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Stimulation of δ_1- and δ_2-opioid receptors produces amnesia in mice

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Abstract

The effects of intracerebroventricular administration of δ_1- and δ_2-selective opioid receptor agonists on spontaneous alternation performance, elevated plus-maze behavior and passive avoidance learning including step-down and step-through types were examined in mice. Although the δ_1-selective opioid receptor agonist, [D-Pen^2,L-Pen^5]enkephalin (DPLPE) (1–10 μg) or the δ_2-selective opioid receptor agonist, [D-Ala^2]deltorphin II (deltorphin) (1–10 μg) did not markedly affect spontaneous alternation performance or elevated plus-maze behavior, DPLPE (1, 3 and/or 10 μg) and deltorphin (3 and 10 μg) inhibited passive avoidance learning including step-down and step-through types. The δ_1-selective opioid receptor antagonist, 7-benzylidenenaltrexone (3.5 ng), and the δ_2-selective opioid receptor antagonist, naltriben (19 ng), significantly antagonized the inhibitory effects of DPLPE (3 μg) and deltorphin (3 μg) on passive avoidance learning, respectively. In contrast, DPLPE (3 μg) or deltorphin (3 μg) did not markedly influence behavioral responses induced by electroshocks during training of passive avoidance learning. Moreover, DPLPE (0.3–3 μg) or deltorphin (0.3–3 μg) failed to significantly affect the radiant heat-induced nociceptive responses. These results suggest that stimulation of δ_1- and δ_2-opioid receptors produces amnesia, depending on the learning tasks used. © 1997 Elsevier Science B.V.

Keywords: [D-Pen^2,L-Pen^5]enkephalin; [D-Ala^2]deltorphin II; Spontaneous alternation performance; Elevated plus-maze behavior; Passive avoidance learning; δ-Opioid receptor; (Mouse)

1. Introduction

Opioid receptors are classified into at least 3 types (μ, δ and κ) (Wüster et al., 1981; Paterson et al., 1983; Martin, 1984) which play an important role in a variety of physiological functions (Pasternak, 1993; Dhawan et al., 1996). The μ, δ and κ-opioid receptors are involved in memory in experimental animals (De Wied et al., 1978; Izquierdo, 1980; Martinez and Rigter, 1980). In particular, selective changes in μ, δ- and κ-opioid receptor binding have been reported in certain limbic regions of the brain in Alzheimer's disease patients with memory dysfunction (Hiller et al., 1987). μ-Opioid receptor agonists such as [D-Ala^2, *N*MePhe^4,Gly-ol]enkephalin and Tyr-D-Arg–Phe-β-Ala–NH_2 attenuate passive avoidance learning and spontaneous alternation performance (Itoh et al., 1994; Ukai et al., 1995c). Although κ-opioid receptor agonists such as dynorphin A-(1–13) and U-50,488H alone fail to influence learning behavior in normal animals, such drugs ameliorate the scopolamine- or pirenzepine-induced disturbance of spontaneous alternation performance and passive avoidance learning (Ukai et al., 1995a,b).

δ-Opioid receptors are further classified into two subtypes such as δ_1 and δ_2 in the brain (Fang et al., 1994; Fowler and Fraser, 1994) on the basis of differential blockade of the action of δ-opioid receptor agonists by different δ-opioid receptor antagonists (Sofuoglu et al., 1991; Jiang et al., 1991). Although [D-Ala^2,D-Leu^5]enkephalin, a δ-opioid receptor agonist, has been demonstrated to produce amnesia (Schulteis et al., 1988), the contribution of δ_1- and δ_2-opioid receptors to memory processes still remains inconclusive.

In an attempt to determine the involvement of δ_1- and δ_2-opioid receptors in learning and memory, we examined the effects of the δ_1-selective opioid receptor agonist [D-Pen^2,L-Pen^5]enkephalin (DPLPE) (Mosberg et al., 1983) and the δ_2-selective opioid receptor agonist [D-Ala^2]deltorphin II (deltorphin) (Erspamer et al., 1989) on spontaneous alternation performance (Sarter et al., 1988; Itoh et al., 1993), elevated plus-maze behavior (Itoh et al., 1990)

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and passive avoidance learning (step-down and step-through type). In addition, the effects of DPLPE and deltorphin were characterized by using the δ_1-selective opioid receptor antagonist, 7-benzylidenenaltrexone (Portoghese et al., 1992; Takemori and Portoghese, 1993) and the δ_2-selective opioid receptor antagonist, naltriben (Sofuoglu et al., 1991; Rady et al., 1994).

2. Materials and methods

2.1. Animals

Male mice of the ddY strain (Nihon SLC, Hamamatsu), weighing between 20 and 30 g, were used. They were housed in groups of eight under standard conditions (22 ± 2°C, 50 ± 10% humidity, light–dark cycle with the light on between 8.00 and 20.00 h), with free access to food and water. Mice were used for the experiments after they had adapted to laboratory conditions for at least 5 days and were naive to each of the tests used in the present study. The experiments were conducted in a sound-attenuated room.

2.2. Spontaneous alternation performance

2.2.1. Apparatus

A black Y-maze made of plywood was used. Each arm was 40 cm long, 12 cm high, 3 cm wide at the bottom and 10 cm wide at the top and positioned at an equal angle.

2.2.2. Procedure

The testing procedure was based upon that of Sarter et al. (1988). Each mouse was placed at the end of one arm and was allowed to move freely through the maze for an 8 min test session. The sequence of arm entries was recorded manually. An alternation was defined as an entry into all three arms on consecutive occasions. The number of maximum alternations was therefore the total number of arms entered minus 2, and the percent alternation was calculated as (actual alternations/maximum alternations) $\times$ 100.

2.3. Elevated plus-maze behavior

2.3.1. Apparatus

The plus-maze was made of plywood and consisted of two open arms (25×8 cm) and two enclosed arms ($25 \times 8 \times 20$ cm). The arm extended from a central platform (8×8 cm). The plus-maze was 50 cm above the floor. The open arms and the central platform were painted white and the enclosed arms were painted black. A white fine line was drawn in the middle of the floor of each enclosed arm.

2.3.2. Procedure

The procedure of the plus-maze test was identical to that of Itoh et al. (1990). In the 1st trial (training) a mouse was placed at the end of one of the open arms facing away from the central platform, and the time it took for the mouse to move from the open arm to either of the enclosed arms (transfer latency) was recorded. If the mouse did not enter the enclosed arm within 90 s, it was pushed gently on the back into the enclosed arm and a transfer latency of 90 s was recorded. Then the mouse was gently taken out of plus-maze 10 s after it had entered the enclosed arm and returned to its home cage. Twenty-four h later, the 2nd trial (retention test) was performed. The mouse was again put into the plus-maze and the transfer latency was again recorded up to a maximum of 90 s.

2.4. Step-down type passive avoidance

2.4.1. Apparatus

The passive avoidance apparatus consisted of a Plexiglas inner box ($30 \times 30 \times 40$ cm high) with a grid floor and a sound-attenuated wooden outer box ($30 \times 30 \times 90$ cm) with a 15 W light. The grid floor consisted of 30 parallel steel rods (0.3 cm in diameter) set 1 cm apart. A wooden platform ($4 \times 4 \times 4$ cm) was placed in the center of the grid floor (Kameyama et al., 1986).

2.4.2. Procedure

In the training period, each mouse was placed gently onto a wooden platform, when the mouse stepped down from the platform and placed all its paws on a grid floor, an intermittent electroshock (60 V, dc, 0.5 s, 1 Hz) was delivered for 15 s. The retention test was done 24 h after training. Each mouse was again placed onto the platform and the step-down latency was measured. An upper cut off time was set at 300 s.

2.4.3. Behavioral responses to electroshocks

The behavioral responses to electroshocks are scored during training of the step-down type of passive avoidance learning according to four degrees, i.e.: 0, no responses; 1, tremor; 2, vocalization; 3, vocalization and jumping.

2.5. Step-through type passive avoidance

2.5.1. Apparatus

The step-through passive avoidance apparatus consisted of an illuminated compartment ($10 \times 15.5 \times 10$ cm), a darkened compartment ($10 \times 15.5 \times 10$ cm), a guillotine door between the compartments and, in the darkened compartment, a grid floor that could be electrified. A 100 W lamp was positioned 40 cm above the floor of the illuminated compartment.

2.5.2. Procedure

The guillotine door was opened and a mouse was placed in the illuminated compartment. The mouse was adapted through the illuminated and darkened compartment for 3 min, and then was returned to its home cage.

After 10 min, the mouse was placed in the illuminated compartment and when it entered the darkened compartment with all four paws (i.e., step-through latency was recorded), the door was closed and scrambled footshock (0.25 mA for 3 s) was delivered via the grid floor. The mouse was then returned to its home cage. Twenty-four h later, the retention test was done by placing the mouse in the illuminated compartment and the step-through latency was recorded up to a maximum of 300 s.

2.6. Effects on nociceptive responses

The latency to tail withdrawal was taken as a measure of the nociceptive response to exposure to radiant heat. The intensity of the thermal stimulus was adjusted to obtain a pre-drug latency ranging from 2 to 5 s. Two pre-drug latencies were measured at 10 min and immediately before injection, and averaged to obtain baseline values. Animals not flicking their tails within 5 s were discarded. To avoid tissue damage, animals not reaching the cut-off time (12 s) of latency were removed from excessive exposure with radiant heat and were assigned a tail-flick latency of 12 s.

2.7. Drugs

DPLPE (American Peptide, Sunnyvale, CA, USA), deltorphin (synthesized by Prof. Y. Sasaki), 7-benzylidenenaltrexone and naltriben (Tocris Cookson, Bristol, UK) were dissolved in sterile isotonic saline solution (Otsuka Pharmaceutical, Tokyo, Japan) and administered into the lateral ventricle (i.c.v.) of the brain according to the method of Haley and McCormick (1957). The injection volume was 5 μl/mouse. The mice were lightly anesthetized with ether before each of the i.c.v. injections. δ-Opioid receptor agonists and antagonists were administered 10 and 20 min before training, respectively.

2.8. Statistical analysis

The step-down and step-through latency was expressed as the median and interquartile ranges, while the latency of nociceptive responses and the score of behavioral responses induced by electroshocks were expressed as the mean ± S.E. All the data were analyzed by a Kruskal–Wallis analysis of variance by ranks. If there were significant H values, post-hoc comparisons were made using a Bonferroni's multiple comparison test (two-tailed). The criterion for statistical significance was $P < 0.05$ in all evaluations.

3. Results

3.1. Effects on spontaneous alternation performance

DPLPE (1–10 μg) ($H = 6.06$, $P > 0.05$) or deltorphin (1–10 μg) ($H = 1.28$, $P > 0.05$) did not affect percent alternation, while a 10 μg dose of deltorphin ($H = 12.37$,

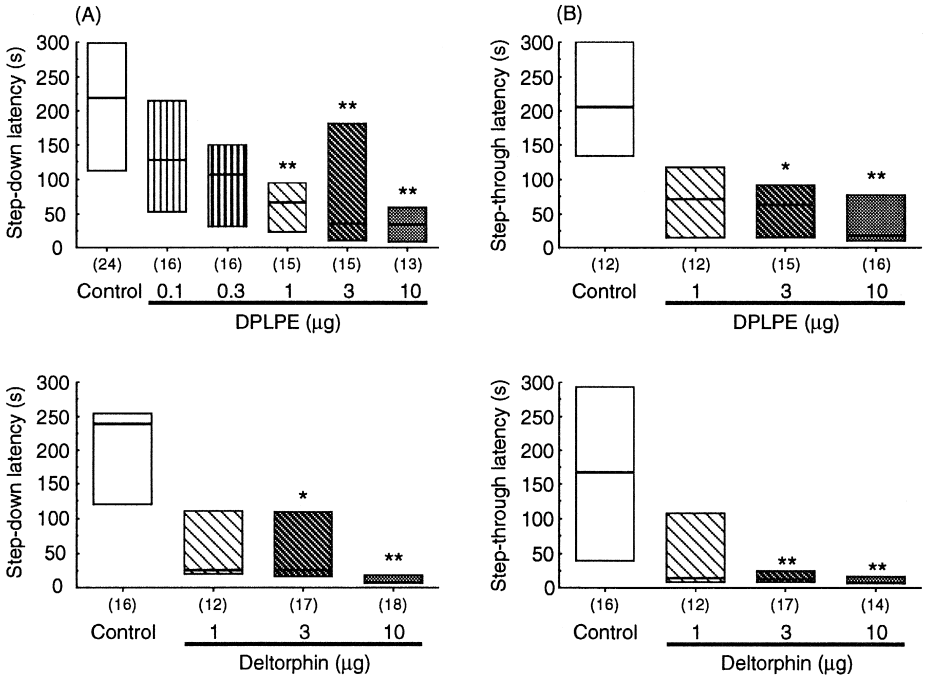

Fig. 1. Effects of [D-Pen^2,L-Pen^5]enkephalin (DPLPE) and [D-Ala^2]deltorphin II (deltorphin) on step-down (A) and step-through latency (B) of passive avoidance learning in mice. δ-Opioid receptor agonists were intracerebroventricularly administered 10 min before training. Each value represents the median and interquartile ranges. The number of mice used is shown in parentheses. $^{*}P < 0.05$; $^{**}P < 0.01$ vs. control.

$P < 0.05$) significantly increased the total arm entries (data not shown).

3.2. Effects on elevated plus-maze behavior

The transfer latency of controls was significantly shorter in retention tests than that in training. DPLPE (1–10 μg) ($H = 8.04$, $P < 0.05$) or deltorphin (1–10 μg) ($H = 2.52$, $P > 0.05$) did not significantly affect transfer latency in retention tests (data not shown).

3.3. Effects on passive avoidance learning

DPLPE (1–10 μg) and deltorphin (3 and 10 μg) significantly decreased step-down ($H = 28.40$, $P < 0.01$ for DPLPE; $H = 23.96$, $P < 0.01$ for deltorphin) and step-through latency ($H = 13.12$, $P < 0.01$ for DPLPE; $H = 19.91$, $P < 0.01$ for deltorphin) in retention tests (Fig. 1). 7-Benzylidenenaltrexone (3.5 ng) and naltriben (19 ng) significantly reversed the DPLPE (3 μg)- and deltorphin (3 μg)-induced reduction of step-down ($H = 25.40$, $P < 0.01$ for DPLPE; $H = 21.65$, $P < 0.01$ for deltorphin) and step-through latency ($H = 36.07$, $P < 0.01$ for DPLPE; $H = 36.48$, $P < 0.01$ for deltorphin) (Fig. 2).

Table 1
Effects of [D-Pen^2,L-Pen^5]enkephalin (DPLPE) and [D-Ala^2]deltorphin II (deltorphin) on nociception as assessed by tail-flick response in mice

Drugs	Dose (μg)	Tail-flick latency (s)	
		pre-drug	10 min after injection
Control		4.9 ± 0.2	5.0 ± 0.3
DPLPE	0.3	5.0 ± 0.2	5.8 ± 0.4
	1	4.8 ± 0.1	5.3 ± 0.1
	3	4.7 ± 0.1	5.6 ± 0.4
Deltorphin	0.3	4.9 ± 0.1	5.1 ± 0.2
	1	4.8 ± 0.1	5.2 ± 0.3
	3	4.8 ± 0.2	6.2 ± 0.4

DPLPE and deltorphin were given intracerebroventricularly 10 min before measurements. Each value represents the mean ± S.E. for 10 mice.

3.4. Behavioral responses to electroshocks during training

Even higher doses of DPLPE (10 μg) or deltorphin (10 μg) did not markedly affect behavioral responses to electroshocks during training of the step-down type of passive avoidance learning ($H = 4.03$, $P > 0.05$). The scores (mean ± S.E.) of each of the groups were as follows: saline (0.9%)-treated group: 2.7 ± 0.1 ($n = 31$), DPLPE

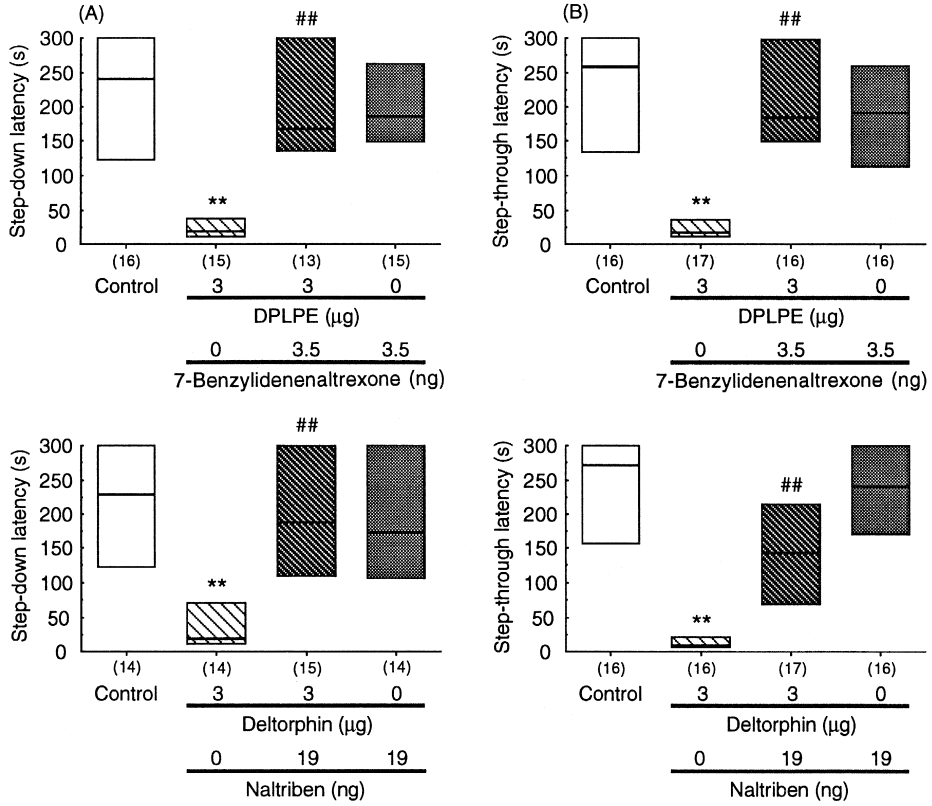

Fig. 2. Effects of [D-Pen^2,L-Pen^5]enkephalin (DPLPE) and [D-Ala^2]deltorphin II (deltorphin) and their combinations with 7-benzylidenenaltrexone and naltriben on step-down (A) and step-through latency (B) of passive avoidance learning in mice. δ-Opioid receptor agonists and antagonists were intracerebroventricularly administered 10 and 20 min before training, respectively. Each value represents the median and interquartile ranges. The number of mice used is shown in parentheses. $^{**}P < 0.01$ vs. control, $^{\#\#}P < 0.01$ vs. each of the agonists alone.

(10 μg)-treated group: 2.6 ± 0.1 ($n = 14$), and deltorphin (10 μg)-treated group: 2.2 ± 0.2 ($n = 13$).

3.5. Effects on nociceptive responses

Either DPLPE (0.3–3 μg) or deltorphin (0.3–3 μg) did not significantly affect the tail-flick latency ($H = 9.30$, $P > 0.05$) (Table 1).

4. Discussion

μ-Opioid receptor agonists such as morphine, [D-Ala^2, *N*MePhe^4,Gly-ol]enkephalin and Tyr-D-Arg–Phe-β-Ala–NH_2 inhibit spontaneous alternation performance associated with spatial working memory and passive avoidance learning (Walker et al., 1991; Itoh et al., 1994; Ukai et al., 1995c). Moreover, the κ-opioid receptor agonist dynorphin A-(1–13) does not influence memory processes in normal animals, whereas it improves the scopolamine- and pirenzepine-induced impairment of spontaneous alternation performance in mice (Itoh et al., 1994; Ukai et al., 1995b) and attenuates the basal forebrain-lesion-induced disturbance of passive avoidance learning in rats (Ukai et al., 1993). It thus appears that stimulation of κ-opioid receptors ameliorates the memory disturbance due to cholinergic dysfunction, while stimulation of μ-opioid receptors results in the disturbance of learning and memory.

Similar to the effects of μ-opioid receptor agonists, the δ_1-selective opioid receptor agonist, DPLPE, and the δ_2-selective opioid receptor agonist, deltorphin, administered before training decreased step-down and step-through latency in retention tests. Furthermore, the δ_1-selective opioid receptor antagonist 7-benzylidenenaltrexone (Takemori and Portoghese, 1993) and the δ_2-selective opioid receptor antagonist naltriben (Rady et al., 1994) reversed the DPLPE- and deltorphin-induced disturbance of passive avoidance learning, respectively, suggesting that activation of δ-opioid receptors including δ_1 and δ_2 sites leads to amnesia. However, it is possible that the reduction of step-down and step-through latency is associated with antinociceptive effects of DPLPE and deltorphin (Hammond et al., 1995; Bhargava et al., 1996). In fact, neither DPLPE nor deltorphin produced any marked antinociceptive effects as indexed by tail-flick response. Therefore, the DPLPE- and deltorphin-induced disturbance of passive avoidance learning would not result from antinociceptive effects of such neuropeptides. The amnesic dose of DPLPE or deltorphin did not significantly affect behavioral responses induced by electroshocks during training, further suggesting that the shortening of step-down and step-through latency is not parallel with the reduction of sensitivity to electroshocks during training. Moreover, δ-opioid receptor agonists have been reported to decrease acetylcholine release in the brain (Mulder et al., 1984; Tjon et al., 1995). It is possible that δ-opioid receptor agonists produce cholinergic dysfunction in the brain, resulting in memory disturbance, because cholinergic neurotransmission is considered to play an important role in cognitive function (Stahl, 1996).

In contrast, DPLPE and deltorphin did not affect spontaneous alternation performance. Spontaneous alternation performance has been used for assessing cognitive function with special reference to spatial working memory (Beninger et al., 1986; Parada-Turska and Turski, 1990; Walker et al., 1991). It thus appears that δ-opioid receptors do not contribute to spatial working memory.

The transfer latency of the controls in retention tests of elevated plus-maze behavior was shorter than that for training, indicating the acquisition of memory. DPLPE or deltorphin did not influence the transfer latency of elevated plus-maze behavior, while the injection schedule in elevated plus-maze behavior was identical to that in passive avoidance learning. It has been reported that a 1 mg/kg dose of scopolamine inhibits passive avoidance learning but not elevated plus-maze behavior. A 3 mg/kg rather than a 1 mg/kg dose of scopolamine should be necessary to interfere with the latter (Itoh et al., 1990). Moreover, glutamatergic neurotransmission has been demonstrated to play a major role in the plus-maze behavior (Itoh et al., 1990). Thus, the elevated plus-maze behavior might be elicited via neuronal mechanisms different from those of passive avoidance learning in which δ-opioid receptors are closely involved.

In conclusion, stimulation of δ-opioid receptors including δ_1 and δ_2 sites disrupts learning, while it is possible that the amnesic effects of δ_1- and δ_2-opioid receptor agonists depend on learning tasks used.

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References

Beninger, R.J., Jhamandas, K., Boegman, R.J., El-Defrawy, S.R., 1986. Effects of scopolamine and unilateral lesions of the basal forebrain on T-maze spatial discrimination and alternation in rats. Pharmacol. Biochem. Behav. 24, 1353–1360.

Bhargava, H.N., Zhao, G.-M., House, R.V., Thomas, P.T., 1996. Effects of chronic administration of 7-benzylidene-7-dehydronaltrexone and naltriben on the antinociceptive actions of δ_1- and δ_2-opioid receptor agonists. Eur. J. Pharmacol. 311, 127–132.

De Wied, D., Bohus, B., van Ree, J.M., Urban, I., 1978. Behavioral and electrophysiological effects of peptides related to lipotropin (β-LPH). J. Pharmacol. Exp. Ther. 204, 570–580.

Dhawan, B.N., Cesselin, F., Raghubir, R., Reisine, T., Bradley, P.B., Portoghese, P.S., Hamon, M., 1996. International union of pharmacol-

ogy. XII. Classification of opioid receptors. Pharmacol. Rev. 48, 567–592.

Erspamer, V., Melchiorri, P., Falconieri-Erspamer, G., Negri, L., Corsi, R., Sverini, C., Barra, D., Shimmaco, M., Kreil, G., 1989. Deltorphins: A family of naturally occurring peptides with high affinity and selectivity for δ opioid binding sites. Proc. Natl. Acad. Sci. USA 86, 5188–5192.

Fang, L., Knapp, R.J., Horvath, R., Matsunaga, T.O., Haaseth, R.C., Hruby, V.J., Porreca, F., Yamamura, H.I., 1994. Characterization of [^{3}H]naltrindole binding to delta opioid receptors in mouse brain and mouse vas deferens: Evidence for delta opioid receptor heterogeneity. J. Pharmacol. Exp. Ther. 268, 836–846.

Fowler, C.J., Fraser, G.L., 1994. μ-, δ-, κ-Opioid receptors and their subtypes: A critical review with emphasis on radioligand binding experiments. Neurochem. Int. 24, 401–426.

Haley, T.J., McCormick, W.G., 1957. Pharmacological effects produced by intracerebral injection of drugs in the conscious mouse. Br. J. Pharmacol. 12, 12–15.

Hammond, D.H., Stewart, P.E., Littell, L., 1995. Antinociception and δ-1 opioid receptors in the rat spinal cord: Studies with intrathecal 7-benzylidenenaltrexone. J. Pharmacol. Exp. Ther. 274, 1317–1324.

Hiller, J.M., Itzhak, Y., Simon, E.J., 1987. Selective changes in mu, delta, and kappa opioid receptor binding in certain limbic regions of the brain in Alzheimer's disease patients. Brain Res. 106, 17–23.

Itoh, J., Nabeshima, T., Kameyama, T., 1990. Utility of an elevated plus-maze for the evaluation of memory in mice: Effects of nootropics, scopolamine and electroconvulsive shock. Psychopharmacology 101, 27–33.

Itoh, J., Ukai, M., Kameyama, T., 1993. Dynorphin A-(1-13) markedly improves scopolamine-induced impairment of spontaneous alternation performance in mice. Eur. J. Pharmacol. 236, 341–345.

Itoh, J., Ukai, M., Kameyama, T., 1994. Dynorphin A-(1-13) potently improves the impairment of spontaneous alternation performance induced by the μ-selective opioid receptor agonist DAMGO in mice. J. Pharmacol. Exp. Ther. 269, 15–21.

Izquierdo, I., 1980. Effect of β-endorphin and naloxone on acquisition, memory, and retrieval of shuttle avoidance and habituation learning in rats. Psychopharmacology 69, 111–115.

Jiang, Q., Takemori, A.E., Sultana, M., Portoghese, P.S., Bowen, W.D., Mosberg, H.I., Porreca, F., 1991. Differential antagonism of opioid delta-antinociception by [D-Ala^2,Leu^5,Cys^6]enkephalin and naltrindole 5′-isothiocyanate: Evidence for delta-receptor subtypes. J. Pharmacol. Exp. Ther. 257, 1069–1075.

Kameyama, T., Nabeshima, T., Kozawa, T., 1986. Step-down-type passive avoidance- and escape-learning method suitability for experimental amnesia models. J. Pharmacol. Methods 16, 39–52.

Martin, W.R., 1984. Pharmacology of opioids. Pharmacol. Rev. 35, 283–323.

Martinez, J.L. Jr., Rigter, H., 1980. Endorphins after acquisition and consolidation of an inhibitory avoidance response in rats. Neurosci. Lett. 19, 197–201.

Mosberg, H.I., Hurst, R., Hurby, V.J., Gee, K., Yamamura, H.I., Galligan, J.J., Burks, T.F., 1983. Bis-penicillamine enkephalins possess highly improved specificity towards delta opioid receptors. Proc. Natl. Acad. Sci. USA 80, 5871–5874.

Mulder, A.H., Wardeh, G., Hogenboom, F., Frankhuyzen, A.L., 1984. κ- and δ-opioid receptor agonists differentially inhibit striatal dopamine and acetylcholine release. Nature 308, 278–280.

Parada-Turska, J., Turski, W.A., 1990. Excitatory amino acid antagonists and memory: Effect of drugs acting at *N*-methyl-D-aspartate receptors in learning and memory tasks. Neuropharmacology 29, 1111–1116.

Pasternak, G.W., 1993. Pharmacological mechanisms of opioid analgesics. Clin. Neuropharmacol. 16, 1–18.

Paterson, S.J., Robson, L.E., Kosterlitz, H.W., 1983. Classification of opioid receptors. Br. Med. Bull. 39, 25–30.

Portoghese, P.S., Sultana, M., Nagase, H., Takemori, A.E., 1992. A highly selective δ_1-opioid receptor antagonist: 7-Benzylidenenaltrexone. Eur. J. Pharmacol. 218, 195–196.

Rady, J.J., Takemori, A.E., Portoghese, P.S., Fujimoto, J.M., 1994. Supraspinal delta receptor subtype activity of heroin and 6-monoacetylmorphine in Swiss Webster mice. Life Sci. 55, 603–609.

Sarter, M., Bodewitz, G., Stephens, D.N., 1988. Attenuation of scopolamine-induced impairment of spontaneous alternation behavior by antagonist but not inverse agonist and agonist β-carbolines. Psychopharmacology 94, 491–495.

Schulteis, G., Martinez, J.L. Jr., Hruby, V.J., 1988. Stimulation and antagonism of opioid δ-receptors produce opposite effects on active avoidance conditioning in mice. Behav. Neurosci. 102, 678–686.

Sofuoglu, M., Portoghese, P.S., Takemori, A.E., 1991. Differential antagonism of delta opioid agonists by naltrindole and its benzofuran analog (NTB) in mice: Evidence for delta opioid receptor subtypes. J. Pharmacol. Exp. Ther. 257, 676–680.

Stahl, S.M., 1996. Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge University Press, Cambridge.

Takemori, A.E., Portoghese, P.S., 1993. The mixed antinociceptive agonist-antagonist activity of β-endorphin (1–27) in mice. Life Sci. 53, 1049–1052.

Tjon, G.H.K., De Vries, T.J., Nestby, P., Wardeh, G., Mulder, A.H., Schoffelmeer, A.N.M., 1995. Intermittent and chronic treatment induces long-lasting changes in δ-opioid receptor-regulated acetylcholine release in rat striatum and nucleus accumbens. Eur. J. Pharmacol. 283, 169–176.

Ukai, M., Kobayashi, T., Kameyama, T., 1993. Dynorphin A-(1–13) attenuates basal forebrain-lesion-induced amnesia in rats. Brain Res. 625, 355–356.

Ukai, M., Kobayashi, T., Shinkai, N., Shan-Wu, X., Kameyama, T., 1995a. Dynorphin A-(1–13) potently improves scopolamine-induced impairment of passive avoidance response in mice. Eur. J. Pharmacol. 274, 89–93.

Ukai, M., Shinkai, N., Kameyama, T., 1995b. κ-Opioid receptor agonists improve pirenzepine-induced disturbance of spontaneous alternation performance in the mouse. Eur. J. Pharmacol. 281, 173–178.

Ukai, M., Kobayashi, T., Mori, K., Shinkai, N., Sasaki, Y., Kameyama, T., 1995c. Attenuation of memory with Tyr-D-Arg–Phe-β-Ala–NH_2, a novel dermorphin analog, with high affinity for μ-opioid receptors. Eur. J. Pharmacol. 287, 245–249.

Walker, D.L., McGlynn, T., Grey, C., Ragozzino, M., Gold, P.E., 1991. Naloxone modulates the behavioral effects of cholinergic agonists and antagonists. Psychopharmacology 105, 57–62.

Wüster, M., Schulz, R., Herz, A., 1981. Multiple opiate receptors in peripheral tissue preparations. Biochem. Pharmacol. 30, 1883–1887.