment acrylic box with a lighted compartment connected to a darkened one by a guillotine door. Mice, as soon as they enter the dark compartment, receive 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. For memory disruption, mice were intraperitoneally (i.p.) injected with amnesic drugs immediately after termination of the training session. VA-100, VA-101, U-50,488H, physostigmine, and piracetam were injected 20 min before the training session. Those mice scoring more than 60 sec in the training session were rejected. The maximum entry latency allowed in the retention session was 180 sec.

Hole Board Test

The hole board test utilizes a 40-cm square plane with 16 flush-mounted cylindrical holes (diameter 3 cm) distributed 4 by 4 in an equidistant, grid-like manner. The mice were placed in the center of the board one by one and left to move about freely for a period of 5 min each. Two photoelectric beams, crossing the plane from mid-point to mid-point of opposite sides, thus dividing the plane into four equal quadrants, automatically signaled the movement of the animals on the surface of the plane. Miniature photoelectric cells in each of the 16 holes recorded the exploration of the holes (head plunging activity) by the mice.

Rota-Rod Test

The apparatus consists of a base platform and a rotating rod of 3 cm diameter with a nonskid surface. The 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-rotation speed of 16 rpm. The integrity of motor coordination was assessed on the basis of the number of falls from the rod in 30 sec, according to Vaught et al. [1985]. Performance time was measured before and 15, 30, and 45 min after s.c. administration of the drugs.

Intracerebroventricular Injection Technique

Intracerebroventricular (i.c.v.) administration was performed under ether anesthesia with isotonic saline as a 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 drug were then 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 1:10 diluted India ink and their brains were examined macroscopically after sectioning. The accuracy of the injection technique was evaluated, with 95% of injections being correct.

Drugs

The following drugs were used: VA-100, VA-101 (prepared in the Dipartimento Farmaco Chimico Tecnologico of University of Siena according to the method described by Cappelli et al. [1996]); D-amphetamine (De Angeli); scopolamine hydrobromide, physostigmine hemisulphate, piracetam, baclofen (Sigma, St. Louis, MO); mecamylamine hydrochloride, U-50,488H methane sulfonatr, nor-binaltorphimine hydrochloride (RBI, Natick, MA).

Drugs were dissolved in isotonic (NaCl 0.9%) saline solution (for i.c.v. and i.p. administration) or dispersed in sodium carboxymethylcellulose 1% (for per os, p.o., administration) immediately before use. Drug concentrations were prepared so that the necessary dose could be administered in a volume of 5 μl per mouse by i.c.v. injection, and 10 ml kg^{-1} by i.p. and p.o. injection.

Statistical Analysis

All experimental results are given as the means ± SEM. 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 < 0.05 were considered significant.

RESULTS
Amnesic Effect of κ-Opioid Receptor Antagonist

The dose–response curve for n-BNI (0.049–4.9 μg per mouse i.c.v.) in the mouse passive avoidance test is shown in Figure 1A. The compound, injected immediately after the training session, produced deficits in passive avoidance behavior. The amnesic action was reached at the dose of 0.49 μg. The maximum effect obtained was of the same intensity of that produced by scopolamine (1.5 mg kg^{-1} i.p.) and dicyclomine (2 mg kg^{-1} i.p.), used as reference drugs (Fig. 1A). Higher doses of n-BNI were not investigated because the dose of 4.9 μg produced the same degree of behavioral impairment of the reference drugs (Fig. 1A).

Prevention of Deficits in Passive Avoidance Behavior by κ-Opioid Receptor Agonists

The deficits in passive avoidance behavior induced by the κ-opioid receptor antagonist n-BNI was prevented by pretreatment with the κ-opioid receptor agonists VA-100 (50 mg kg^{-1} p.o.) and VA-101 (100 mg kg^{-1} p.o.), injected 20 min before the training session. Both κ-opioid agonists enhanced the entrance latency up to a value comparable to that produced by control animals (Fig. 1B). VA-100 and VA-101, at 10 and 50 mg kg^{-1} i.p., respectively, were completely ineffective (Fig. 1B). The antiamnesic effect of VA-100 and VA-101 was comparable
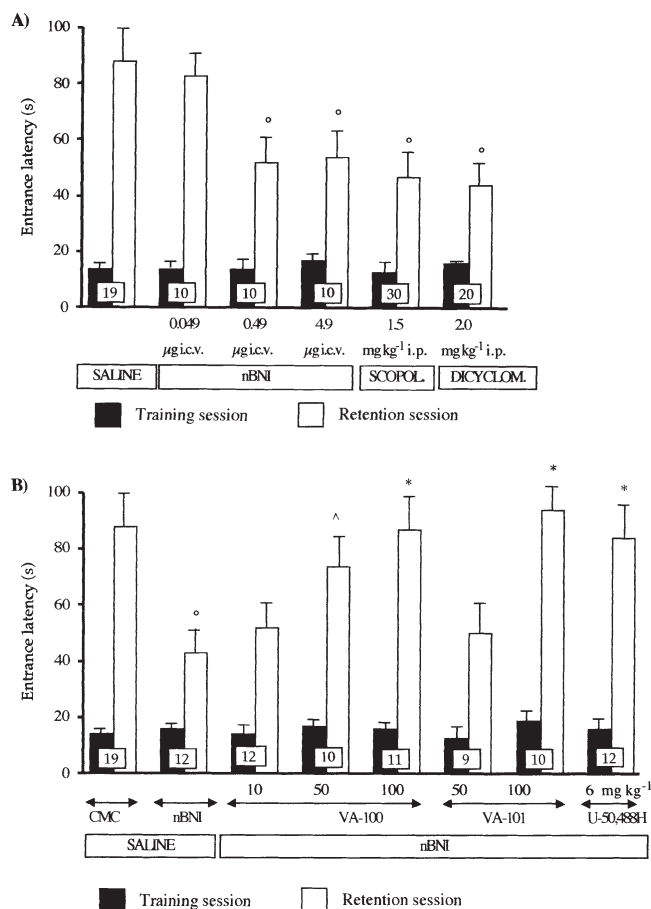

Fig. 1. Dose–response curve of n-BNI in comparison with scopolamine (1.5 mg kg^{-1} i.p.) and dicyclomine (2 mg kg^{-1} i.p.) in mouse passive avoidance test (**A**) and effect on amnesia induced by n-BNI (4.9 μg per mouse i.c.v.) of VA-100 (p.o.), VA-101 (p.o.). and U-50,488H (p.o.) (**B**). VA-100, VA-101, and U-50,488H were administered 20 min before training session while n-BNI, scopolamine, and dicyclomine were injected immediately after training session. Inside the columns is the number of mice. $°P < 0.01$ in comparison with saline/CMC-treated mice; $^P < 0.05$; $*P < 0.01$ in comparison with n-BNI-treated mice.

to that produced by the κ-opioid receptor agonist U-50,488H (6.0 mg kg^{-1} p.o.) (Fig. 1B).

VA-100 (50-100 mg kg^{-1} p.o.) and VA-101 (100 mg kg^{-1} p.o.) were also able to completely prevent scopolamine (1.5 mg kg^{-1} i.p.; Figs. 2, 3), mecamylamine (20 mg kg^{-1} i.p.; Fig. 4), diphenhydramine (20 mg kg^{-1} i.p.; Fig. 5), and baclofen (2 mg kg^{-1} i.p.; Fig. 5) induced deficits in passive avoidance behavior. The doses of 25 mg kg^{-1} p.o. for VA-100 and of 50 mg kg^{-1} p.o. for VA-101 were unable to protect against scopolamine- (Figs. 2, 3) and mecamylamine-induced (Fig. 4) deficits in passive avoidance behavior.

The antiamnesic effect produced by VA-100 and VA-101 was comparable to that produced by the well-known nootropic drug piracetam (30 mg kg^{-1} i.p.) and the cholinesterase inhibitor physostigmine (0.2 mg kg^{-1} i.p.), as illustrated in Figure 3.
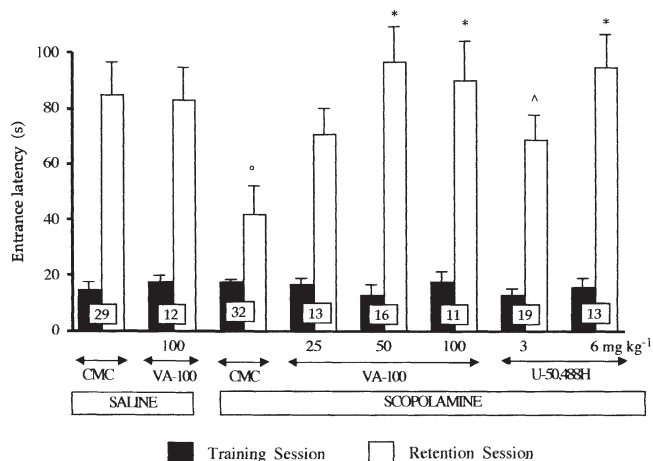
Fig. 2. Effect of VA-100 in comparison with U-50,488H on amnesia induced by scopolamine (1.5 mg kg^{-1} i.p.) in mouse passive avoidance test. VA-100 (p.o.) and U-50,488H (p.o.) were administered 20 min before training session while scopolamine was injected immediately after training session. Inside the columns is the number of mice. $^{\circ}P < 0.01$ in comparison with CMC-treated mice. $^{\wedge}P < 0.05$; *$P < 0.01$ in comparison with scopolamine-treated mice.

Fig. 4. Effect of VA-100 and VA-101 on amnesia induced by mecamylamine (20 mg kg^{-1} i.p.) in mouse passive avoidance test. VA-100 (p.o.) and VA-101 (p.o.) were administered 20 min before training session while mecamylamine was injected immediately after training session. Inside the columns is the number of mice. $^{\circ}P < 0.01$ in comparison with CMC-treated mice. *$P < 0.01$ in comparison with mecamylamine-treated mice.

Doses of VA-100 and VA-101 higher than 100 mg kg^{-1} p.o. were not investigated because a complete prevention of n-NBI-, scopolamine-, mecamylamine-, diphenhydramine-, and baclofen-induced amnesia had already been reached.

VA-100 and VA-101, when given alone, at the highest doses used had no effect on mouse passive avoidance test in comparison with saline-treated mice (Figs. 2, 3). No statistically significant difference among the entrance latencies for each compound tested in the training session of the passive avoidance test was observed (Figs. 1–5).
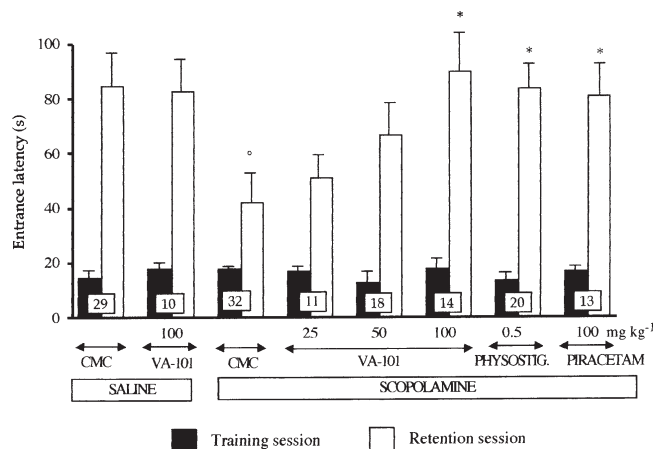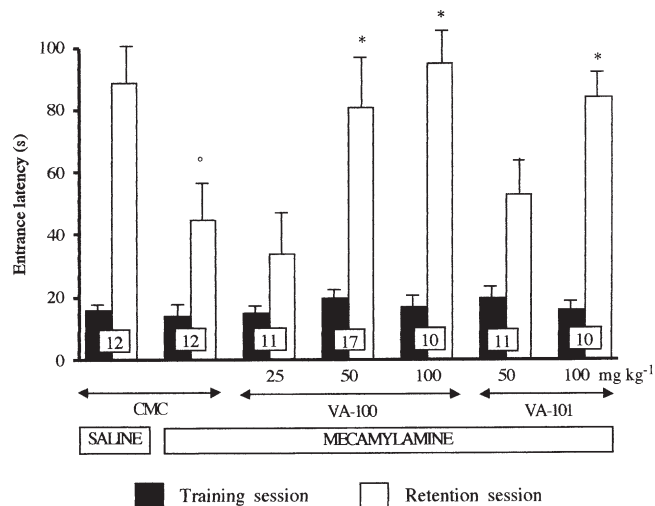
The administration schedule for VA-100 and VA-101 was selected on the basis of results obtained from time-course studies (data not shown).

Effect of κ-Opioid Receptor Agonists and Antagonists on Mouse Rota-Rod and Hole Board Tests

It should be noted that the κ-opioid agonists and antagonists we investigated elicited their modulatory effect on cognitive processes without changing either gross behavior or motor coordination, as revealed by the rota-
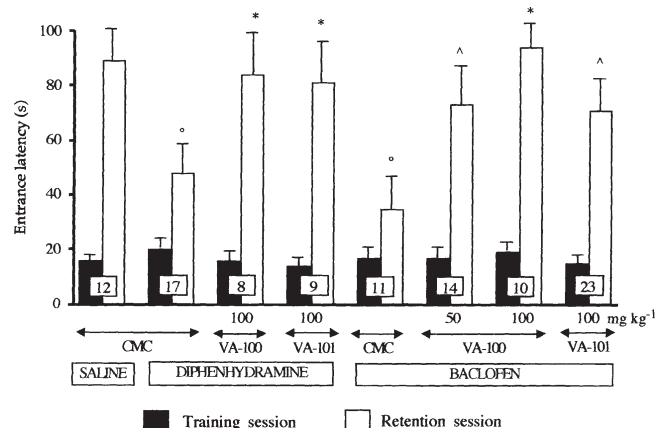
Fig. 3. Effect of VA-101 in comparison with physostigmine and piracetam on amnesia induced by scopolamine (1.5 mg kg^{-1} i.p.) in mouse passive avoidance test. VA-101 (p.o.), physostigmine (p.o.) and piracetam (p.o.) were administered 20 min before training session while scopolamine was injected immediately after training session. Inside the columns is the number of mice. $^{\circ}P < 0.01$ in comparison with CMC-treated mice. *$P < 0.01$ in comparison with scopolamine-treated mice.

Fig. 5. Effect of VA-100 and V A-101 on amnesia induced by diphenhydramine (20 mg kg^{-1} i.p.) and baclofen (2 mg kg^{-1} i.p.) in mouse passive avoidance test. VA-100 and VA-101 were administered 20 min before training session, diphenhydramine and baclofen were injected immediately after training session. Inside the columns is the number of mice. $^{\circ}P < 0.01$ in comparison with CMC-treated mice. $^{\wedge}P < 0.05$; *$P < 0.01$ in comparison with diphenhydramine or baclofen-treated mice.

rod test (Table 1). None of the drugs, administered at the highest active doses, increased the number of falls from the rotating rod in comparison with saline-treated mice (Table 1). The number of falls in the rota-rod test progressively decreased since mice learned how to balance on the rotating rod.

The spontaneous motility and inspection activity of mice was unmodified by administration of the κ-opioid agonists VA-100 and VA-101 and of the κ-opioid antagonist n-BNI, as revealed by the hole board (Fig. 6) test in comparison with saline-treated mice. In this, test D-amphetamine (2 mg kg^{-1} i.p.), used as a reference drug, increased both parameters evaluated.

DISCUSSION

The present results demonstrate that the administration of the κ-opioid receptor antagonist n-BNI provokes amnesia in the mouse passive avoidance test of a severity comparable to that induced by the amnesic drugs scopolamine and dicyclomine. This amnesic effect was centrally mediated, since it was obtained after intracerebroventricular administration.

The amnesia induced by n-BNI was prevented by the κ-opioid receptor agonists VA-100, VA-101, and U-50,488H, indicating the important role played by the κ-opioid receptors in modulating learning and memory processes. The blockade of these opioid receptors impair cognitive functions that are, by contrast, improved by stimulation of κ receptors. VA-100 and VA-101 exerted an antiamnesic action of an efficacy comparable to that shown by the well-known κ-opioid agonist U-50,488H, even if the potency of the two compounds is lower than that detected for U-50,488H. However, VA-100 and VA-101 can represent a useful pharmacological tool to investigate the physiological role of κ-opioid receptors.

VA-100 and VA-101, as well as U-50,488H, are also able to prevent amnesia induced by the antimuscarinic drug scopolamine, with a procognitive effect similar to that exerted by the cholinesterase inhibitor physostigmine and the nootropic drug piracetam. This experimental results are in agreement with previous data reporting that dynorphin A-(1-13) ameliorates the scopolamine- and pirenzepine-induced memory impairment of step-down type passive avoidance response and spontaneous alternation performance [Ukai et al., 1997b]. Furthermore, it has been reported that the κ-opioid agonist U-50,488H improves scopolamine- and pirenzepine-induced memory impairment in mice and rats [Ukai et al., 1995; Hiramatsu et al., 1998]. Dynorphin A-(1-13) is also able to protect against amnesia induced by hypofunctionality of the cholinergic system not related to an antagonism of the muscarinic receptors. Dynorphin A-(1-13) attenuates basal forebrain-lesion-induced amnesia in rats obtained by the injection of the cholinergic neurotoxin ibotenic acid [Ukai et al., 1993] and β-amyloid peptide (25-35)-amnesia in a mouse passive avoidance paradigm [Hiramatsu et al.,2000]. Dynorphin A-(1-13) also prevents amnesia in mice induced by galanin [Kameyama et al., 1994], an ACh releaser inhibitor [Fisone et al., 1987], and by cycloheximide [Ukai et al., 1996], a protein synthesis inhibitor endowed with amnesic properties mainly due to an impairment of the neuronal cholinergic system [Nabeshima et al., 1988].

VA-100 and VA-101 prevented amnesia induced by the nicotinic antagonist mecamylamine. The observation that the κ-opioid agonist U-50,488H improves mecamylamine-induced memory impairment in mice and rats [Ukai et al., 1995; Hiramatsu et al., 1998] confirmed our results. However, mecamylamine amnesia underlies an impairment of the cholinergic system. It has been reported that nicotine enhances cholinergic transmission through the activation of presynaptic nicotinic receptors [McGehee et al., 1995], whereas mecamylamine significantly decreases the release of ACh from rat hippocampus revealed by a microdialysis technique [Hiramatsu et al., 1998]. Taking into account these observations, the prevention exerted by κ-opioid agonists of memory deficits induced by nicotinic antagonists is also related to an antimuscarinic mechanism.

TABLE 1. Effect of nor-Binaltorphimine, VA-100, VA-101, and U-50,448H in Mouse Rota Rod Test

| | | | Falls in 30 sec | | |
| | | | | After treatment | |
Treatment	Dose	Before treatment	15 min	30 min	45 min
Saline	5 μl icv	3.7 ± 0.6	2.5 ± 0.3	1.8 ± 0.4	1.4 ± 0.3
CMC	10 ml kg^{-1} po	3.8 ± 0.4	2.0 ± 0.2	1.8 ± 0.3	0.8 ± 0.2
nBNI	4.9 μg icv	3.9 ± 0.4	2.6 ± 0.4	1.5 ± 0.2	0.6 ± 0.2
U-50,488H	6 mg kg^{-1} po	4.0 ± 0.4	2.5 ± 0.4	1.9 ± 0.3	0.7 ± 0.2
VA-100	100 mg kg^{-1} po	3.6 ± 0.5	2.2 ± 0.4	1.5 ± 0.3	1.1 ± 0.3
VA-100	200 mg kg^{-1} po	3.8 ± 0.4	4.4 ± 0.5*	3.6 ± 0.4*	2.6 ± 0.4*
VA-101	100 mg kg^{-1} po	3.5 ± 0.4	2.4 ± 0.3	1.1 ± 0.3	1.0 ± 0.2
VA-101	200 mg kg^{-1} po	3.9 ± 0.3	4.1 ± 0.5*	3.8 ± 0.3*	3.1 ± 0.4*

*$P < 0.01$ in comparison with saline or CMC controls. Each value represents the mean of five mice.
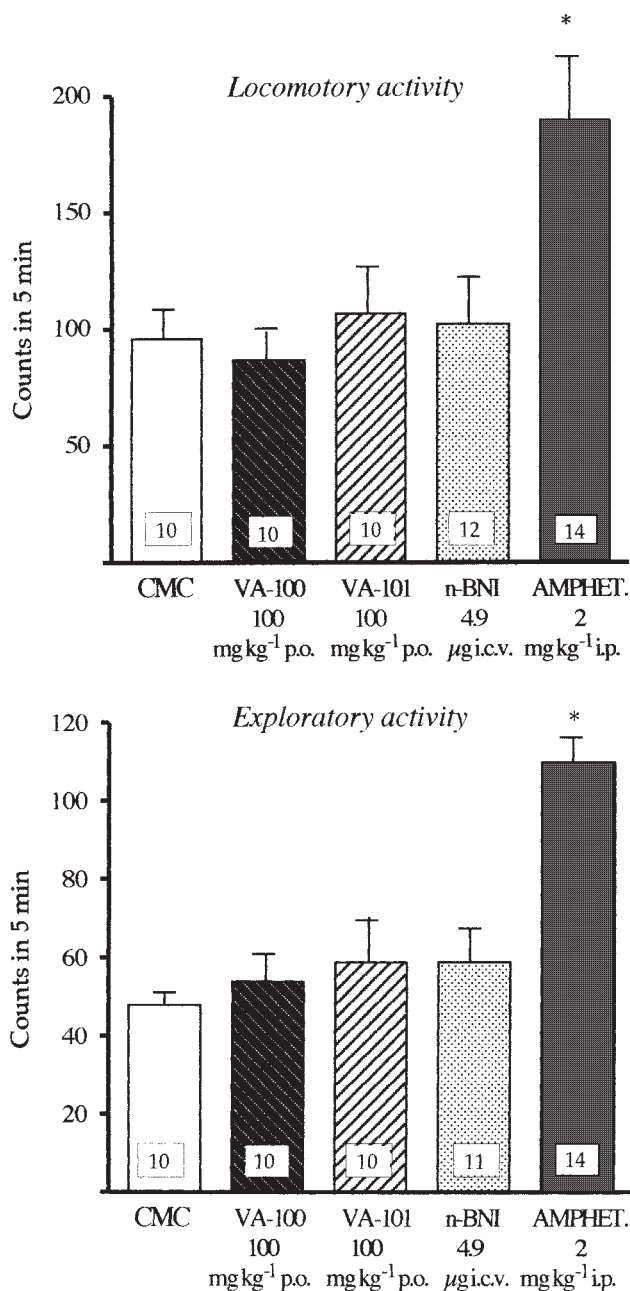
Fig. 6. Lack of effect of VA-100, VA-101, and n-BNI in comparison with amphetamine in mouse hole board test. Test was performed 15–25 min after drug administration. Inside the column is the number of mice. *$P < 0.01$ in comparison with saline-controls.

VA-100 and VA-101 prevented amnesia induced by administration of the GABA$_B$ agonist baclofen and the H$_1$-antagonist diphenhydramine, indicating that κ-opioid receptor agonists were able to prevent amnesia induced not only by antimuscarinic drugs, but also through a mechanism that does not involve the blockade of the cholinergic system. The antagonist of a GABA$_B$-mediated effect by κ-opioid agonists is confirmed by previous results reporting that κ-opioid receptor activation inhib-

ited GABA$_B$-mediated IPSPs in the guinea pig ventral tegmental area [Shoji et al., 1999]. Furthermore, baclofen, at low i.c.v. doses unable to induce antinociception, attenuated the increase of the pain threshold induced by U-50,488H [Suh et al., 1995]. The prevention of U-50,488H antinociception by the H$_1$-antagonist cyproheptadine in the rat tail flick test [Suh et al., 1999] supported the hypothesis of a possible correlation between activation of κ-opioid receptors and antagonism of H$_1$ receptors suggested by our results on passive avoidance.

The experimental data obtained by the use of two new and selective κ-opioid agonists VA-100 and VA-101, indicate that activation of κ-opioid receptors improves pharmacologically induced cognitive deficits.

The κ-opioid receptor agonists and antagonists, at the highest doses used, did not modify the animals' gross behavior. Nor did these compounds impair motor coordination, as revealed by the rota-rod test, or modify locomotor and inspection activity, as indicated by the hole board test. We can thus suppose that the effects produced by κ-opioid receptor modulators were not imputable to compromised viability. Higher doses of all compounds were not investigated since the maximum amnesic (n-BNI) and antiamnesic (VA-100, VA-101) effect was already reached.

In conclusion, these results confirm the important role played by κ-opioid receptors in the regulation of memory processes. On these bases, the κ-opioid receptor agonists could be useful in the treatment of cognitive deficits while κ-opioid receptor antagonists may represent pharmacological tools for investigation of new potential antiamnesic drugs.

REFERENCES

Cappelli A, Anzini M, Vomero S, Menziani MC, De Benedetti PG, Sbacchi M, Clark GD, Mennuni L. 1996. Synthesis, biological evaluation and quantitative receptor docking simulations of 2-[(acylamino)ethyl]-1,4-benzodiazepines as novel tifluadom-like ligands with high affinity and selectivity for κ-opioid receptors. J Med Chem 39:860–867.

Castellano C. 1975. Effects of morphine and heroin on discrimination, learning and consolidation in mice. Psychopharmacologia 42:235–331.

Colombo PJ, Martinez JL Jr, Bennet EL, Rosenzweig MR. 1992. κ-Opioid receptor activity modulates memory for peck-avoidance training in the 2-day-old chick. Psychopharmacology 108:235–341.

Fisone G, Wu Chun F, Consolo S, Nordstrom O, Brynne N, Bartfai T, Melander T, Hokfelt T. 1987. Galanin inhibits acetylcholine release in the ventral hippocampus of the rat: histochemical, autoradiographic, *in vivo,* and *in vitro* studies. Proc Natl Acad Sci USA 84:7339–7343.

Flood JF, Cherkin A, Morley JE. 1987. Antagonism of endogenous opioids modulates memory processing. Brain Res 422:218–234.

Haley TJ, McCormick WG. 1957. Pharmacological effects produced by intracerebral injection of drugs in the conscious mouse. Br J Pharmacol Chemother 12:12–15.

Hiramatsu M, Sasaki M, Kameyama T. 1995. Effects of dynorphin A-

(1-13) on carbon monoxide-induced delayed amnesia in mice studied in a step-down type passive avoidance task. Eur J Pharmacol 282:185–191.

Hiramatsu M, Hyodo T, Kameyama T. 1996. U-50488H, a selective κ-opioid receptor agonist, improves carbon monoxide-induced delayed amnesia in mice. Eur J Pharmacol 315:119–125.

Hiramatsu M, Murasawa H, Nabeshima T, Kameyama T. 1998. Effects of U-50,488H on scopolamine-, mecamylamine- and dizocilpine-induced learning and memory impairment in rats. J Pharmacol Exp Ther 284:858–867.

Hiramatsu M, Inoue K, Kameyama T. 2000. Dynorphin A-(13) and (2-13) improve β-amyloid peptide-induced amnesia in mice. Neuroreport 11:431–435.

Introini-Collison IB, Cahill L, Baratti CM, Mcgaugh JL. 1987. Dynorphin induces task-specific impairment of memory. Psychobiology 15:171–176.

Itoh J, Ukai M, Kameyama T. 1993a. Dynorphin A-(1-13) potently prevents memory dysfunctions induced by transient cerebral ischemia in mice. Eur J Pharmacol 234:9–15.

Itoh J, Ukai M, Kameyama T. 1993b. U-50,488H, a κ-opioid receptor agonist, markedly prevents memory dysfunctions induced by transient cerebral ischemia in mice. Brain Res 619:223–228.

Izquierdo I, Netto CA. 1990. Dual action of posttraining naloxone on memory. Behav Neural Biol 53:140–145.

Izquierdo I, De Almeida MA, Emiliano VR. 1985. Unlike β-endorphin, dynorphin does not cause retrograde amnesia for shuttle avoidance or inhibitory avoidance learning in rats. Psychopharmacology 27:216–218.

Jarvik ME, Kopp R. 1967. An improved one-trial passive avoidance learning situation. Psychol Rep 21:221–224.

Kameyama T, Ukai M, Miura M. 1994. Dynorphin A-(1-13) potently improves galanin-induced impairment of memory processes in mice. Neuropharmacology 33:1167–1169.

McGehee DS, Heath MJS, Gelber S, Devay P, Role LW. 1995. Nicotine enhancement of fast excitatory synaptic transmission in CNS by presynaptic receptors. Science 269:1692–1696.

Nabeshima T, Noda Y, Itoh K, Kameyama T. 1988. Role of cholinergic and GABAergic neuronal systems in cycloheximide-induced amnesia in mice. Pharmacol Biochem Behav 31:405–411.

Raynor K, Kong H, Chen Y, Yasuda K, Yu L, Bell GI, Reisine T. 1994. Pharmacological characterization of the cloned κ-, δ- and μ-opioid receptors. Mol Pharmacol 45:330–334.

Schultieis G, Martinez JL. 1990. ICI 174,864, a selective delta opioid antagonist, reverses the learning impairment produced by (leu)ekephalin. Psychopharmacology 100:102–109.

Shoji Y, Delfs J, Williams JT. 1999. Presynaptic inhibition of GABA(B)-mediated synaptic potentials in the ventral tegmental area during morphine withdrawal. J Neurosci 19:2347–2355.

Suh HW, Song DK, Kim YH, Choi YS, Yoo JS, Tseng LF. 1995. Differential modulation by muscimol and baclofen on antinociception induced by morphine, β-endorphin, D-Pen2,5-enkephalin and U50,488H administered intracerebroventricularly in the mouse. Naunyn Schmied Arch Pharmacol 352:614–619.

Suh HW, Chung KM, Kim YH, Huh SO, Song DK. 1999. Effects of histamine receptor antagonists injected intrathecally on antinociception induced by opioids administered intracerebroventricularly in the mouse. Neuropeptides 33:121–129.

Tilson H, McLamb R, Hong J. 1986. Behavioral effects of centrally administered dynorphin and (D-Ala^2-D-leu)enkephalin (DADLE) in rats. Neuropeptides 8:193–206.

Ukai M, Kobayashi T, Kameyama T. 1993. Dynorphin A-(1-13) attenuates basal forebrain-lesion-induced amnesia in rats. Brain Res 22:355–356.

Ukai M, Shinkai N, Kameyama T. 1995. κ-opioid receptor agonists improve pirenzepine-induced disturbance of spontaneous alternation performance in the mouse. Eur J Pharmacol 81:173–178.

Ukai M, Shan-Wu Y, Kobayashi T, Kameyama T. 1996. Systemic administration of dynorphin A-(1-13) markedly inmproves cycloheximide-induced amnesia in mice. Eur J Pharmacol 313:11–15.

Ukai M, Takada A, Sasaki Y, Kameyama T. 1997a. Stimulation of δ$_1$- and δ$_2$-opioid receptors produces amnesia in mice. Eur J Pharmacol 338:1–6.

Ukai M, Itoh J, Kobayashi T, Shinkai N, Kameyama T. 1997b. Effects of the κ-opioid dynorphin A-(1-13) on learning and memory in mice. Behav Brain Res 83:169–172.

Vaught J, Pelley K, Costa LG, Sether P, Enna SJ. 1985. A comparison of the antinociceptive responses to GABA-receptor agonists THIP and baclofen. Neuropharmacology 24:211–216.