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Effects of dynorphin A-(1–13) on carbon monoxide-induced delayed amnesia in mice studied in a step-down type passive avoidance task

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Abstract

The effects of dynorphin A-(1–13) on carbon monoxide (CO)-induced amnesia in mice were investigated using a step-down type passive avoidance task. Memory deficiency occurred in mice when training commenced 7 days after CO exposure although it was not produced 1 day after CO exposure. The median step-down latency in the retention test of the CO-exposed group was significantly shorter than that of the control group. Administration of dynorphin A-(1–13) (1.5 nmol/mouse i.c.v.) 15 min before the first training session prolonged the step-down latency in the CO-exposed group. Dynorphin A-(1–13) administered immediately after the first training session or administered 15 min before the retention test also prolonged the step-down latency in the CO-exposed group. To determine whether this effect of dynorphin A-(1–13) was mediated via κ-opioid receptors, we attempted to block its action using a κ-opioid receptor antagonist (nor-binaltorphimine). Nor-binaltorphimine (5.44 nmol/mouse i.c.v.) blocked the effect of dynorphin A-(1–13) on delayed amnesia. However, dynorphin A-(1–13) (0.5, 1.5 and 5.0 nmol/mouse) did not facilitate the acquisition of memory in normal mice. These results suggest that dynorphin A-(1–13) modulates the κ-opioid receptor-mediated opioid neuronal system, and that it ameliorates the disruptive effect of CO on acquisition, consolidation and/or recall of memory.

Keywords: Dynorphin A-(1–13); Cholinergic neuronal system; CO (carbon monoxide); Delayed amnesia; Learning; Nor-binaltorphimine; κ-Opioid receptor; Passive avoidance

1. Introduction

It is well known that cholinergic neuronal systems play an important role in the cognitive deficits associated with ageing and neurodegenerative diseases (Bartus et al., 1982; Beninger et al., 1989; Coyle et al., 1993; Kameyama et al., 1986; Levin, 1992; 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 ageing. Recent studies have indicated that neuropeptides modulate learning and memory processes in experimental animals. Of particular interest was the observation that an endogenous κ-opioid agonist, dynorphin A-(1–13), improves the scopolamine-induced impairment of spontaneous alternation performance in mice (Itoh et al., 1993a), which is related to working memory (Sarter et al., 1988; Stone et al., 1991). 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. Transient ischemic attack is also known to induce a deficiency in the supply of oxygen and produce irreversible neuronal damage very slowly in the hippocampal CA1 subfield.

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Furthermore, carbon monoxide (CO) has been reported to cause deterioration of memory function (Ando et al., 1987; Bunnell and Horvath, 1988), and memory deficits develop insidiously over the days following recovery from CO intoxication in humans (Ginsberg, 1979). On the other hand, delayed neuronal death can also be produced after CO exposure in mice (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, 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. In the present study, we investigated whether dynorphin A-(1–13) ameliorates CO-induced amnesia using a step-down type passive avoidance task.

2. Materials and methods

2.1. Animals

Seven-week-old male *ddY* mice (Nihon SLC, Japan) were kept in a regulated environment (23 ± 1°C, 50 ± 5% humidity), with a 12-h light/dark cycle (light on 8 a.m.–8 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. Jpn., 1992, 99: 35A) and the interministerial decree from May 25th, 1987 (the Ministry of Education).

2.2. Drugs

Dynorphin A-(1–13) (dynorphin, Peptide Institute, Japan) and nor-binaltorphimine dihydrochloride (nor-binaltorphimine, Research Biochemicals International, MA, USA) were dissolved in 0.9% saline. Drugs were administered into the lateral ventricle (intracerebroventricularly, 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. 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. Dynorphin was administered (i.c.v.) 15 min before, immediately after the training session, or 15 min before the retention 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 to remove air. 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 chronic convulsions were observed and maintained in that state for 5–7 s in the vessel. As a result, CO exposure lasted for between 30 and 55 s. Under these conditions, the mortality rate ranged from 10 to 20%. Previously, we had shown that CO exposure induced hypothermia (Ishimaru et al., 1991). Thus, in the present study, mice were kept on a hot plate (KN-205D, Natsume, Japan) for 2 h to maintain their body temperature at 38–39°C. In each experiment, 10–18 mice were normally used per group. Some experiments were repeated and the data from all experiments were added.

2.4. Step-down type passive avoidance task

A step-down type of passive avoidance task was used, as previously described (Hiramatsu et al., 1992). 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, 38 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 0.15 and 0.38 mA.

2.5. Training

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 also showed shorter step-down latency in the retention test (data not shown).

2.6. Retention test

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.

2.7. 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 = flinch, 0 = no response. Shock sensitivity was shown as the total score, which was the sum of each score for 15 s.

2.8. Experimental schedules

Behavioral experiments were carried out 7 days after CO exposure. In experiment 1, nor-binaltorphimine and dynorphin were administered i.c.v. 30 and 15 min, respectively, before the first training session, and then the retention test was performed after 24 h. In experiment 2, dynorphin was administered immediately after the first or second training session and retention testing was performed after 24 h. In experiment 3, training was performed 7 days after CO exposure, and 24 h later the retention test was carried out. Dynorphin was administered 15 min before the retention test. In experiment 4, dynorphin was administered 15 min before the training session to normal mice to determine whether it has memory enhancing effects in itself. In this case, an electric current (1 Hz, 500 ms, 60 V DC) was delivered over a period of 3 s and training was performed only once. These electric shock conditions were used to investigate whether the drugs facilitate the passive avoidance response, because the control animals trained with a shock of the same duration showed a poor avoidance response compared to that of the animals trained with a shock of long duration (15 s) (Ichihara et al., 1989).

2.9. Statistical analysis

The data were expressed in terms of median, interquartile, and 10th and 90th percentile ranges. Significant differences were 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.

3. Results

3.1. Experiment 1: pre-training administration

Effects of dynorphin on acquisition of memory in CO-exposed mice

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

Table 1
Effects of dynorphin A-(1–13) on sensitivity to electric shocks during the first training period in normal and CO-exposed mice

Treatment	Dose (nmol/mouse)	*n*	Median	Range
(A)				
Normal group				
Dynorphin	0	20	11.5	(7.75–14.0)
CO-exposed group				
Dynorphin	0	18	13.5	(12.25–14.75)
Dynorphin	0.5	22	13.0	(11.0–15.0)
Dynorphin	1.5	22	13.5	(11.0–15.0)
Dynorphin	5.0	21	12.0	(9.0–14.0)
(B)				
Normal group				
Dynorphin	0	16	13.0	(11.5–14.0)
CO-exposed group				
Dynorphin + nor-binaltorphimine	0 + 0	16	9.0	(7.0–12.5)
Dynorphin + nor-binaltorphimine	1.5 + 0	14	12.0	(9.0–15.0)
Dynorphin + nor-binaltorphimine	1.5 + 5.44	15	8.0	(6.25–12.0)
Dynorphin + nor-binaltorphimine	0 + 5.44	15	9.0	(6.5–12.25)

Mice were exposed to CO 3 times with 1-h intervals as described in the Materials and methods section. The shock sensitivity was measured 7 days after CO exposure during the first training period. Mice were treated intracerebroventricularly with nor-binaltorphimine (5.44 nmol/mouse) and dynorphin A-(1–13) (dynorphin; 1.5 nmol/mouse) 30 and 15 min, respectively, before the first training session. The following scores were given based on the response to each electric shock (1 Hz, 500 ms, 38 V, D.C.). The shock sensitivity is shown as the total scores which were the sum of each score for 15 s as follows: 2 = vocalization, 1 = flinch, 0 = no response. Each value for shock sensitivity shows the median and range (first and third quartiles). *n* shows the number of mice used.

training (Fig. 1), indicating the induction of amnesia by such exposure (delayed amnesia). Administration of dynorphin (1.5–5.0 nmol/mouse) 15 min before the first training session prolonged the step-down latencies in the CO-exposed group, producing a bell-shaped curve (Fig. 1). The effects of dynorphin (1.5 nmol) were significant. On the other hand, a higher dose of dynorphin (5.0 nmol) had no significant effect on the step-down latencies. Dynorphin induced no significant changes in the response to electric shocks or in locomotor activity at the same dose range as used in the passive avoidance task (Table 1A).

Effects of nor-binaltorphimine on dynorphin-mediated amelioration of CO-induced delayed amnesia in mice

To determine whether the effects of dynorphin were mediated via κ-opioid receptors, we attempted to block its action using a selective 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 (Itoh et al., 1993a,b). Nor-binaltorphimine injected 15 min prior to the injection of dynorphin (1.5 nmol) blocked the effects of dynorphin on delayed amnesia induced by pre-training CO exposure (Fig. 2). There was no significant effect of nor-binaltorphimine itself at the dose used (5.44 nmol) in the CO-exposed group (Fig. 2) and in the control group as shown by the median and interquartile ranges; control group ($n = 13$), 282.0 (200.5–300.0); nor-binaltorphimine-treated group ($n = 13$), 233.0 (141.3–300.0).

Analysis of variance of the data for the response to electric shocks, i.e. flinch and vocalization, revealed a significant overall drug effect ($F(4,71) = 10.8$, $P <$ 0.05). At the dosage used in the present study, however, subsequent between-group comparisons indicated that none of the pair comparisons showed significant differences (Table 1B).

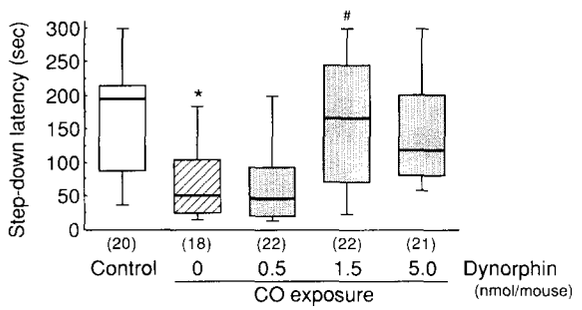

Fig. 1. Effects of dynorphin A-(1–13) administered before the first training session on CO-induced delayed amnesia. Mice were exposed to CO 3 times with 1-h intervals as described in the Materials and methods section. Training was carried out 7 days after CO exposure. Mice were treated intracerebroventricularly with dynorphin A-(1–13) (dynorphin; 0.5–5.0 nmol/mouse) 15 min before the first training session, and the retention test was carried out 24 h after training. Each step-down latency value shows the median (horizontal bar), first and third quartiles (vertical column) and 10th and 90th percentiles (vertical line). Figures in parentheses show the number of mice used. $^{*}P < 0.05$ vs. normal control (Mann-Whitney U-test), $^{\#}P < 0.05$ vs. CO alone (Bonferroni's test).

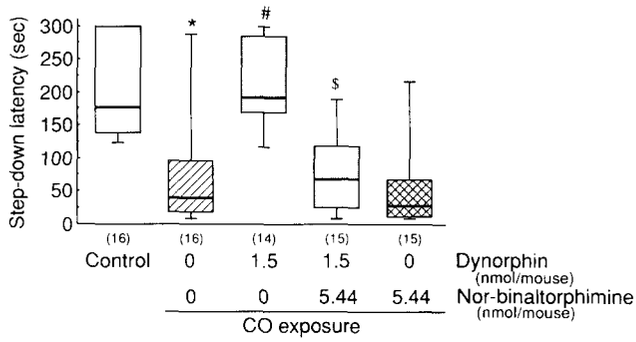

Fig. 2. Antagonism by nor-binaltorphimine of the effects of dynorphin A-(1–13) on CO-induced delayed amnesia in mice. Training was carried out 7 days after CO exposure. Mice were treated intracerebroventricularly with nor-binaltorphimine (5.44 nmol/mouse) and dynorphin A-(1–13) (dynorphin) 30 and 15 min, respectively, before the first training session, and the retention test was carried out 24 h after training. Each step-down latency value shows the median (horizontal bar), first and third quartiles (vertical column) and 10th and 90th percentiles (vertical line). Figures in parentheses show the number of mice used. $^{*}P < 0.05$ vs. normal control (Mann-Whitney U-test), $^{\#}P < 0.05$ vs. CO alone, $^{\$}P < 0.05$ vs. dynorphin alone (Bonferroni's test).

3.2. Experiment 2: administration of dynorphin immediately after the training session

To determine whether dynorphin modifies acquisition and/or consolidation of memory, it was administered immediately after the first training session. Dynorphin (1.5 nmol) significantly improved the shortened step-down latencies in the retention test in CO-exposed mice (Fig. 3A). It is possible that dynorphin may affect acquisition in the second training session. Although dynorphin tended to improve CO-induced delayed amnesia, however, the step-down latencies in the retention test were not significantly different from those in CO-exposed mice when dynorphin was injected immediately after the second training session (Fig. 3B).

3.3. Experiment 3: administration of dynorphin before the retention test

To determine whether dynorphin modifies memory recall, it was administered 15 min before the retention test. Dynorphin (1.5 nmol) significantly improved the shortened step-down latencies in the retention test in CO-exposed mice (Fig. 4). Although there was no significant difference, the step-down latencies in control mice were shorter than those of the previous experiment (Figs. 1–3).

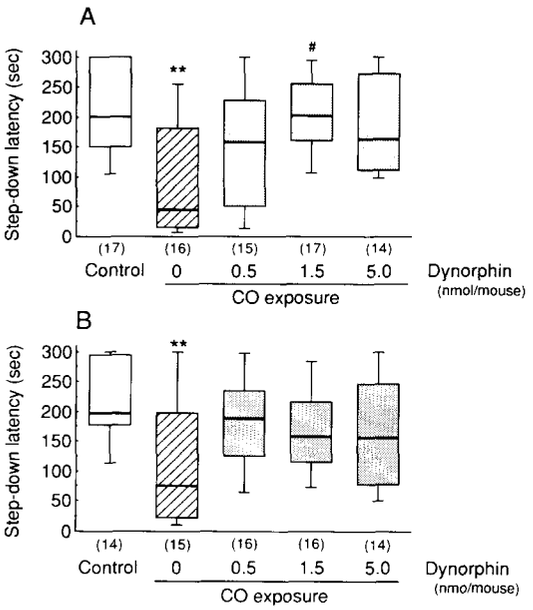

Fig. 3. Effects of dynorphin A-(1–13) administered after training on CO-induced delayed amnesia in mice. Mice were exposed to CO 3 times with 1-h intervals as described in the Materials and methods section. Training was carried out 7 days after CO exposure. Mice were treated intracerebroventricularly with dynorphin A-(1–13) (dynorphin; 0.5–5.0 nmol/mouse) immediately after the first (A) or second (B) training session, and the retention test was carried out 24 h after training. Each step-down latency value shows the median (horizontal bar), first and third quartiles (vertical column) and 10th and 90th percentiles (vertical line). Figures in parentheses show the number of mice used. $^{**}P < 0.01$ vs. normal control (Mann-Whitney U-test); $^{\#}P < 0.05$ vs. CO alone (Bonferroni's test).

3.4. Experiment 4: effects of dynorphin in normal mice

As shown in Figs. 1–4, dynorphin improved the deficiency in learning and memory ability in CO-exposed mice with three different drug treatment schedules. Dynorphin, therefore, may itself facilitate acquisition and/or consolidation of memory in normal mice. In this experiment, dynorphin was administered 15 min before the training session which elicits less acquisition of memory. The median, with the interquartile ranges of step-down latency, in control mice was 48.0 (35.8–140.3) s (Fig. 5). This result indicated that control mice trained with a shock of short duration (3 s) had a poor avoidance response compared to the step-down latency under other experimental conditions, i.e. 195 (90–230) s (Fig. 1). Dynorphin (0.5–5.0 nmol) did not alter the step-down latencies in the retention test in normal mice (Fig. 5).

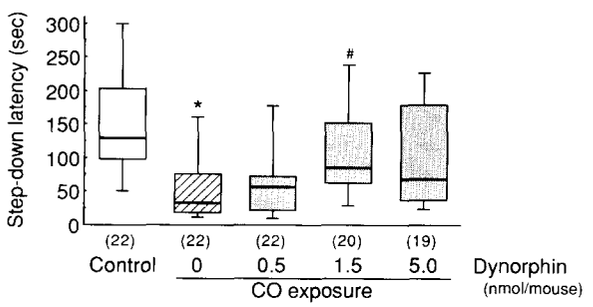

Fig. 4. Effects of dynorphin A-(1–13) administered before retention testing in CO-exposed mice. Mice were exposed to CO 3 times with 1-h intervals as described in the Materials and methods section. Training was carried out 7 days after CO exposure. Mice were treated intracerebroventricularly with dynorphin A-(1–13) (0.5–5.0 nmol/mouse) 15 min before the retention testing, carried out 24 h after training. Each step-down latency value shows the median (horizontal bar), first and third quartiles (vertical column) and 10th and 90th percentiles (vertical line). Figures in parentheses show the number of mice used. $^{*}P < 0.05$ vs. normal control (Mann-Whitney U-test); $^{\#}P < 0.05$ vs. CO alone (Bonferroni's test).

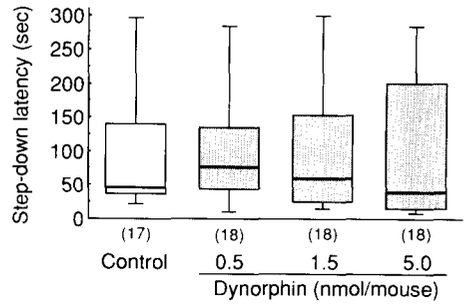

Fig. 5. Effects of dynorphin A-(1–13) on normal mice in the passive avoidance task. Mice were treated intracerebroventricularly with dynorphin A-(1–13) (0.5–5.0 nmol/mouse) 15 min before the training session, and the retention test was carried out 24 h after training. Each step-down latency value shows the median (horizontal bar), first and third quartiles (vertical column) and 10th and 90th percentiles (vertical line). Figures in parentheses show the number of mice used.

4. Discussion

Learning and memory presumably consist of a series of steps for 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 14 days for passive avoidance performance (delayed amnesia) (Nabeshima et al., 1991). In this model, animals exhibit dysfunction in the cholinergic neurons in the frontal cortex, striatum and hippocampus which are important brain regions in learning and memory. In fact, as some cholinergic-enhancing drugs ameliorate this CO-induced delayed amnesia (Hiramatsu et al., 1992; Yoshida et al., 1992), reduced cholinergic neuronal function may be one of the mechanisms underlying memory dysfunction fol-

lowing CO exposure (Hiramatsu et al., 1992; Nabeshima et al., 1991). Therefore, we elected to conduct training 7 days after CO exposure, and to perform the retention test 1 day after training. In the present study, administration of dynorphin before or immediately after the training session, or before the retention test prolonged the step-down latencies in CO-exposed mice.

Recently, dynorphin has been reported to improve the scopolamine-induced impairment of spontaneous alternation performance in mice (Itoh et al., 1993a). This ameliorating effect of dynorphin was almost completely antagonized by nor-binaltorphimine, a κ-opioid receptor antagonist (Itoh et al., 1993a). In the present study, pre-training administration of dynorphin improved CO-induced memory dysfunction, in agreement with the previous findings described above. The antiamnesic effects of dynorphin on delayed amnesia induced by pre-training CO exposure were blocked by administration of nor-binaltorphimine (5.44 nmol) prior to injection of dynorphin. 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 that showed no significant effects on spontaneous alternation performance in mice (Itoh et al., 1993a). These results suggest that dynorphin 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). They hypothesized that elevated 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 with μ-opioid receptors than dynorphin A-(1–13) (Leslie, 1987). Therefore, dynorphin possesses opposite actions on learning and memory depending on the fragments and their affinity with receptor subtypes. In agreement with this hypothesis, we have recently found that U-50,488H, a selective κ-opioid receptor agonist, improves CO-induced amnesia (data not shown).

Treatment with dynorphin immediately after the first training session improved CO-induced delayed amnesia. However, administration of dynorphin immediately after the second training session failed to significantly improve CO-induced delayed amnesia, although a tendency to do so was observed. Interestingly, administration of dynorphin prior to the retention test also improved CO-induced delayed amnesia. These findings clearly indicate that acquisition of memory could occur even when delayed amnesia was observed 7 days after CO exposure. That is, in this model, recall of memory is also impaired by CO exposure. These results suggest that dynorphin potentiates consolidation and/or retention and also facilitates recall in CO-exposed mice.

In contrast, although dynorphin has memory-enhancing effects in CO-exposed mice, administration of dynorphin failed to facilitate acquisition of memory in normal mice. This finding is in agreement with those of a previous report which indicated that dynorphin has no effect on spontaneous alternation performance in normal mice (Itoh et al., 1993a). As described above, dysfunction in the cholinergic neuronal system is induced by CO exposure. Therefore, it is suggested that dynorphin facilitates learning and memory by acting on the impaired cholinergic system. This hypothesis may be supported by the previous finding that dynorphin potentiates learning in basal forebrain-lesioned rats in a step-through-type passive avoidance task (Ukai et al., 1993). Furthermore, endogenous κ-opioid agonists may not exert tonic (inhibitory) control on the regulation of neurotransmission, because nor-binaltorphimine, at the dosage used in the present study, did not modify the 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 dynorphin was bell-shaped. High concentrations of dynorphins have been reported to produce neurotoxic effects by releasing excitatory amino acids through non-opioid mechanisms (Faden, 1992; Skilling et al., 1992). However, the higher dose of dynorphin (5.0 nmol) used in the present study did not modify the step-down latency in normal mice. Therefore, this dose of dynorphin may not induce excitotoxicy. κ-Opioid agonists are known to have many effects on the central nervous system, including alterations in spontaneous activity, antinociception and aversively motivating effects (Spanagel et al., 1992; Bals-Kubik et al., 1993). Therefore, pre-training administration of dynorphin may alter locomotor activity, pain sensitivity to electric shocks and/or motivation, and these effects may alter the training conditions in a non-specific manner. Evaluation of the pain response (flinch and vocalization) to electric shocks showed that the drug tested in avoidance studies had no significant effect on pain sensitivity. Even the higher dose of dynorphin (5.0 nmol) used here did not induce changes in locomotor activity or pain sensitivity as compared with the control group. Therefore, the dosages used in the present study were below that required to alter either shock sensitivity or locomotor activity.

In conclusion, although the precise interaction between the κ-opioidergic and the cholinergic systems in the central nervous system is unknown, it is possible to speculate that dynorphin directly and/or indirectly ac-

tivates only the impaired cholinergic system. We believe that dynorphin may be effective in various forms of cognitive disturbances related to the dysfunction of the cholinergic neuronal system with beneficial effects on learning and memory. However, considerable research will be necessary to fully understand the potential utility of dynorphin or κ-opioid agonists in the treatment of cognitive dysfunction.

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