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U-50488H, a selective κ-opioid receptor agonist, improves carbon monoxide-induced delayed amnesia in mice

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Abstract

The effects of trans-(±)-3,4-dichloro-*N*-methyl-*N*-(2-[1-pyrrolidinyl] cyclohexyl) benzeneacetamide methanesulfonate salt (U-50488H) on carbon monoxide (CO)-induced amnesia in mice were investigated using spontaneous alternation and step-down type passive avoidance tasks. The lower percentage alternation and shorter median step-down latency in the retention test of the CO-exposed group indicated that memory deficiency occurred in mice when behavioral testing commenced 5–7 days after CO exposure. Administration of U-50488H (0.21 and 0.64 μmol/kg s.c.) 25 min before spontaneous alternation performance or the first training session of the passive avoidance task improved the CO-induced impairment of alternation performance and passive avoidance tasks. To determine whether the effect of U-50488H was mediated via κ-opioid receptors, we attempted to block its action using a selective κ-opioid receptor antagonist (nor-binaltorphimine). Nor-binaltorphimine (5.44 nmol/mouse i.c.v.) blocked the effect of U-50488H on CO-induced delayed amnesia. Furthermore, a low dose of scopolamine (0.41 μmol/kg s.c.) also blocked the ameliorating effect of U-50488H. U-50488H (0.21–2.15 μmol/kg s.c.) did not facilitate the acquisition of memory in normal mice. These results suggest that U-50488H modulates the κ-opioid receptor-mediated opioid neuronal system and activates the cholinergic neuronal system, and that it ameliorates the disruptive effect of CO on acquisition and/or consolidation of memory.

Keywords: Carbon monoxide (CO); U-50488H, (trans-(±)-3,4-dichloro-*N*-methyl-*N*-(2-[1-pyrrolidinyl] cyclohexyl) benzeneacetamide methanesulfonate salt); Nor-binaltorphimine dihydrochloride; Amnesia, delayed; κ-Opioid receptor; Cholinergic neuronal system

1. Introduction

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; Beninger et al., 1989; Coyle et al., 1983; Newhouse, 1990). Although investigation of learning and memory has focused primarily on cholinergic neurotransmission, reports of increased κ-opioid receptor density in the brain of Alzheimer's patients (Hiller et al., 1987) and dynorphin A-(1-8)-like immunoreactivity in the hippocampus of aged rats (Jiang et al., 1989) suggest that disruption of opioidergic neurotransmission may also play a role in the cognitive deficits associated with Alzheimer's disease and aging. Recent studies have indicated that neuropeptides modulate learning and memory processes in experimental animals (Kovacs and De Wied, 1994). Of particular interest was the observation that an endogenous κ-opioid receptor agonist, dynorphin A-(1-13), improves the scopolamine-induced impairment of spontaneous alternation performance in mice (Itoh et al., 1993) and carbon monoxide (CO)-induced delayed amnesia (Hiramatsu et al., 1995, 1996c). However, whether dynorphins improve memory function is still controversial. For example, post-training administration of dynorphin A-(1-13) has no effect on inhibitory avoidance or shuttle avoidance responses (Izquierdo et al., 1985), and impairs retention of inhibitory avoidance but not of Y-maze discrimination (Introini-Collison et al., 1987).

Multi-infarct dementia may be caused by a deficiency in the supply of oxygen and glucose to the brain as a result of impaired brain circulation (Hachinski et al., 1974). Transient ischemic insult is also known to induce a deficiency in the supply of oxygen and produce irreversible neuronal damage very slowly in the hippocampal CA1 subfield (Kirino, 1982). Furthermore, CO has been reported to cause deterioration of memory function (Ando et al., 1987; Bunnell and Horvath, 1988), and memory deficits

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develop insidiously over the days following recovery from CO intoxication in humans (Ginsberg, 1979). On the other hand, delayed neuronal damage can also be produced after CO exposure in mice (Hiramatsu et al., 1994; Ishimaru et al., 1991), and deficiencies in learning and memory occur in mice exposed to CO before training (Nabeshima et al., 1990). This memory deficiency develops in a delayed manner, more than 3 days after CO exposure (delayed amnesia) (Nabeshima et al., 1991). Using this model, we have demonstrated that these animals exhibit dysfunction in the cholinergic neurons in the frontal cortex, striatum and hippocampus (Nabeshima et al., 1991). Some nootropics such as nefiracetam and NIK-247 (9-amino-2,3,5,6,7,8-hexahydro-1*H*-cyclopenta(*b*)-quinoline monohydrate hydrochloride), which may facilitate cholinergic neuronal systems (Sarter, 1991), improve the CO-induced memory deficit (Hiramatsu et al., 1992; Yoshida et al., 1992). Therefore, CO exposure can provide an amnesic model for the investigation of memory deterioration, especially for progressive memory dysfunction (Hiramatsu et al., 1996a). As described above, although dynorphin A-(1-13) improved CO-induced amnesia, it is still unclear whether the ameliorating effects of dynorphin A-(1-13) are the result of activation of κ-opioid receptors. Therefore, in the present study, we investigated, using two types of behavioral tasks, whether U-50488H, a selective κ-opioid receptor agonist, ameliorates CO-induced amnesia.

2. Materials and methods

2.1. Animals

7-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/dark cycle (light on 08:00–20:00 h) 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 (1992, Fol. Pharmacol. Jpn. 99, 35A) and the interministerial decree from 25 May 1987 (Ministry of Education).

2.2. Drugs

U-50488H (trans-($\pm$)-3,4-dichloro-*N*-methyl-*N*-(2-[1-pyrrolidinyl] cyclohexyl) benzene-acetamide methanesulfonate salt; Sigma, St. Louis, MO, USA), nor-binaltorphimine dihydrochloride (nor-binaltorphimine; Research Biochemicals International, Natick, MA, USA) and scopolamine hydrobromide (scopolamine; Tokyo Chemical Industry, Japan) were dissolved in 0.9% saline. Drugs were administered intracerebroventricularly (i.c.v.) into the lateral ventricle of the mouse brain according to the method of Haley and McCormick (1957) in a volume of 5 μl/mouse under brief ether anesthesia. Control animals were injected with vehicle i.c.v. under brief ether anesthesia. Nor-binaltorphimine was administered i.c.v. 30 min before the first training session. U-50488H and scopolamine were administered (s.c.) 25 and 30 min, respectively, before the alternation performance or the training session of the passive avoidance test.

2.3. CO exposure

Each mouse was put into a transparent plastic vessel (diameter 6 cm, height 10 cm) with a pipe feeding into it and two holes at the bottom as air outlets. The mice were exposed to pure CO gas 3 times at 1-h intervals at a rate of 10 cc/min (Hiramatsu et al., 1992). The animals were exposed to CO each time until clonic convulsions were observed and they were held in this state for 6–10 s in the vessel. As a result, CO exposure lasted for 30–60 s. Under these conditions, the mortality rate ranged from 10 to 20%. Previously, we had shown that CO exposure induces hypothermia (Ishimaru et al., 1991). Thus, in the present study, the mice were kept on a hot plate (KN-205D; Natsume, Japan) for 2 h to maintain their body temperature at 38–39°C.

2.4. Spontaneous alternation performance

Immediate working memory performance was assessed by recording spontaneous alternation behavior in a single session in a Y-maze. The maze was 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 been completely placed in the arm. Alternation was defined as successive entries into the three arms, on the overlapping triplet sets. 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. Alternation performance was assessed 5 days after CO exposure.

2.5. Step-down type passive avoidance task

A step-down type of passive avoidance task was used, as described previously (Hiramatsu et al., 1992). The apparatus consisted of a transparent acrylic rectangular cage ($30 \times 30 \times 40$ cm high) with a grid floor with a wooden platform ($4 \times 4 \times 4$ cm) in the center, set in a semi-soundproof wooden outer box ($35 \times 35 \times 90$ cm high). Illumination was provided by a 15-W illumination

lamp above the apparatus. An electric current (1 Hz, 500 ms, 39 V DC) was delivered to the grid floor by an isolated stimulator (SEN-3201; Nihon Koden, Japan). When mice were placed in the test cage, the electrical resistance varied between 100 and 250 kΩ. Therefore, each mouse received an electric shock varying between 0.16 and 0.39 mA.

Training was carried out 7 days after CO exposure. 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 (first training). To minimize variability, training was performed twice with an interval of 2 h. In the second training session, an electric shock was delivered again for 15 s when the mouse stepped down from the platform. In this second session, training was terminated if the mouse escaped from the grid floor back up onto the platform. Training was also terminated if the mouse did not step down onto the grid floor within 60 s. Mice that received an electric shock in the second training session again showed shorter step-down latency in the retention test (data not shown).

The retention test was carried out 24 h after the first training session in a manner similar to the training except that no electric shock was delivered to the grid floor. Each mouse was placed on the platform and step-down latency was recorded. An upper cut-off time of 300 s was set.

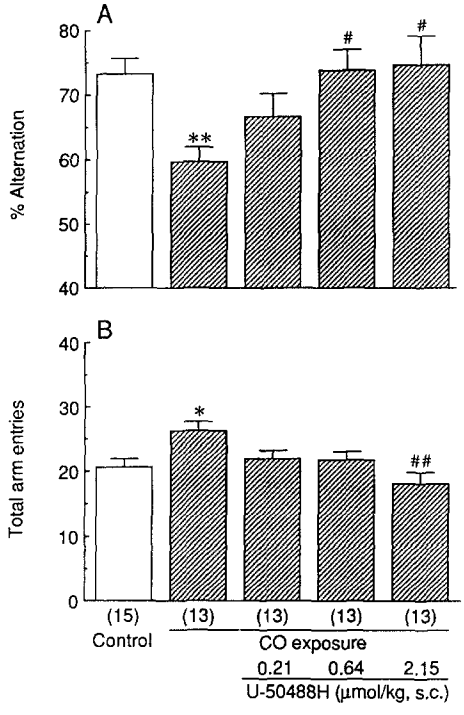

Fig. 1. Effects of U-50488H on the CO-induced impairment of spontaneous alternation (A) and total arm entries (B) in the Y-maze. Mice were exposed to CO 3 times with 1-h intervals as described in Section 2. Spontaneous alternation performance was examined 5 days after CO exposure. Mice were treated with U-50488H (0.21–2.15 μmol/kg s.c.) 25 min before the test. The data are expressed as means ± S.E.M. In parentheses the number of mice used is given. * $P < 0.05$, ** $P < 0.01$ vs. normal control (Mann-Whitney U-test), # $P < 0.05$, ## $P < 0.01$ vs. CO alone (Bonferroni's test).

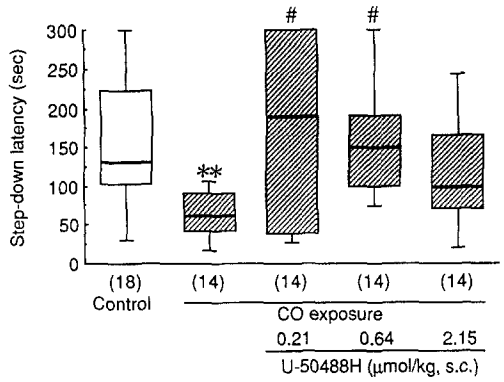

Fig. 2. Effects of U-50488H on acquisition in CO-exposed mice in the passive avoidance test. Mice were exposed to CO 3 times with 1-h intervals as described in Section 2. Training was carried out 7 days after CO exposure. Mice were treated with U-50488H (0.21–2.15 μmol/kg s.c.) 25 min before the first training session, and the retention test was carried out 24 h after training. Step-down latency values are shown as median (horizontal bar), first and third quartiles (vertical column) and 10th and 90th percentiles (vertical line). In parentheses the number of mice used is given. ** $P < 0.01$ vs. normal control (Mann-Whitney U-test), # $P < 0.05$ vs. CO alone (Bonferroni's test).

2.6. Responses to electric shock

The responses to electric shock during the first training session were recorded. The following scores were given based on the responses to electric shock: 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.

2.7. Statistical analysis

The data from spontaneous alternation tests are expressed as means ± S.E.M. and those from passive avoidance tests are expressed in terms of median, interquartile, and 10th and 90th percentile ranges. The significance of differences was evaluated using the Mann-Whitney U test for comparisons of two groups and the 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 U-50488H on the CO-induced impairment of spontaneous alternation performance

In the Y-maze test, repeated CO exposure decreased the percentage alternation in a time-dependent manner. A significant difference from the control level was observed 3 days after CO exposure and persisted for at least 7 days

Table 1
Effects of U-50488H on sensitivity to electric shocks during the first training period in normal and CO-exposed mice

Treatment	Dose (μmol/kg)	n	Median	Range
Normal group				
Control	0	28	11.5	(7.0–15.0)
U-50488H	0.21	10	13.0	(12.0–15.0)
U-50488H	0.64	10	11.0	(9.0–15.0)
U-50488H	2.15	6	10.5	(10.0–11.0)
CO-exposed group				
Control	0	14	10.5	(10.0–16.0)
U-50488H	0.21	14	11.5	(10.0–14.0)
U-50488H	0.64	14	11.0	(7.0–13.0)
U-50488H	2.15	14	11.0	(8.0–14.0)

Mice were exposed to CO 3 times with 1-h intervals as described in Section 2. Shock sensitivity was measured 7 days after CO exposure during the first training period. Mice were treated s.c. with U-50488H (0.21–2.15 μmol/kg) 25 min before the first training session. The following scores were given based on the response to each electric shock (1 Hz, 500 ms, 39 V, D.C.). Shock sensitivity is shown as the total scores which were the sum of each score for 15 s as follows: 2, vocalization; 1, flinching; 0, no response. Values for shock sensitivity are shown as the median and range (first and third quartiles). n, the number of mice used.

after the exposure (Hiramatsu et al., 1994). When mice were exposed 3 times to CO, the percentage alternation 5 days after exposure decreased significantly (Fig. 1A). Administration of U-50488H (0.64 μmol/kg) 25 min before the test session in the Y-maze significantly reversed the CO-induced delayed amnesia (Fig. 1A), with no change in the total number of arm entries (Fig. 1B). Although a higher dose of U-50488H (2.15 μmol/kg) also reversed the CO-induced amnesia, it decreased the total number of arm entries.

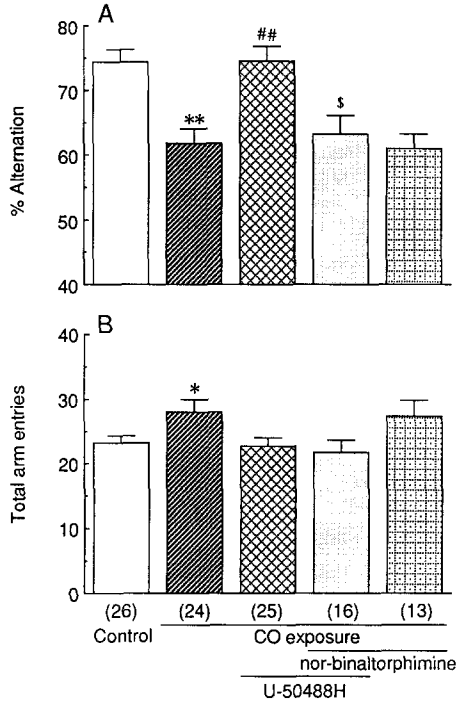

Fig. 3. Antagonism by nor-binaltorphimine of the effects of U-50488H on CO-induced impairment of spontaneous alternation (A) and total arm entries (B) in the Y-maze. Spontaneous alternation performance was examined 5 days after CO exposure. Mice were treated with nor-binaltorphimine (5.44 nmol/mouse i.c.v.) and with U-50488H (0.64 μmol/kg s.c.) 30 and 25 min, respectively, before the test. The data are expressed as means ± S.E.M. In parentheses the number of mice used is given. * $P < 0.05$, ** $P < 0.01$ vs. normal control (Mann-Whitney U-test), $^{\#\#}$ $P < 0.01$ vs. CO alone, $^{\$}$ $P < 0.05$ vs. U-50488H alone (Bonferroni's test).

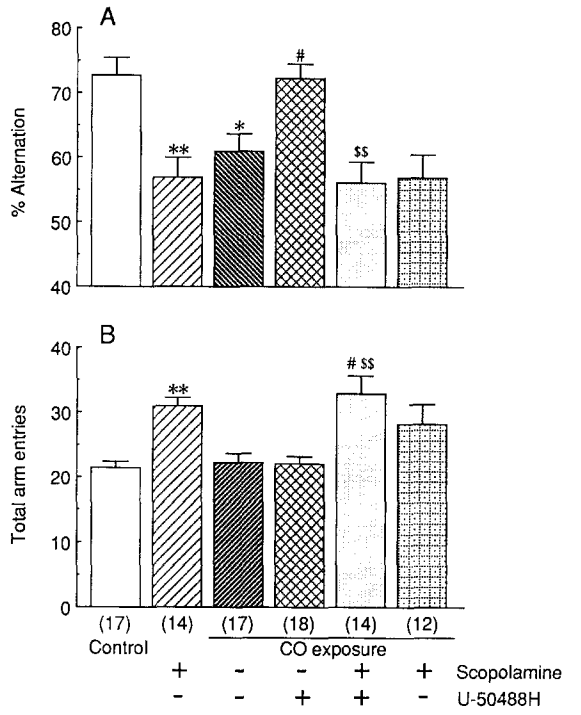

Fig. 4. Antagonism by scopolamine of the effects of U-50488H on CO-induced impairment of spontaneous alternation (A) and total arm entries (B) in the Y-maze. Spontaneous alternation performance was examined 5 days after CO exposure. Mice were treated with scopolamine (0.41 μmol/kg s.c.) and with U-50488H (0.64 μmol/kg s.c.) 30 and 25 min, respectively, before the test. The data are expressed as means ± S.E.M. In parentheses the number of mice used is given. * $P < 0.05$, ** $P < 0.01$ vs. normal control (Mann-Whitney U-test), $^{\#}$ $P < 0.05$ vs. CO alone, $^{\$\$}$ $P < 0.01$ vs. U-50488H alone (Bonferroni's test).

3.2. Effects of U-50488H on acquisition of memory in CO-exposed mice in the passive avoidance test

The median for step-down latencies in the retention test was significantly shorter than that of the control group when mice were exposed to CO 7 days before training (Fig. 2), indicating the induction of amnesia by such exposure (delayed amnesia). Administration of U-50488H (0.21 and 0.64 μmol/kg) 25 min before the first training session significantly prolonged the step-down latencies in the CO-exposed group in the retention test, producing a bell-shaped curve (Fig. 2). On the other hand, a higher dose of U-50488H (2.15 μmol/kg) had no significant effect on the step-down latencies in the retention test. U-50488H induced no significant changes in the response

to electric shocks at the same dose range as used in the passive avoidance test (Table 1).

3.3. Effects of nor-binaltorphimine on U-50488H-mediated improvement of CO-induced impairment of alternation performance

To determine whether the effects of U-50488H were mediated via κ-opioid receptors, we attempted to block its action using a selctive κ-opioid receptor antagonist, nor-binaltorphimine (5.44 nmol/mouse). This dose of nor-binaltorphimine is sufficient to block the effects of κ-opioid receptor agonists (Hiramatsu et al., 1995; Itoh et al., 1993). Nor-binaltorphimine injected 5 min prior to the injection of U-50488H (0.64 μmol/kg) blocked the effects of U-50488H on the CO-exposure-induced impairment of the alternation performance (Fig. 3A). There was no significant effect of nor-binaltorphimine itself at the dose used (5.44 nmol) in the CO-exposed group (Fig. 3A).

3.4. Effects of scopolamine on U-50488H-mediated improvement of CO-induced impairment of alternation performance

To determine whether the effects of U-50488H were mediated by cholinergic neuronal systems, we attempted to block its action with a low dose of a muscarinic acetylcholine receptor antagonist, scopolamine (0.41 μmol/kg). This dose of scopolamine is equivalent to 0.125 mg/kg. Pre-administration of scopolamine completely abolished

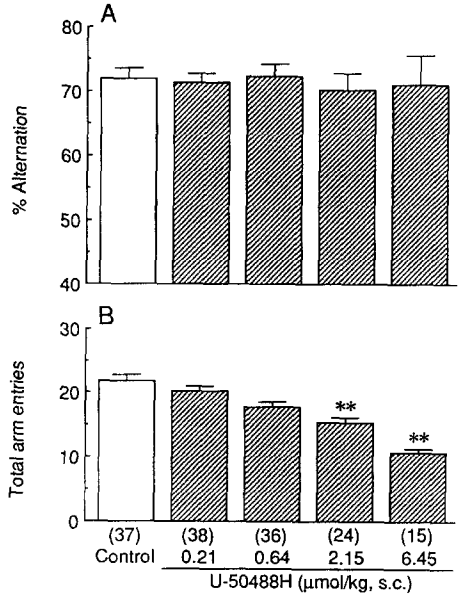

Fig. 5. Effects of U-50488H on spontaneous alternation (A) and total arm entries (B) in the Y-maze in normal mice. Mice were treated with U-50488H (0.21–6.45 μmol/kg s.c.) 25 min before the test. The data are expressed as means ± S.E.M. In parentheses the number of mice used is given. ** $P < 0.01$ vs. normal control (Bonferroni's test).

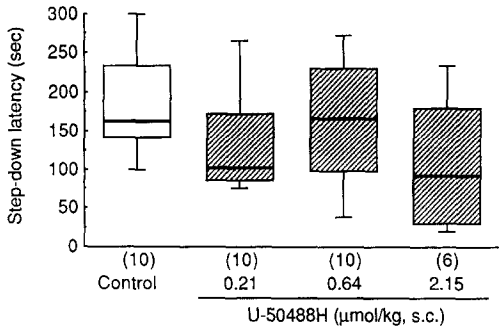

Fig. 6. Effects of U-50488H on the passive avoidance response in normal mice. Mice were treated with U-50488H (0.21–2.15 μmol/kg s.c.) 25 min before the first training session, and the retention test was carried out 24 h after training. Step-down latency values are shown as median (horizontal bar), first and third quartiles (vertical column) and 10th and 90th percentiles (vertical line). In parentheses the number of mice used is given.

the U-50488H-mediated improvement of CO-induced impairment of alternation performance (Fig. 4A). Although scopolamine itself impaired the spontaneous alternation performance, it did not potentiate the CO-induced impairment (Fig. 4A).

3.5. Effects of U-50488H on learning and memory in normal mice

As shown in Figs. 1–4, U-50488H improved the learning and memory ability deficiency in CO-exposed mice in two different behavioral tasks. U-50488H, therefore, may itself facilitate acquisition and/or consolidation of memory in normal mice. As shown in Fig. 5A, U-50488H (0.21–6.45 μmol/kg) administered 25 min before the behavioral tests did not change the percentage alternation. Doses of U-50488H (2.15 and 6.45 μmol/kg) significantly decreased the total arm entries (Fig. 5B). U-50488H (0.21–2.15 μmol/kg) also did not prolong step-down latency, but at the dose of U-50488H (2.15 μmol/kg), tended to shorten latency (Fig. 6).

4. Discussion

Learning and memory presumably consist of a series of steps, acquisition, consolidation, retention and retrieval. Nabeshima et al. (1990) reported that deficiencies in acquisition, consolidation and retention occur when CO exposure is initiated before training, at the time of acquisition of memory and after memory consolidation. Memory deficiency develops in a delayed manner, more than 3 days after CO exposure and persists for at least 7–14 days for spontaneous alternation performance and passive avoidance performance (delayed amnesia) (Hiramatsu et al., 1994; Nabeshima et al., 1991). In this model, the animals exhibit dysfunction in the cholinergic neurons in the frontal

cortex, striatum and hippocampus which are brain regions important in learning and memory. In fact, as some cholinergic-enhancing drugs ameliorate this CO-induced delayed amnesia (Hiramatsu et al., 1992, 1994; Yoshida et al., 1992), reduced cholinergic neuronal function may be one of the mechanisms underlying memory dysfunction following CO exposure (Hiramatsu et al., 1994; Nabeshima et al., 1991). Therefore, we elected to conduct behavioral tests 5–7 days after CO exposure.

Dynorphin A-(1-13) has been reported to improve the scopolamine-induced impairment of spontaneous alternation performance (Itoh et al., 1993) and CO-induced delayed amnesia in mice (Hiramatsu et al., 1995, 1996c). This amelioration by dynorphin A-(1-13) was almost completely antagonized by nor-binaltorphimine, a κ-opioid receptor antagonist (Hiramatsu et al., 1995; Itoh et al., 1993). In the present study, pre-training administration of U-50488H, a selective κ-opioid receptor agonist, also improved CO-induced memory dysfunction, in agreement with earlier findings described above. The anti-amnesic effects of U-50488H on delayed amnesia induced by pre-training CO exposure were blocked by administration of nor-binaltorphimine (5.44 nmol) prior to injection of U-50488H. Nor-binaltorphimine itself had no significant effects on locomotor activity or the step-down latency in either CO-exposed or normal mice, in agreement with a previous report of no significant effects on spontaneous alternation performance in mice (Itoh et al., 1993). Furthermore, a low dose of scopolamine, a muscarinic cholinergic receptor antagonist, abolished the effects of U-50488H. These results suggest that U-50488H may be capable of ameliorating cholinergic dysfunction via the κ-opioidergic system. Jiang et al. (1989) reported that dynorphin A-(1-8)-like immunoreactivity was increased in the aged rat brain and this elevation was found only in the hippocampus and frontal cortex. The increase in dynorphin A-(1-8)-like immunoreactivity in the aged hippocampus was associated with a decline in spatial learning memory (Jiang et al., 1989). The authors hypothesized that increased dynorphin A-(1-8) might be the cause of the behavioral impairment. It has been reported that stimulation of μ-opioid receptors impairs the memory process (Patterson et al., 1989). Dynorphin A-(1-8) possesses a higher affinity for μ-opioid receptors than does dynorphin A-(1-13) (Leslie, 1987). Therefore, dynorphin has opposite effects on learning and memory, depending on the fragments and their affinity with receptor subtypes. In agreement with this hypothesis, the present results confirmed that U-50488H, a selective κ-opioid receptor agonist, improves CO-induced amnesia.

In contrast, although U-50488H has memory-enhancing effects in CO-exposed mice, administration of U-50488H failed to facilitate the acquisition of memory in normal mice. This finding is in agreement with those previously reported, indicating that dynorphin A-(1-13) has no effect on spontaneous alternation performance or passive avoidance performance in normal mice (Hiramatsu et al., 1995; Itoh et al., 1993). As described above, dysfunction in the cholinergic neuronal system is induced by CO exposure (Hiramatsu et al., 1994; Nabeshima et al., 1991). Therefore, it is suggested that κ-opioid receptor agonists facilitate learning and memory by acting on the impaired cholinergic system. This hypothesis may be supported by the finding that dynorphin A-(1-13) potentiates learning in basal forebrain-lesioned rats in a step-through-type passive avoidance task (Ukai et al., 1993) because the cholinergic system in the cortex was disrupted in this model (Fuji et al., 1993). Recently, we have shown that galanin, an endogenous neuropeptide, significantly impairs the acquisition of learning and recall of memory and decrease in acetylcholine release. Dynorphin A-(1-13) improves the galanin-induced impairment of memory accompanied by block of the reductions in acetylcholine release in rats (Hiramatsu et al., 1996b). Furthermore, endogenous κ-opioid receptor agonists may not exert a tonic (inhibitory) control on the regulation of neurotransmission, because nor-binaltorphimine, at the dose used in the present study, did not modify alternation performance or step-down latency. Therefore, the κ-opioidergic system in the brain may play an important role in modulating learning and memory when the cholinergic system has been impaired.

The dose-response curve for the effects of U-50488H was bell-shaped. κ-Opioid receptor agonists are known to have many effects on the central nervous system, including alterations of spontaneous activity, antinociception and aversive motivation (Bals-Kubik et al., 1993; Spanagel et al., 1992). Therefore, pre-training administration of U-50488H may alter locomotor activity, pain sensitivity to electric shocks and/or motivation, and these effects may alter the behavioral test conditions in a non-specific 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. However, the high doses of U-50488H caused analgesic effects (5.4 μmol/kg = 2.5 mg/kg) and sedation (10.8 μmol/kg = 5 mg/kg) as reported previously (Von Voigtlander et al., 1983). Thus, κ-opioid receptor agonists, even at lower doses that do not change shock sensitivity and cause sedation, have beneficial effects on learning and memory.

In conclusion, although the precise nature of the interaction between the κ-opioidergic and the cholinergic systems in the central nervous system is unknown, it is possible to speculate that κ-opioid receptor agonists directly and/or indirectly activate only the impaired cholinergic system. We believe that U-50488H may be effective in the treatment of various forms of cognitive disturbances related to dysfunction of the cholinergic neuronal system with beneficial effects on learning and memory. However, considerable research will still be necessary to fully understand the potential utility of dynorphin or κ-opioid receptor agonists in the treatment of cognitive dysfunction.

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