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Effects of Dynorphin A (1-13) on Carbon Monoxide-Induced Delayed Amnesia in Mice

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HIRAMATSU, M., M. SASAKI, T. NABESHIMA AND T. KAMEYAMA. *Effects of dynorphin A (1-13) on carbon monoxide-induced delayed amnesia in mice.* PHARMACOL BIOCHEM BEHAV **56**(1) 73–79, 1997.—The effects of dynorphin A (1-13) on carbon monoxide (CO)-induced amnesia in mice were investigated. Memory deficiency was apparent during *Y*-maze testing 5 days after CO exposure (delayed amnesia). Percent alternation in the CO-exposed group was significantly lower than that in the control group. Administration of dynorphin A (1-13) (1.5 nmol, i.c.v.) 15 min before the *Y*-maze test session reversed the impairment of spontaneous alternation performance in the CO-exposed group. To determine whether this effect was mediated via kappa opioid receptors, we attempted to block the effect of dynorphin A using the kappa opioid receptor antagonist nor-binaltorphimine. Nor-binaltorphimine (5.44 nmol, i.c.v.) blocked the effect of dynorphin A (1-13) on delayed amnesia. Dynorphin A (1-13) did not affect the impairment of alternation induced by the blockade of NMDA-receptors by dizocilpine (MK-801), but significantly prevented the impairment induced by mecamylamine. These results suggest that dynorphin A (1-13) modulates the kappa receptor-mediated opioid neuronal system, and reverses the impairment of spontaneous alternation performance induced by CO exposure. **Copyright © 1997 Elsevier Science Inc.**

Dynorphin A (1-13) Cholinergic neuronal system Carbon monoxide Delayed amnesia Learning
Nor-binaltorphimine Kappa opioid receptor Spontaneous alternation performance

IT is well known that cholinergic neuronal systems play an important role in the cognitive deficits associated with aging and neurodegenerative diseases (2,3,6,26,27,37,42). Although investigation of learning and memory has focused primarily on cholinergic neurotransmission, reports of increased kappa opioid receptor density in the brain of Alzheimer's patients (12) and dynorphin A (1-8)-like immunoreactivity in the hippocampus of aged rats (25) 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. Of particular interest was the observation that an endogenous kappa opioid agonist, dynorphin A (1-13), reverses the scopolamine-induced impairment of spontaneous alternation performance (22) and carbon monoxide (CO)-induced delayed amnesia in mice (16). 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 (24), and impairs retention of inhibitory avoidance, but not of *Y*-maze discrimination (19).

CO has been reported to cause deterioration of memory function (4, 31), and memory deficits develop insidiously over the days following recovery from CO intoxication in man (9, 11,31). Delayed neuronal damage can also be produced after CO exposure in mice (20), and deficiencies in learning and memory occur in mice when exposed to CO before training (36). This memory deficiency develops in a delayed manner, more than 3 days after CO exposure (35). This model may involve, as do the ischemia models in gerbils, rats and mice, neurotoxicity induced by excitatory amino acids such as gluta-

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mate, since dizocilpine (MK-801), an N-methyl-D-aspartate (NMDA) receptor non-competitive antagonist, fully protects against CO-induced learning impairment and delayed amnesia (30). It is well known that NMDA receptors also play a crucial role in the neurophysiological processes underlying learning and memory (7,33,40,46). These findings suggest that reduced NMDA receptor-mediated glutamatergic neurotransmission may also be involved in CO-induced learning impairment.

Scopolamine, a muscarinic acetylcholine receptor blocker, is widely used for investigating cholinergic influences on learning ability in experimental animals. As mentioned above, since several neurotransmitter systems have been implicated in learning and memory dysfunction in disease states, CO exposure can provide a good amnesic model for the investigation of memory deterioration. For example, using this model, we demonstrated that low doses of nicotine, a nicotinic acetylcholine receptor agonist, reverse CO-induced delayed amnesia, indicating that nicotinic receptors may be involved in CO-induced amnesia (17). In the present study, we investigated whether dynorphin A (1-13) reverses CO-induced amnesia, using spontaneous alternation performance in a *Y*-maze test as the dependent variable. Moreover, we tested the effects of dynorphin A (1-13) on amnesia induced by the nicotinic receptor antagonist mecamylamine, and the NMDA receptor antagonist, MK-801.

METHOD

Animals

Seven-week-old male ddY mice (Japan SLC, Inc., Japan) were kept in a regulated environment (23 ± 1°C, 50 ± 5% humidity), with a 12 h light/dark cycle (light on 08:00 h–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 (Folia Pharmacol. Japon., 1992, 99: 35A) and the interministerial decree from May 25th, 1987 (the Ministry of Education).

Drugs

Dynorphin A (1-13) (dynorphin, Peptide Institute, Inc., Japan) and nor-binaltorphimine dihydrochloride (nBNI, Research Biochemicals International, MA) were dissolved in 0.9% saline. Drugs were administered into the lateral ventricle of the mouse brain according to the method of Haley and McCormick (10) in a volume of 5 μl under brief ether anesthesia. Control animals were injected with vehicle i.c.v. in the same way. nBNI was administered intracerebroventricularly (i.c.v.) 30 min before the test session, and dynorphin was administered (i.c.v.) 15 min before the test session. Dizocilpine (MK-801; (+)-5-methyl-10,11-dihydro-5H-dibenzo (a,d)cyclohepten-5,10-imine maleate (a generous gift from Dr. A.K. Cho, U.C.L.A., USA) and mecamylamine hydrochloride (Sigma, MO) were dissolved in saline and administered subcutaneously 20 min before and intraperitoneally 30 min before examination of spontaneous alternation performance, respectively.

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 ml/min (14). Animals were exposed to CO each time until chronic convulsions were observed and maintained in that state for 5–7 s in the vessel. This protocol led to CO exposure times between 30 and 55 s. Under these conditions, the mortality rate ranged from 10–20%. Previously, we showed that CO exposure induced hypothermia (20). 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 used per group. Some experiments were repeated and the data from all experiments were pooled.

Spontaneous Alternation Performance

Immediate working memory performance was assessed by recording spontaneous alternation behavior in a single session in a *Y*-maze made of black painted wood. Each arm was 40 cm long, 12 cm high, with a width of 3 cm at the bottom and 10 cm at the top. The arms converged in an equilateral triangular central area. The procedure was basically the same as that described previously (43): 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. Arm entry was considered to be completed when the hind paws of the mouse passed completely over the threshold of the arm. Alternation was defined as successive entries into the three arms, on the overlapping triplet sets. The percentage alternation was calculated as the ratio of actual to possible alternations (defined as the total number of arm entries minus two), multiplied by 100.

Statistical Analysis

The data are expressed as means ± S.E.M. Significant differences were evaluated using the Mann-Whitney U-test for comparisons between two groups and Kruskal-Wallis nonparametric one-way analysis of variance followed by Bonferroni's test for multiple comparisons. The criterion for statistical significance was $p < 0.05$.

RESULTS

Effects of Dynorphin A (1-13) on the CO-Induced Impairment of Spontaneous Alternation Performance

In a *Y*-maze test, successive periods of CO exposure decreased percent alternation in a time-dependent manner. Significant differences from control levels were observed 3 days after CO exposure and lasted for at least 7 days after exposure (13). When mice were exposed 3 times to CO, the percent alternation 5 days after exposure decreased significantly (Fig. 1A). However, differences between control and CO-exposed groups in the total number of arm entries during the 8-min session were not significant (Fig. 1B). Pretreatment with dynorphin A (1-13) (1.5 nmol) 15 min before the test session in the *Y*-maze test significantly reversed the CO-induced delayed amnesia in a dose-dependent fashion (Fig. 1A). The dose-effect function for dynorphin A (1-13) was bell-shaped. There were no differences in the number of arm entries among groups (Fig. 1B).

Effects of nBNI on Dynorphin A (1-13)-Mediated Reversal of CO-Induced Delayed Amnesia in Mice

To determine whether the effects of dynorphin A (1-13) were mediated via kappa opioid receptors, we attempted to block dynorphin A's action using the kappa-selective opioid receptor antagonist nBNI at a dose of 5.44 nmol, a dose shown previously to be sufficient to block the effects of kappa opioid

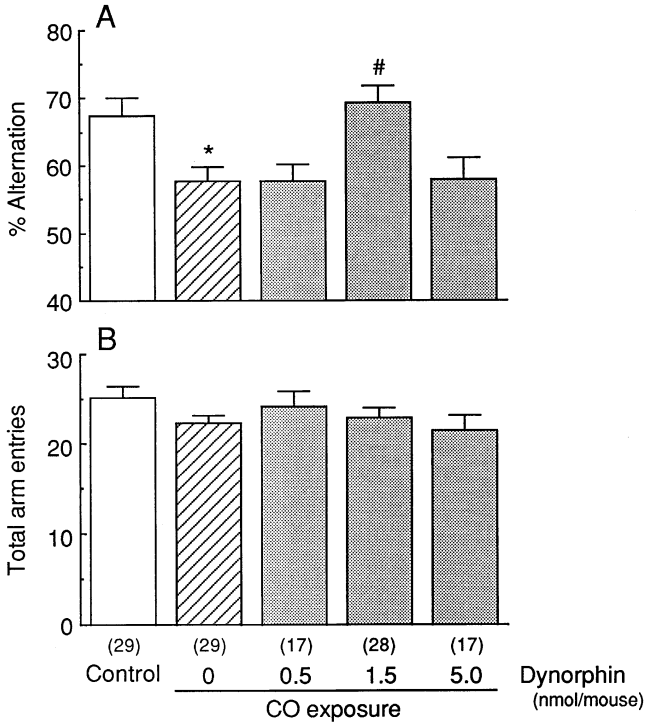

FIG. 1. Effects of dynorphin A (1-13) on the CO-induced impairment of spontaneous alternation (A) and total arm entries (B) in the *Y*-maze. Mice were exposed to CO 3 times with 1-h intervals as described in the Methods section. Alternation performance tests were carried out 5 days after CO exposure. Mice were treated intracerebroventricularly with dynorphin A (1-13) (dynorphin; 0.5 - 5.0 nmol/mouse) 15 min before the test session. Figures in parentheses show the numbers of mice used. $*p < 0.05$ vs. normal control (Mann-Whitney U-test), $\#p < 0.05$ vs. CO alone (Bonferroni's test).

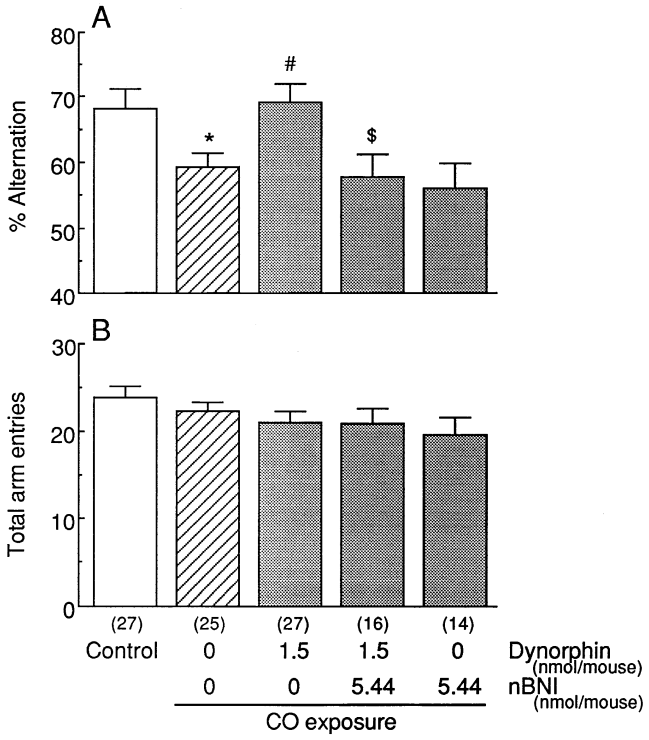

FIG. 2. Antagonism by nor-binaltorphimine of the effects of dynorphin A (1-13) on CO-induced impairment of spontaneous alternation (A) and total arm entries (B) in the *Y*-maze. Alternation performance was tested 5 days after CO exposure. Mice were treated intracerebroventricularly with nor-binaltorphimine (nBNI; 5.44 nmol/mouse) and dynorphin A (1-13) (dynorphin) 30 and 15 min, respectively, before the test session. Figures in parentheses show the numbers 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).

receptor agonists (22,23). nBNI injected 15 min prior to the injection of dynorphin A (1-13) (1.5 nmol) blocked the effects of dynorphin on delayed amnesia induced by CO exposure (Fig. 2A). There was no significant effect of nBNI itself at the dose used in the CO-exposed group.

At the dosage used in the present study, the drugs had no significant effect on locomotor activity in terms of the number of total arm entries.

Effects of Dynorphin A (1-13) on MK-801-Induced Impairment of Spontaneous Alternation Performance in Mice

As shown in Fig. 3A, administration of MK-801 (3.0 μmol/kg, i.p.) 20 min before the test session induced severe impairment of spontaneous alternation performance. Dynorphin A (1-13) (0.5 - 5.0 nmol) did not reverse the MK-801-induced amnesia (Fig. 3A). At this dose of MK-801, the number of total arm entries was significantly increased, which was taken to be a reflection of MK-801-induced hyperactivity. However, dynorphin A (1-13) did not affect the MK-801-induced hyperactivity at the dose used in this experiment.

To further demonstrate that dynorphin A (1-13) could not reverse the MK-801-induced amnesia, a lower dose of MK-801 (1.5 μmol/kg, i.p.) was used, because at higher doses this agent might completely and insurmountably block NMDA receptor-mediated learning and memory processes. The lower dose of MK-801 also impaired spontaneous alternation performance, although amnesia was less severe. Dynorphin A (1-13) did not reverse amnesia induced by the lower dose of MK-801 (Fig. 4A). A higher dose of dynorphin A (1-13) (5.0 nmol) enhanced the MK-801-induced amnesia.

Effects of Dynorphin A (1-13) on the Mecamylamine-Induced Impairment of Spontaneous Alternation Performance in Mice

The effects of dynorphin A (1-13) on percent alternation and number of total arm entries in mecamylamine-treated mice are shown in Fig. 5. Mecamylamine (49 μmol/kg, i.p.), a nicotinic acetylcholine receptor antagonist, administered 30 min before the test session, significantly decreased both percent alternation and the number of total arm entries. In this model, dynorphin A (1-13) (1.5 nmol) significantly reversed the mecamylamine-induced decrease in the percent alternation (Fig. 5A), with no effect on the decrease in locomotion (Fig. 5B).

DISCUSSION

Systemic administration of muscarinic cholinergic antagonists such as scopolamine impairs the performance of experimental animals in a wide variety of learning and memory tasks, including inhibitory (passive) avoidance (26) and spatial maze tasks (5,48). However, recent studies have shown that quisqualic acid, an excitatory amino acid, injected into the

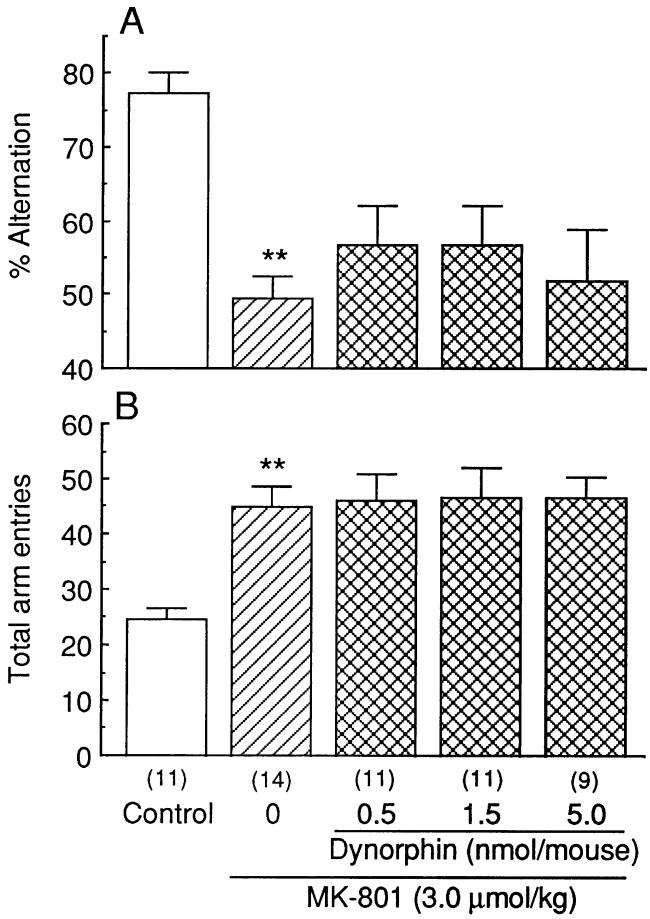

FIG. 3. Effects of dynorphin A (1-13) on MK-801-induced impairment of spontaneous alternation (A) and increases in total arm entries (B) in the *Y*-maze. Mice were treated subcutaneously with MK-801 (3.0 μmol/kg) 20 min before the test session. Mice were treated intracerebroventricularly with dynorphin A (1-13) (dynorphin; 0.5 - 5.0 nmol/mouse) 15 min before the test session. Figures in parentheses show the numbers of mice used. $^{**}p < 0.01$ vs. normal control (Mann-Whitney U-test).

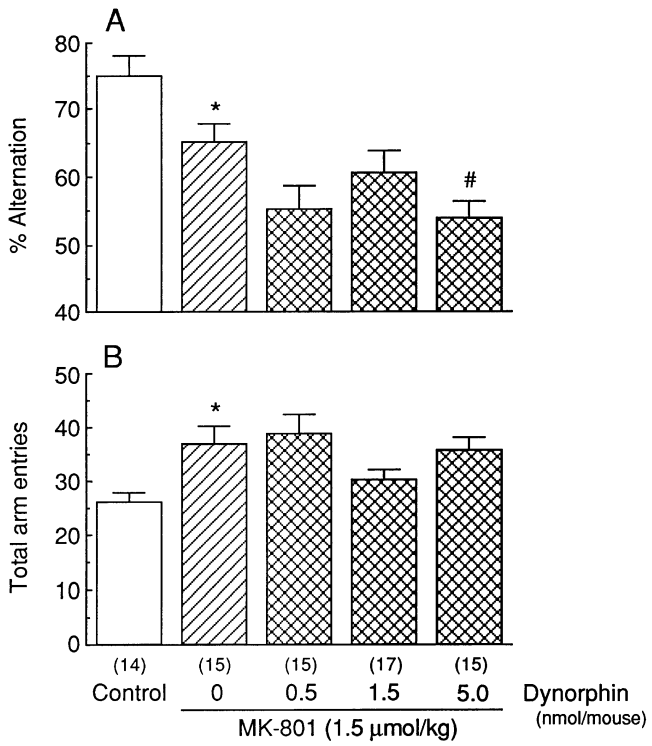

FIG. 4. Effects of dynorphin A (1-13) on MK-801-induced impairment of spontaneous alternation (A) and increases in total arm entries (B) in the *Y*-maze. Mice were treated subcutaneously with MK-801 (1.5 μmol/kg) 20 min before the test session. Mice were treated intracerebroventricularly with dynorphin A (1-13) (dynorphin; 0.5 - 5.0 nmol/mouse) 15 min before the test session. Figures in parentheses show the numbers of mice used. $^{*}p < 0.05$ vs. normal control (Mann-Whitney U-test). $\#p < 0.05$ vs. MK-801 alone (Bonferroni's test).

nucleus basalis of Meynert reduces cholinergic input to the cortex more completely than does ibotenic acid, but produces only minimal memory deficits (8). Furthermore, not only have large decreases in numbers of muscarinic binding sites been reported in the brain of Alzheimer's disease patients, but also decreases in nicotinic sites (47). Thus, independent manipulation of cholinergic receptor subtypes in experimental animals may provide an inadequate model of cognitive dysfunction. Consistent with this conclusion, the cholinergic dysfunction observed in aging and Alzheimer's disease is accompanied by changes in other neurotransmitter systems, such as peptidergic (12, 25) and noradrenergic (44) systems, which may be important in memory modulation.

The hypoxia induced by CO exposure has been shown to involve excitatory amino acid-induced neurotoxicity. Moderate neuronal damage has been observed in the hippocampal CA1 subfield (20,21), which appears to parallel the onset of delayed amnesia in a passive avoidance test (35) and the impairment of spontaneous alternation behavior (29). 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, some cholinergic-enhancing drugs have been shown to reverse this CO-induced delayed amnesia (14,49). Low doses of nicotine, a nicotinic acetylcholine receptor agonist, also improved CO-induced amnesia, indicating that reduced cholinergic neuronal function is one of the mechanisms underlying memory dysfunction following CO exposure (14,17,35). Based on these findings, we tested dynorphin A (1-13) using CO exposure as an amnesia model for the investigation of memory deterioration.

In the present study, dynorphin reversed CO-induced impairment of spontaneous alternation performance, in agreement with previous findings indicating reversal of the scopolamine-induced impairment of alternation performance in mice (22). These ameliorative effects of dynorphin were almost completely antagonized by nBNI (22), a kappa opioid receptor antagonist (Fig. 2A). nBNI itself had no significant effect on locomotor activity, or percent alternation in either CO-exposed or normal mice. These results suggest that dynorphin can ameliorate cholinergic dysfunction via the kappa opioidergic system. This hypothesis is supported by the previous finding that dynorphin potentiates learning in basal forebrain-lesioned rats in a step-through-type passive avoidance task (45).

Jiang et al. (25) 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.

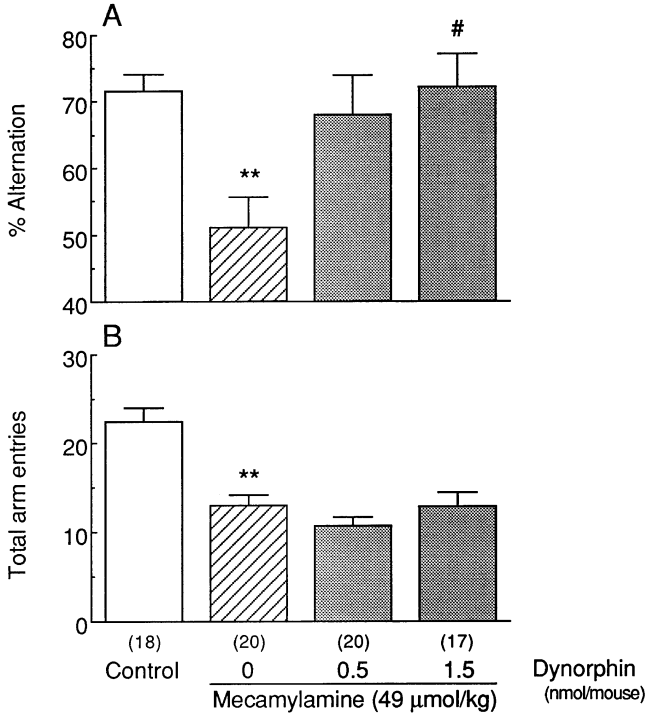

FIG. 5. Effects of dynorphin A (1-13) on mecamylamine-induced impairment of spontaneous alternation (A) and decreases in total arm entries (B) in the *Y*-maze. Mice were treated intraperitoneally with mecamylamine (49 μmol/kg) 30 min before the test session. Mice were treated intracerebroventricularly with dynorphin A (1-13) (dynorphin; 0.5 and 1.5 nmol/mouse) 15 min before the test session. Figures in parentheses show the numbers of mice used. $^{**}p < 0.01$ vs. normal control (Mann-Whitney U-test), $\#p < 0.05$ vs. mecamylamine alone (Bonferroni's test).

The increase in dynorphin A (1-8)-like immunoreactivity in the aged hippocampus was associated with a decline in spatial learning memory (25). However, in this study, endogenous kappa opioid agonists may not have exerted tonic (inhibitory) control over the regulation of neurotransmission, because nBNI at the dosage used did not modify the percent alternation in normal mice. There is evidence that high concentrations of dynorphin decrease [^{14}C]-acetylcholine release (34) and that activation of kappa opioid receptors by dynorphin has no effect on K^+- or glutamate-evoked acetylcholine release in rat striatal slices (1). However, we found using a microdialysis technique that a low dose of dynorphin which has no effect on acetylcholine release in normal rats prevents galanin-induced decreases in acetylcholine release (15). These results, together with the present findings, suggest that dynorphin can compensate for dysfunction in the hippocampal formation, and that the kappa opioidergic system in the brain plays an important role in modulating learning and memory when the cholinergic system is impaired.

Mecamylamine, a nicotinic receptor blocker, induced impairment of spontaneous alternation performance (28). Since low doses of nicotine improve CO-induced amnesia, nicotinic cholinergic dysfunction also appears to be involved in CO-induced amnesia (17). It is of interest that dynorphin also antagonized mecamylamine-induced amnesia. It has been reported that mecamylamine acts, in part, as an NMDA receptor antagonist (38). Administration of NMDA antagonists such as MK-801 and AP-5 impairs spontaneous alternation behavior and spatial memory in the Morris water maze (28,33). In the present study, however, dynorphin did not reverse MK-801-induced amnesia. Therefore, NMDA-receptor mediated mechanisms may not be involved in the ameliorative effects of dynorphin after CO exposure.

The dose-response curve for the effect of dynorphin was bell-shaped. Since dynorphin does not act exclusively on cholinergic synapses, possible effects on other neurotransmitter systems cannot be excluded (23). In fact, the impairment of spontaneous alternation performance induced by scopolamine is reversed by the blockade of dopamine D2 receptors, indicating that the effect of dynorphin on the scopolamine-induced impairment of spontaneous alternation performance involves the inhibition of dopaminergic activity mediated by kappa opioid receptors (23). Dynorphin inhibits dopamine agonist-induced hyperactivity, diminishes striatal and mesolimbic dopamine release, and reduces the release of [^{3}H]-dopamine from cultured neurons (41). Moreover, central catecholamines appear to be involved in the acquisition and maintenance of learning associated with aversion (18,39). However, the dosages used in the present experiment caused no significant changes in locomotor activity indicating that they were below those required for alteration of dopaminergic neurotransmission. In agreement with this hypothesis, we previously reported that dynorphin A (1-13) at doses higher than 2.5 nmol inhibited dopamine release as measured by microdialysis (32). However, further analysis is required to characterize these neurotransmitter interactions.

In conclusion, although the precise nature of the interaction between the kappa opioidergic and the cholinergic systems in the central nervous system is unknown, dynorphin may activate only the impaired cholinergic system. Thus, dynorphins may be effective for various forms of cognitive disturbances related to the dysfunction of the cholinergic neuronal system, and may have beneficial effects on learning and memory.

ACKNOWLEDGEMENT

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