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Improvement by low doses of nociceptin on scopolamine-induced impairment of learning and/or memory

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Abstract

The effects of fmol doses of nociceptin/orphanin FQ on scopolamine-induced impairment of learning and/or memory were examined using spontaneous alternation of Y-maze and step-down type passive avoidance tasks. While fmol doses of nociceptin alone had no effect on spontaneous alternation or passive avoidance behavior in normal mice, administration of nociceptin (10 and/or 100 fmol/mouse) 30 min before spontaneous alternation performance or the training session of the passive avoidance task, significantly improved the scopolamine-induced impairment of spontaneous alternation and passive avoidance behavior. This ameliorating effect was not antagonized by nocistatin (0.5 and 5.0 nmol/mouse, i.c.v.), naloxone benzoylhydrazone (2.3, 11.2, and 56.1 μmol/kg, s.c.) or nor-binaltorphimine (4.9 nmol/mouse, i.c.v.). These results indicated that very low doses of nociceptin ameliorate impairments of spontaneous alternation and passive avoidance induced by scopolamine, and suggested that this peptide has bidirectional modulatory effects on learning and memory; impairment at high doses and amelioration at low doses.

Keywords: Nocistatin; Naloxone benzoylhydrazone; κ-Opioid receptor; Spontaneous alternation; Passive avoidance

1. Introduction

Since the isolation of nociceptin, an endogenous ligand for the opioid receptor-like 1 orphan (ORL1) receptor (Meunier et al., 1995; Reinscheid et al., 1995), a number of studies have been performed to elucidate the relationship between nociceptin and opioid peptides. Nociceptin is structurally similar to dynorphin A but lacks the N-terminal tyrosine characteristic of opioid peptides and is derived from a novel precursor (Nothacker et al., 1996). Furthermore, although the anatomy of the nociceptin system has been described in the rat brain (Anton et al., 1996; Sim et al., 1996; Sim and Childers, 1997), it is important to compare the effects of nociceptin and κ-opioid peptides on learning and memory function to define the role of ORL1 receptors in the brain because the dynorphin A may interact to ORL1 receptor in some extent (Zhang and Yu, 1995) and nociceptin postsynaptically modulates the excitability of hippocampal pyramidal neurons through ORL1 and κ-opioid receptors linked to different K^+ channels (Madamba et al., 1999).

Opioid peptides acting on opioid receptors can modulate hippocampal synaptic functions. Although ORL1 receptors, which display a high degree of sequence homology with classical opioid receptors, are abundant in the hippocampus, little is known regarding their role in synaptic function. Sandin et al. (1997) showed that nociceptin microinjected into the hippocampus impaired spatial learning in rats. Yu et al. (1997) suggested that nociceptin could function as an inhibitory modulator regulating synaptic transmission and synaptic plasticity in the hippocampus. Further, Manabe et al. (1998) showed that mice lacking the nociceptin receptor have better learning ability and memory, and larger long-term potentiation in the hippocampal CA1 region than control mice. Recently, we also reported that intracerebroventricular (i.c.v.) administration of nmol amounts of nociceptin induced a lower percentage alternation and shorter median step-down latency in the retention test in normal mice (Hiramatsu and Inoue, 1999a,b). These findings suggested that activation of ORL1 receptors causes impairment of learning and memory processes.

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When administered intracerebroventricularly to mice, nociceptin induces hyperalgesia, suppresses opioid-mediated analgesia and reduces motor activity (Reinscheid et al., 1995) or stimulates locomotor and exploratory behavior (Florin et al., 1996) depending on the dosage used. On the other hand, injection of dynorphin A or U-50,488H (*trans*-(±)-3,4-dichloro-*N*-methyl-*N*-(2-[1-pyrrolidinyl] cyclohexyl) benzene-acetamide methanesulfonate salt), κ-opioid receptor agonists, showed a biphasic effect on memory; low doses tended to enhance, while high doses significantly impaired memory in 2-day-old chicks (Colombo et al., 1992). Therefore, the role of nociceptin in memory formation may depend biphasically on the dosage of agonist used.

It is well known that cholinergic neuronal systems play an important role in the cognitive deficits associated with aging and neurodegenerative diseases (Bartus et al., 1982; Newhouse, 1990). We reported previously that the κ-opioid receptor agonist dynorphin A-(1–13) improved impairments of learning and memory in mice and rats by not only κ-opioid receptor-mediated, but also non-opioid mechanisms (Itoh et al., 1993; Hiramatsu et al., 1995, 1996, 1997, 1998a,b, 2000) via cholinergic neuronal systems. Here, we investigated whether nociceptin has such biphasic effects in vivo using a scopolamine-induced learning and memory impairment model. A preliminary account of these findings has been reported (Hiramatsu and Inoue, 1999c).

2. Materials and methods

2.1. Animals

Seven-week-old male ddY mice (Japan SLC, Japan) were kept in a regulated environment (23 ± 1°C, 50 ± 5% humidity), with a 12-h light/12-h dark cycle (light on 8:00 a.m.–8:00 p.m.) and given food and tap water ad libitum. Experimental protocols concerning the use of laboratory animals were approved by the committee of Meijo University and followed the guidelines of the Japanese Pharmacological Society (Folia Pharmacol. Japon., 1992, 99:35A) and the interministerial decree of May 25th, 1987 (the Ministry of Education).

2.2. Drugs

Nociceptin, nocistatin (Peptide Inst., Osaka, Japan) and nor-binaltorphimine dihydrochloride (Research Biochemicals International, MA, USA) were dissolved in 0.9% saline. Naloxone benzoylhydrazone (Research Biochemicals International) was dissolved in 1.0% acetic acid and diluted with 0.9% saline. Both peptides were administered 30 min before the Y-maze session or the training session of the passive avoidance test into the lateral ventricle (i.c.v.) of the mouse brain according to the method of Haley and McCormick (1957) in a volume of 5 μl/mouse under brief ether anesthesia. Scopolamine hydrobromide (scopolamine, Tokyo Chemical Industry, Japan) and dizocilpine ((+)-MK-801; (+)-5-methyl-10,11-dihydro-5*H*-dibenzo (*a*,*d*)cyclohepten-5,10-imine maleate, a generous gift from Dr. A.K. Cho, UCLA, USA), were dissolved in 0.9% saline and injected subcutaneously (s.c.) just before administration of these peptides. Control animals were injected with vehicle i.c.v. under brief ether anesthesia.

2.3. Spontaneous alternation behavior

Immediate working memory performance was assessed by recording spontaneous alternation behavior in a single session in a Y-maze (Hiramatsu et al., 1997) made of black painted wood. Each arm was 40 cm long, 12 cm high, 3 cm wide at the bottom and 10 cm wide at the top, and converged in an equilateral triangular central area. The procedure was basically the same as that described previously (Sarter et al., 1988): each mouse, naive to the maze, was placed at the end of one arm and allowed to move freely through the maze during an 8-min session. The series of arm entries was recorded visually. Entry was considered to be completed when the hind paws of the mouse had completely entered the arm. Alternation was defined as successive entries into the three different arms (A, B or C) on overlapping triplet sets (ex. ACBA-BACBAB = 5). Percentage alternation was calculated as the ratio of actual to possible alternation (defined as the total number of arm entries minus two), multiplied by 100 as shown in the following equation:

$$\%\,\text{Alternation} = \{(\text{Number of alternations})/(\text{Total arm entries} - 2)\} \times 100$$

2.4. Step-down type passive avoidance task

A step-down type of passive avoidance task was used, as described previously (Hiramatsu et al., 1995) with some modifications. The apparatus consisted of a transparent acrylic rectangular cage (30 × 30 × 40 cm high) with a grid floor with a wooden platform (4 × 4 × 4 cm) in the center, set in a semi-soundproof wooden outer box (35 × 35 × 90 cm high). Illumination was provided by a 15-W illumination lamp above the apparatus. An electric current (1 Hz, 500 ms, 80 V, DC) was delivered to the grid floor with an isolated stimulator (SEN-3201, Nihon Koden, Japan).

Each mouse was placed on the wooden platform. When the mouse stepped down from the platform onto the grid floor, an electric shock was delivered for 15 s. The retention test was carried out 24 h after the training session in a similar manner except that no electric shock was delivered to the grid floor. Each mouse was placed on the platform

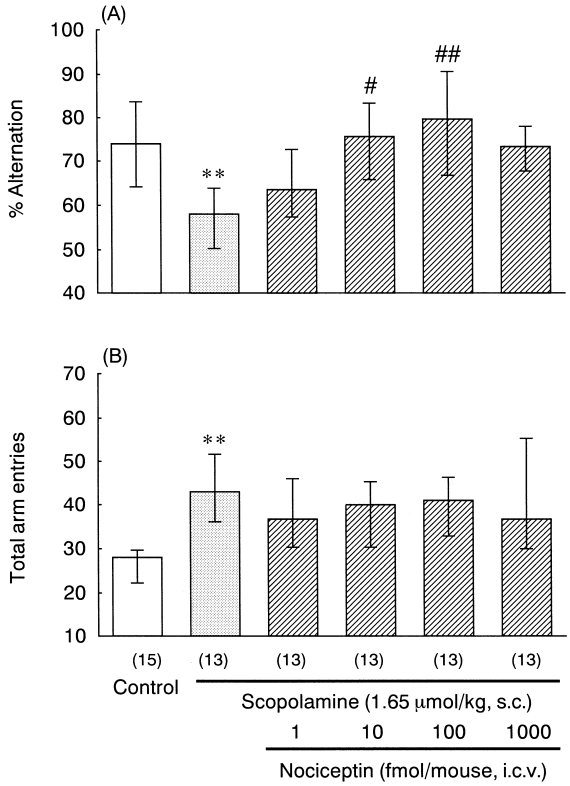

Fig. 1. Effects of nociceptin on scopolamine-induced impairment of spontaneous alternation (A) and total arm entries (B) in the Y-maze. Mice were treated with nociceptin (1, 10, 100 and 1000 fmol/mouse, i.c.v.) 30 min before testing, and scopolamine (1.65 μmol/kg, s.c.) was injected immediately before nociceptin. Data are shown as median and interquartile ranges. Figures in parentheses show the numbers of mice used. $^{**}P < 0.01$ vs. control (Mann–Whitney *U*-test). $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. scopolamine alone (Bonferroni's test).

and step-down latency was recorded. An upper cut-off time of 300 s was set.

2.5. Responses to electric shock

The responses to electric shock during the training session were recorded. The following scores were given based on the responses to electric shock: 3 = jumping, 2 = vocalization, 1 = flinching, 0 = no response. Shock sensitivity is shown as the total score, which was the sum of each score for 15 s.

2.6. Data analysis

The behavioral data are expressed in terms of median, interquartile, and/or 10th and 90th percentile ranges. The significance of differences was evaluated using the Mann–Whitney *U*-test for comparisons between two groups and Kruskal–Wallis non-parametric one-way analysis of variance followed by Bonferroni's test for multiple comparisons. The criterion for significance was $P < 0.05$ in all statistical evaluations.

3. Results

3.1. Effects of nociceptin on scopolamine-induced impairment of spontaneous alternation performance

In the Y-maze test, scopolamine (1.65 μmol/kg, s.c.) significantly decreased the percentage alternation (Fig. 1A). Nociceptin (1–1000 fmol/mouse, i.c.v.) improved the impairment of spontaneous alternation induced by scopolamine and the effects of nociceptin at doses of 10 and 100 fmol/mouse were significant (Fig. 1A). Scopolamine markedly increased the total number of arm entries (Fig. 1B). Nociceptin (1–1000 fmol/mouse) showed no apparent effects on scopolamine-induced increases in the total number of arm entries (Fig. 1B).

3.2. Effects of nociceptin on scopolamine-induced impairment of learning and memory in the passive avoidance test

In the passive avoidance test, scopolamine (0.1 μmol/kg, s.c.) significantly shortened the step-down latency. Nociceptin (10–1000 fmol/mouse) 30 min before

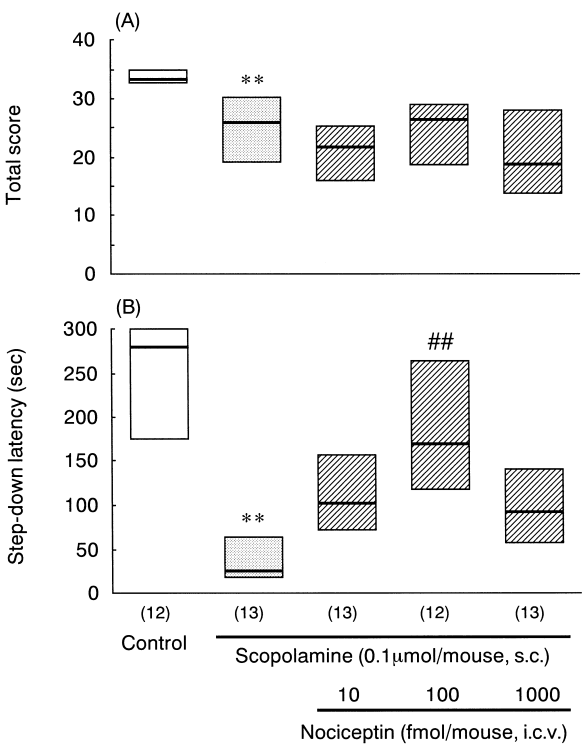

Fig. 2. Effects of nociceptin on scopolamine-induced responses to electric shocks (A) and step-down latency (B) in passive avoidance test. Mice were treated with nociceptin (10, 100 and 1000 fmol/mouse, i.c.v.) 30 min before the training session, and the retention test was carried out 24 h after training. Scopolamine (0.1 μmol/kg, s.c.) was injected immediately before nociceptin. Data are shown as median (horizontal bar), first and third quartiles (vertical column) and 10th and 90th percentiles (vertical line). Figures in parentheses show the numbers of mice used. $^{**}P < 0.01$ vs. control (Mann–Whitney *U*-test). $^{\#\#}P < 0.01$ vs. scopolamine alone (Bonferroni's test).

Table 1
Effects of nociceptin on step-down latency and sensitivity to electric shocks during the training period in mice
Mice were treated with nociceptin (10–1000 fmol/mouse, i.c.v.) 30 min before the training session. The following scores were given based on the response to each electric shock (1 Hz, 500 ms, 80 V, DC). Shock sensitivity is shown as the total score which was the sum of each score for 15 s as follows: 3 = jumping, 2 = vocalization, 1 = flinching, 0 = no response. Values are shown as the median and range (first and third quartiles). *N* shows the number of mice used.

Treatment	Dose (fmol/mouse)	*N*	Step-down latency median (range)	Sensitivity median (range)
Control	0	9	300.0 (198.0–300.0)	38.0 (33.0–39.0)
Nociceptin	10	10	244.5 (166.5–300.0)	37.5 (34.5–38.8)
	100	10	252.0 (178.5–300.0)	32.5 (27.3–36.8)
	1000	10	267.0 (162.8–300.0)	33.0 (32.0–34.8)

the training session in the passive avoidance test reversed the scopolamine-induced impairment of learning and memory with a bell-shaped curve and the effects of nociceptin at a dose of 100 fmol were significant (Fig. 2).

3.3. Effects of nociceptin on the response to electric shocks

Low doses of nociceptin (10–1000 fmol/mouse) alone induced no significant changes in the response to electric shocks at the same dose range as used in the passive avoidance test (Table 1). Co-administration of scopolamine and nociceptin (10–1000 fmol/mouse) also induced no significant changes in the response to electric shocks compared with scopolamine alone, while scopolamine itself decreased the response to electric shocks (Fig. 2).

3.4. Effects of nociceptin and its combination with nocistatin, naloxone benzoylhydrazone or nor-binaltorphimine on scopolamine-induced impairment of learning and memory in the Y-maze test

We have previously reported that high doses of nociceptin (1.5 and/or 5.0 nmol/mouse, i.c.v.) significantly impaired learning and/or memory, and nocistatin (5.0 nmol/mouse, i.c.v.) antagonized this impairment induced by nociceptin without changing motor activity or responses to electric shocks (Hiramatsu and Inoue, 1999b). It has been reported that the anti-nociceptive effects of nociceptin were antagonized by naloxone benzoylhydrazone, a κ_3-opioid receptor agonist. Furthermore, κ_1-opioid receptor agonists such as dynorphin A-(1–13), improved scopo-

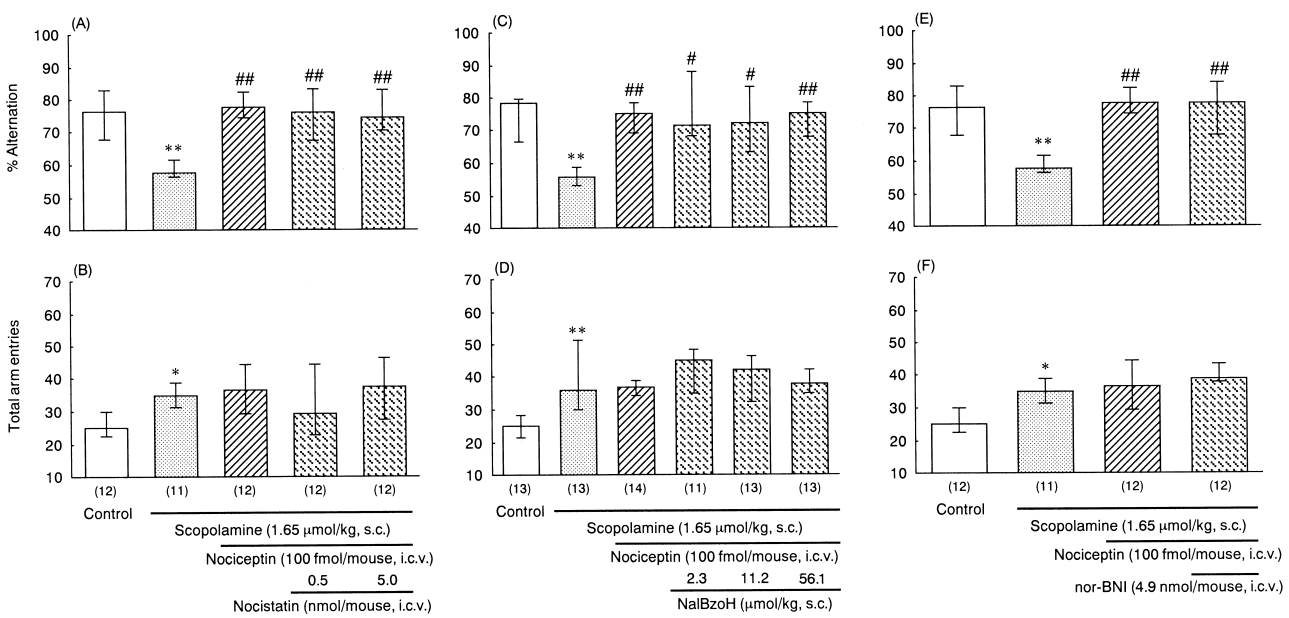

Fig. 3. Effects of nociceptin alone and in combination with nocistatin (A, B), naloxone benzoylhydrazone (C, D) or nor-binaltorphimine (E, F) on scopolamine-induced impairment of spontaneous alternation (A, C and E) and total arm entries (B, D and F) in the Y-maze. Mice were treated with nociceptin (100 fmol/mouse, i.c.v.), naloxone benzoylhydrazone (NalBzoH, 2.3, 11.2 and 56.1 μmol/kg, s.c.), and/or nor-binaltorphimine (nor-BNI, 4.9 nmol/mouse, i.c.v.) 30 min before testing. Scopolamine (1.65 μmol/kg, s.c.) was injected immediately before the other agents. Data are shown as median and interquartile ranges. Figures in parentheses show the numbers of mice used. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control (Mann–Whitney *U*-test), $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. scopolamine alone (Bonferroni's test).

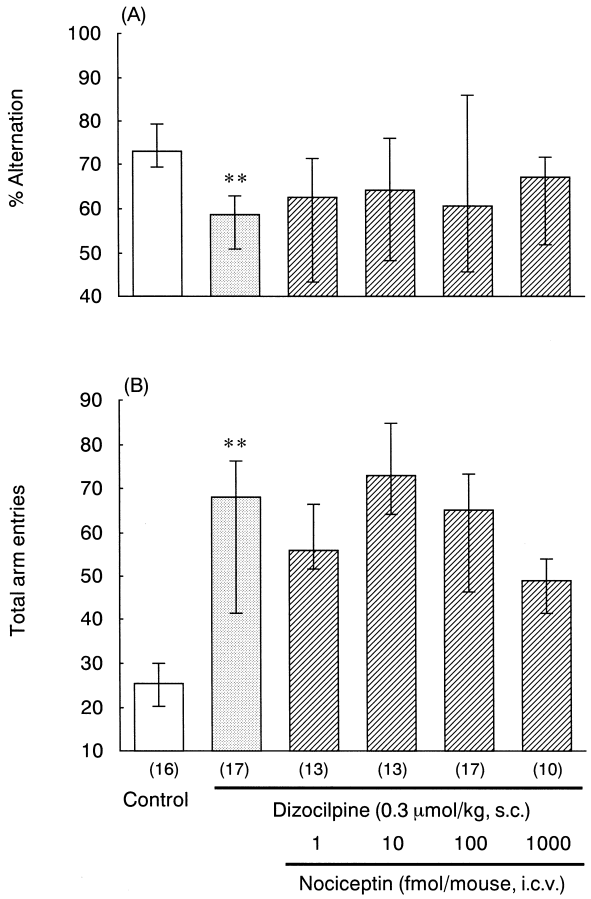

Fig. 4. Effects of nociceptin on dizocilpine-induced impairment of spontaneous alternation (A) and total arm entries (B) in the Y-maze. Mice were treated with nociceptin (1, 10, 100 and 1000 fmol/mouse, i.c.v.) 30 min before testing, and dizocilpine (0.3 μmol/kg, s.c.) was injected immediately before nociceptin. Data are shown as median and interquartile ranges. Figures in parentheses show the numbers of mice used. $^{**}P < 0.01$ vs. control (Mann–Whitney *U*-test).

lamine-induced impairment of learning and memory (Itoh et al., 1993; Hiramatsu et al., 1996). Therefore, to elucidate the mechanism responsible for the ameliorating effects of nociceptin, nocistatin, naloxone benzoylhydrazone and nor-binaltorphimine were selected. None of these drugs antagonized the effect of nociceptin on scopolamine-induced impairment of spontaneous alternation performance (Fig. 3A, B, C). Naloxone benzoylhydrazone (2.3, 11.2 and 56.1 μmol/kg, s.c.) alone did not induce any significant changes in normal mice or scopolamine-induced impairment of spontaneous alternation (data not shown).

3.5. Effects of nociceptin on dizocilpine-induced impairment of spontaneous alternation performance

In the Y-maze test, dizocilpine (0.3 μmol/kg, s.c.) significantly decreased the percentage alternation. Nociceptin (1–1000 fmol/mouse) had no significant effects on the impairment of spontaneous alternation induced by dizocilpine (Fig. 4).

3.6. Effects of nociceptin on acquisition of memory in the passive avoidance test and spontaneous alternation performance in the Y-maze in normal mice

Nociceptin (10–1000 nmol/mouse) 30 min before the training session also showed no significant effect on the step-down latencies in the retention test over the same dose range as used in the passive avoidance test in normal mice (Table 1).

Administration of nociceptin (1–1000 fmol/mouse, i.c.v.) 30 min before the test session in the Y-maze showed no apparent behavioral disturbances and no changes in the number of total arm entries in normal mice (Table 2).

4. Discussion

Although structurally similar to endogenous opioid peptides, especially dynorphin A, nociceptin possesses different characteristics in its pharmacological profile in that it does not bind strongly to classical opioid receptors (Reinscheid et al., 1995; Meunier, 1997). In contrast with our previous results regarding dynorphin A-(1–13), nociceptin has been reported to impair learning and/or memory. For example, nociceptin injected into the hippocampus markedly impaired spatial learning in the rat (Sandin et al., 1997), and nociceptin, but not the inactive analog des-[Phe^1]nociceptin, inhibited the induction of long-term potentiation (Yu et al., 1997). Furthermore, Manabe et al. (1998) reported that mice lacking the nociceptin receptor possessed greater learning ability and had better memory than control mice. We reported recently that nmol amounts

Table 2
Effects of nociceptin on percentage alternation and total arm entries in Y-maze test in normal mice
Mice were treated with nociceptin (1–1000 fmol/mouse, i.c.v.) 30 min before testing. Values are shown as the median and range (first and third quartiles). *N* shows the number of mice used.

Treatment	Dose (fmol/mouse)	*N*	% Alteration median (range)	Total arm entries median (range)
Control	0	11	74.1 (67.1–76.4)	24.0 (19.0–27.5)
Nociceptin	1	11	76.0 (67.8–83.5)	20.0 (18.0–23.5)
	10	11	75.0 (67.4–80.5)	24.0 (20.0–25.0)
	100	11	74.3 (61.5–77.5)	22.0 (19.0–26.5)
	1000	11	73.9 (67.9–81.3)	25.0 (19.5–30.0)

of nociceptin, which is in the same dose range used by these other groups, decreased the percentage of alternation in the Y-maze and shortened the step-down latency in passive avoidance tests (Hiramatsu and Inoue, 1999a,b). Mamiya et al. (1999) also reported that nociceptin (10 pmol, i.c.v.) impaired the passive avoidance performance. These findings suggested that the nociceptin system has negative roles in learning and memory at the whole-animal level.

Interestingly, the present results showed that extremely low doses of nociceptin (fmol order) alleviated scopolamine-induced impairment of learning and/or memory without affecting motor activity or response to electric shocks. This finding is completely contrast to previous reports indicating that nociceptin induced impairment of learning and memory (Sandin et al., 1997; Manabe et al., 1998; Hiramatsu and Inoue, 1999a,b; Mamiya et al., 1999). Therefore, to elucidate the mechanism of action of the ameliorating effects of nociceptin, nocistatin, naloxone benzoylhydrazone and nor-binaltorphimine were selected. Nocistatin has been reported to block nociceptin-induced allodynia and hyperalgesia (Okuda-Ashitaka et al., 1998) and learning and/or memory impairment (Hiramatsu and Inoue, 1999b). Since nocistatin does not bind to the ORL1 receptor (Okuda-Ashitaka et al., 1998), it may have functionally antagonistic roles in the central nervous system. In the present study, however, nocistatin did not block the improvement by nociceptin on scopolamine-induced impairment of spontaneous alternation performance.

Recent studies have suggested a close relationship between the pharmacological κ_3-opioid receptor and the ORL1 receptor (Mathis et al., 1997). Naloxone benzoylhydrazone acted as a κ_3-opioid receptor agonist, competed with [^{3}H]nociceptin binding and attenuated the nociceptin-induced inhibition of cAMP accumulation in cultured cells (Noda et al., 1998). Furthermore, behavioral studies demonstrated that naloxone benzoylhydrazone completely inhibited nociceptin-induced hyperalgesia and hypolocomotion (Noda et al., 1998) and impairment of learning and memory (Hiramatsu and Inoue, 1999b; Mamiya et al., 1999). Therefore, it is likely that naloxone benzoylhydrazone can act as a potent antagonist of the nociceptin receptor in vivo. In the present study, however, naloxone benzoylhydrazone did not antagonize the improvement by nociceptin of scopolamine-induced impairment of spontaneous alternation performance. Naloxone benzoylhydrazone itself did not induce any significant changes in percent alternation in normal mice or scopolamine-induced impairment of spontaneous alternation.

κ-Opioid receptor agonists such as dynorphin A-(1–13) improved scopolamine-induced impairment of learning and memory, and this effect was antagonized by a κ_1-opioid receptor antagonist, nor-binaltorphimine (Itoh et al., 1993; Hiramatsu et al., 1996). Therefore, we tested whether nor-binaltorphimine also antagonized the effect of nociceptin on scopolamine-induced impairment of learning and/or memory. Nor-binaltorphimine also did not antagonize the improvement by nociceptin of scopolamine-induced impairment of spontaneous alternation. Mathis et al. (1997) reported that an antisense oligodeoxynucleotide targeting the first coding exon of κ_3-opioid receptor potently blocked nociceptin hyperalgesia without interfering with nociceptin analgesia, while antisense probes based upon the second and third coding exons only prevented analgesia. Antisense oligodeoxynucleotides based upon the second and third coding exons of this clone selectively blocked the analgesic actions of naloxone benzoylhydrazone (Pan et al., 1995). Together, these results strongly suggested that the behavioral action of nociceptin involves more than one receptor. Therefore, our results suggested that the effects of low doses of nociceptin are probably mediated through a novel nociceptin receptor subtype. To confirm this hypothesis, selective ORL1 receptor antagonists for each subtype are required.

Alternative explanation is that nociceptin may interact directly with cholinergic receptors or release of acetylcholine. Recently, Itoh et al. (1999) have reported that high concentration of nociceptin (10^{-5} M) reduced acetylcholine release, but 10^{-6} M nociceptin did not change it in the rat striatum. Therefore, they concluded that nociceptin may act as a neuropeptide which inhibits acetylcholine release in the striatum via ORL1 receptor. This finding is in good agreement with the reports that high doses of nociceptin impair learning and memory in mice (Hiramatsu and Inoue, 1999a,b,c; Mamiya et al., 1999) and rats (Sandin et al., 1997). Therefore, our findings suggest that acetylcholine release may not have important roles at low doses of nociceptin, because the dosage of nociceptin was much low compared with their experimental condition.

Nociceptin is known to have many effects on the central nervous system including alteration of spontaneous activity, anti-nociception and aversive motivation (Meunier et al., 1995; Reinscheid et al., 1995; Florin et al., 1996). Therefore, pre-training administration of nociceptin may alter locomotor activity, pain sensitivity to electric shocks and/or motivation, and these effects may alter the behavioral test conditions in a nonspecific manner. Evaluation of the pain response (flinching and vocalization) to electric shocks showed that the drug tested in avoidance studies had no significant effect on pain sensitivity as compared with the control group. Total arm entries after nociceptin injection indicated that low doses of this peptide had no effect on locomotor activity. In fact, the doses used in the present study were extremely low and no results have been reported using this drug in this dose range regarding mnemonic function. It is of interest to investigate the mechanism responsible for this effect of nociceptin.

Dynorphin A-(1–13) has been reported to improve the scopolamine-induced impairment of spontaneous alternation performance (Itoh et al., 1993) and carbon monoxide-induced delayed amnesia in mice (Hiramatsu et al., 1995, 1997) via a κ-opioid receptor-mediated mechanism since

this amelioration by dynorphin A-(1–13) was almost completely antagonized by nor-binaltorphimine, a κ_1-opioid receptor antagonist (Itoh et al., 1993; Hiramatsu et al., 1995). However, it has also been reported that dynorphin A-(1–13) exerts so-called 'non-opioid effects' (Faden, 1992; Hiramatsu et al., 2000). Interestingly, we have recently shown that the des-[Tyr^1]dynorphin analogs, dynorphin A-(2–13) and [Phe^1]dynorphin A-(1–13) also improved scopolamine-induced learning and/or memory impairment, and these effects were not antagonized by nor-binaltorphimine (Hiramatsu et al., 1998a, 2000). The amelioration by nociceptin might be mediated via these 'non-opioid effects.' While low doses of nociceptin could not ameliorate dizocilpine-induced impairment of spontaneous alternation, our recent study showed that these dynorphin A derivatives ameliorated dizocilpine-induced impairment of learning and memory (Hiramatsu et al., 1998a; Inoue et al., 1999). Although dynorphin A derivatives act on both cholinergic and glutaminergic systems, nociceptin may only act on cholinergic system. Therefore, the mode of action may be different between nociceptin-mediated and κ-opioidergic systems in regulating the processes of learning and memory.

In conclusion, the results of our study provided the first evidence that injection of an extremely low concentration of nociceptin improves on scopolamine-induced impairment of learning and memory. Although the functional significance of these findings remains to be established, we believe that our data have implications for the further understanding of the role of neuropeptide systems in the hippocampus for learning and memory.

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