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The role of δ-opioid receptors in the discriminative stimulus properties of a low dose of methamphetamine

Tsutomu Suzuki [a,*], Tomohisa Mori [a], Minoru Tsuji [a], Miwa Misawa [a], Hiroshi Nagase [b]

[a] *Department of Pharmacology, School of Pharmacy, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142, Japan*
[b] *Basic Research Laboratories, Toray Industries, Inc., Kamakura 248, Japan*

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Abstract

The effects of selective μ-, δ- and κ-opioid receptor agonists and antagonists on the discriminative stimulus properties of methamphetamine were examined in rats that had been trained to discriminate between methamphetamine (0.4 mg/kg) and saline. Methamphetamine produced a dose-related increase in methamphetamine-appropriate responses in all of the rats. In generalization tests, neither morphine (a μ-opioid receptor agonist: 0.3–10 mg/kg) nor 3,4-dichloro-*N*-[2-(1-pyrrolidinyl)cyclohexo]benzeneacetamide (U50,488H: a κ-opioid receptor agonist: 1.0–8.0 mg/kg) generalized to the discriminative stimulus properties of methamphetamine. A newly synthesized non-peptide selective δ-opioid receptor agonist 2-methyl-4aα-(3-hydroxyphenyl)-1,2,3,4,4a,5,12,12aα-octahydroquinolino(2,3,3,-g)isoquinoline (TAN-67: 32 mg/kg) partially generalized (70% methamphetamine-appropriate responses) to the discriminative stimulus properties of methamphetamine. In combination tests, pretreatment with the μ- and κ-opioid receptor antagonists, β-funaltrexamine (9.0 mg/kg) and nor-binaltorphimine (10 mg/kg), respectively, had little or no influence on the discriminative stimulus properties of methamphetamine. In contrast, pretreatment with naltrindole (a non-selective δ-opioid receptor antagonist: 3.0 mg/kg) or naltriben (a selective δ_2-opioid receptor antagonist: 1.0 mg/kg), but not with 7-benzylidenenaltrexone (a selective δ_1-opioid receptor antagonist: 0.5 and 1.0 mg/kg), significantly attenuated the discriminative stimulus properties of methamphetamine. However, naltrindole (3.0 mg/kg) did not significantly attenuate the discriminative stimulus properties of methamphetamine at a higher training dose (1.0 mg/kg). Our findings may have some bearing on the relative importance of the role of δ-opioid (especially δ_2-opioid) receptors in the discriminative stimulus properties of a low dose of methamphetamine. © 1997 Elsevier Science B.V.

Keywords: Methamphetamine; δ-Opioid receptor; Drug discrimination; TAN-67

1. Introduction

The properties of drugs that mediate their discriminative stimulus properties are related to their subjective effects in humans (Schuster and Johanson, 1988). Therefore, the drug discrimination procedure has been used to classify psychostimulants, such as cocaine, amphetamine and methamphetamine, according to similarities in their discriminative stimulus properties and has provided relevant information about their neuropharmacological mechanisms (Johanson and Fischman, 1989). Furthermore, psychostimulants as well as opioids (μ- and δ-opioids) produce other behavioral effects (e.g., reinforcing effects, hyperlocomotion and stereotypes) in animals. Studies on these behavioral effects, including discriminative stimulus properties, provide useful information regarding the abuse liability of psychostimulants and opioids. It is well known that psychostimulants and opioids can modify the release of dopamine from the terminals of dopaminergic neurons (Di Chiara and Imperato, 1988; Spanagel et al., 1990), and that the dopaminergic (especially the mesolimbic) system plays a primary role in these behavioral effects (Cooper, 1991; Cunningham et al., 1992). The possible involvement of opioid receptors in some behavioral effects of psychostimulants has also been recently reported. For example, the non-selective opioid receptor antagonists naloxone and naltrexone attenuate the psychostimulant-induced threshold-lowering effects on brain stimulation (Bain and Kornetsky, 1987), self-administration (De Vry et al., 1989; Schaefer and Michael, 1990), place preference (Houdi et al., 1989; Suzuki et al., 1992) and hyperlocomotion (Houdi et al., 1989; Hooks et al., 1992). In addition, the amphetamine-induced release of dopamine from the terminals

* Corresponding author. Tel.: (81-3) 5498-5787; Fax: (81-3) 3787-0036; e-mail: suzuki@hoshi.ac.jp

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of dopaminergic neurons is reduced by naloxone (Hooks et al., 1992). These results suggest that endogenous opioids may be involved in the mediation of the behavioral effects of psychostimulants through a dopaminergic system.

Pharmacological, behavioral and biochemical studies on opioids have revealed the existence of several opioid receptor types: μ-, δ- and κ-opioid receptors (Martin et al., 1976; Lord et al., 1977; Chavkin and Goldstein, 1981). Chronic treatment with cocaine alters μ- and κ-opioid receptor binding (Unterwald et al., 1992, 1994). The discriminative stimulus properties and reinforcing effects of cocaine are potentiated and attenuated by μ- and κ-opioid receptor agonists, respectively, in rats and monkeys (Suzuki et al., 1992, 1995; Spealman and Bergman, 1992). δ-Opioid receptor antagonists can attenuate the discriminative stimulus properties of cocaine (Suzuki et al., 1994a), the place preferences associated with cocaine and methamphetamine (Menkens et al., 1992; Suzuki et al., 1994b) and the hyperlocomotion produced by amphetamine (Jones et al., 1993). However, the role of opioid receptors in the behavioral effects of psychostimulants has not yet been fully clarified.

Highly selective opioid receptor agonists or antagonists are essential pharmacological tools for investigating pharmacological effects mediated by different types of opioid receptors. Recently, selective μ-, δ- and κ-opioid receptor antagonists have been synthesized and more recently, Nagase et al. (1994) synthesized a non-peptide selective δ-opioid receptor agonist, 2-methyl-4a α-(3-hydroxyphenyl)-1,2,3,4,4a,5,12,12a α-octahydro-quinolino(2,3,3,-g)isoquinoline (TAN-67), which could be administered peripherally, like the prototypical μ-opioid receptor agonist morphine and the κ-opioid receptor agonist U50,488H. The present study was designed to investigate the relative contribution of the opioid system to the discriminative stimulus properties of methamphetamine in rats. Therefore, selective μ-, δ- and κ-opioid receptor agonists and antagonists were tested for their ability to generalize or to attenuate the discriminative stimulus properties of methamphetamine, respectively.

2. Materials and methods

2.1. Animals

Male Fischer 344 rats (Charles River Japan, Atsugi, Japan) were maintained at 200–230 g (80% free-feeding weight). Water was available ad libitum for all of the rats in their home cages. The rats were housed in individual cages at a room temperature of 22 ± 1°C with a 12 h light–dark cycle (light on 8.00 a.m. to 8.00 p.m.).

2.2. Apparatus

Experiments were conducted in operant chambers (Model GT 8810; O'Hara, Tokyo, Japan) equipped with 2 levers, with a food-cup mounted midway between the levers. White lamps were installed above each of the levers. Chambers were enclosed within sound- and light-attenuating boxes and supplied with white noise to mask extraneous sound. A 20 mg food pellet (O'Hara) was delivered when the animal pressed the correct lever.

2.3. Discrimination training

Discrimination training was performed according to the method of Suzuki et al. (1994a). Briefly, after the response rates had stabilized under a fixed ratio (FR) of 10, so that the rat received 40 reinforcements during 4 consecutive sessions, the rats were divided into two experimental groups. One group of rats ($n = 8$) was trained to discriminate between a low dose of methamphetamine (0.4 mg/kg) and saline. The other group of rats ($n = 5$) was trained to discriminate between a high dose of methamphetamine (1.0 mg/kg) and saline. Methamphetamine or saline was administered i.p. 15 min before each session in a daily sequence of SDDSSDDSSD (D = drug, S = saline). Training sessions were 15 min in duration and this phase of training was continued until all of the rats performed up to the required criterion (accuracies of at least 83% (first food pellet ≤ 12 responses) for 5 consecutive sessions). Discrimination training was continued even after the criterion was attained.

2.4. Testing procedure

After the animals attained the criterion, dose–response, generalization, combination and antagonism tests were initiated. Test sessions were performed after the discrimination criterion described above had been satisfied in at least 3 consecutive sessions. In the dose–response and generalization tests, rats were placed in the operant box until they had made 10 responses on either lever or until 5 min had elapsed after the drugs were administered. The combination test sessions consisted of 4 FR components to determine four-point cumulative dose–response curves for methamphetamine (0.05–0.4 mg/kg or 0.25–1.0 mg/kg). The cumulative dosing procedure has been described elsewhere (Suzuki et al., 1994a). Briefly, methamphetamine was administered 15 min before the first component. In each component, rats were placed in the operant box until they had made 10 responses on either lever or until 5 min (component time) had elapsed without a reinforcer. After the first component was finished (5 min had elapsed), drugs were administered again. This procedure was repeated three times. Thus, the entire procedure took 80 min ($(15 + 5$ min$) \times 4$). The pretreatment times and doses of drugs in the present study were 30 min for 0.3–10 mg/kg morphine and 1.0–8.0 mg/kg U50,488H; 1 h for 1.0–56 mg/kg TAN-67, 3.0 mg/kg naltrindole, 0.5 and 1.0 mg/kg naltriben and 1.0 and 3.0 mg/kg 7-benzylidenenaltrexone; 4 h for 10 mg/kg nor-binaltorphimine

and 24 h for 9.0 mg/kg β-funaltrexamine. If the rats did not make 10 responses during each component, the response was judged to have been disrupted.

2.5. Drugs

The drugs used in the present study were methamphetamine hydrochloride (Dainippon Pharmaceutical, Osaka, Japan), morphine hydrochloride (Sankyo, Tokyo, Japan), 3,4-dichloro-*N*-[2-(1-pyrrolidinyl)cyclohexo]benzeneacetamide (U50,488H) hydrochloride, 2-methyl-4a α-(3-hydroxyphenyl)-1,2,3,4,4a,5,12,12a α-octahydroquinoline methanesulfonate (TAN-67), naltrindole hydrochloride, naltriben methanesulfonate hydrate, 7-benzylidenenaltrexone tartrate, β-funaltrexamine hydrochloride (Research Biochemicals International, Natick, MA, USA) and nor-binaltorphimine hydrochloride. U50,488H, TAN-67, naltrindole, naltriben, 7-benzylidenenaltrexone and nor-binaltorphimine were synthesized by us. All of the drugs were dissolved in saline.

2.6. Data analysis

During the training sessions, accuracy was defined as the number of correct responses before the first food pellet. During the test session, performance was expressed as a percentage of the total responses before the first food pellet. During the test sessions, performance was defined as the number of drug-lever responses, expressed as a percentage of the total responses upon completion of FR 10. The drug was considered to have generalized to the discriminative stimulus properties of methamphetamine if more than 80% of the responses were on the drug lever. The response rate was calculated as the total number of responses before 10 responses on either lever divided by the time (minutes) taken to complete the first ratio. The results following pretreatment with saline and drugs were compared using a two-way (group × cumulative dose) repeated measures analysis of variance (ANOVA).

3. Results

Rats acquired the ability to discriminate between 0.4 mg/kg methamphetamine and saline in an average of approximately 26 sessions. Once rats attained the criterion, drug–saline discrimination stabilized and was maintained with a high degree of accuracy. During the dose–response tests, methamphetamine (0.05–0.4 mg/kg) produced a dose-related increase in methamphetamine-appropriate responses and a high dose of methamphetamine engendered methamphetamine-appropriate responses more than 80% of the time in all of the rats (Fig. 1).

In the generalization tests, 0.3–10 mg/kg morphine and 1.0–8.0 mg/kg U50,488H did not engender methamphetamine-appropriate responding, and the response rates

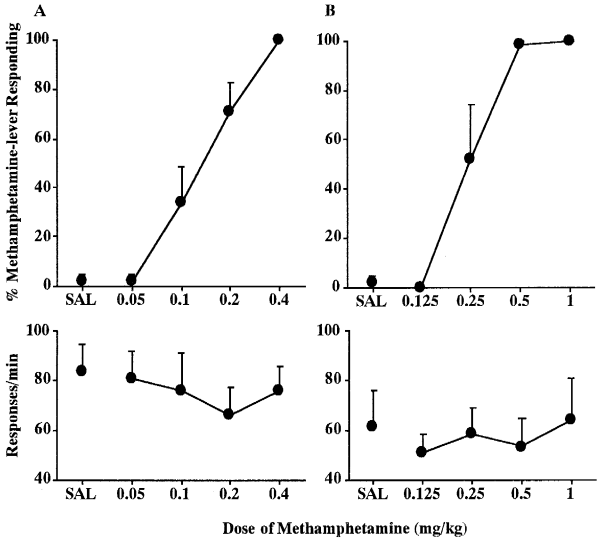

Fig. 1. Effect of methamphetamine on the discriminative stimulus properties of methamphetamine in rats that had been trained to discriminate between 0.4 mg/kg (A) or 1.0 mg/kg (B) methamphetamine and saline. Each point represents the mean percentage of methamphetamine-appropriate responding and the mean response rates with S.E.M. for 8 (A) or 5 (B) animals.

decreased as the dose of morphine and U50,488H increased (Fig. 2). The responses of seven of eight and two of six rats were disrupted at the highest doses of morphine and U50,488H, respectively. However, 3.0–56 mg/kg TAN-67 only partially (70.0% responses on the methamphetamine-lever at 30 mg/kg) generalized to the discriminative stimulus properties of methamphetamine (Fig. 2) and the response rates decreased as the dose increased. The responses of one of the eight rats were disrupted at the highest (56 mg/kg) dose of TAN-67. In addition, the partial generalization of 30 mg/kg TAN-67 was significantly reversed by δ-opioid receptor antagonists (3.0 mg/kg naltrindole, 0.5 mg/kg naltriben or 1.0 mg/kg 7-benzylidenenaltrexone), as measured by a paired Students' *t*-test (20 min pretreatment with TAN-67) (Fig. 3).

In the combination tests, pretreatment with either β-funaltrexamine or nor-binaltorphimine did not significantly affect the dose-response curve for methamphetamine, compared with pretreatment with saline (Fig. 4). Pretreatment with 3.0 mg/kg naltrindole or 1.0 mg/kg naltriben, but not 0.5 mg/kg naltriben, significantly shifted the dose–response curve for methamphetamine to the right, compared with pretreatment with saline ($F(1,48) = 8.33$, $P < 0.01$ and $F(1,48) = 5.20$, $P < 0.05$, respectively) (Fig. 5A and Fig. 6A). However, the response to the training dose of methamphetamine was not blocked by these antagonists. Pretreatment with 1.0 and 3.0 mg/kg 7-benzylidenenaltrexone slightly shifted the dose–response curve for methamphetamine to the right, but this change was not significant (Fig. 6B). Furthermore, to confirm the effects of naltrindole on the discriminative stimulus properties of methamphetamine, we also examined the effects of nal-

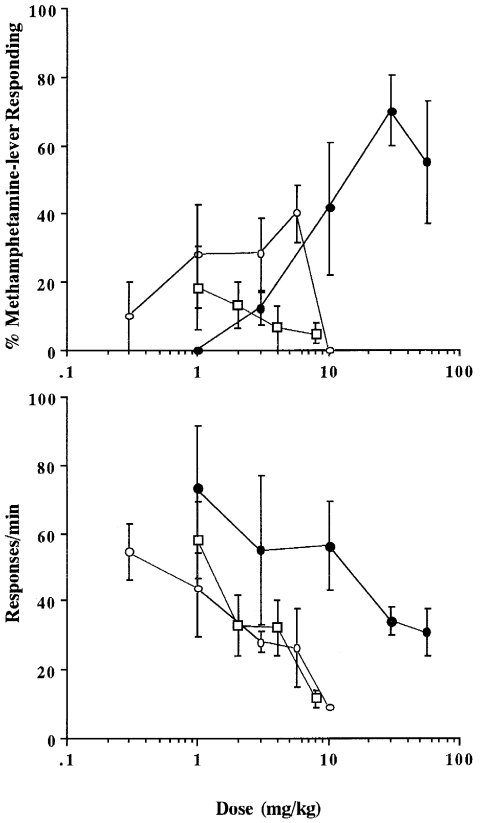

Fig. 2. Generalization of morphine (open circles), TAN-67 (closed circles) and U50,488H (open squares) to the discriminative stimulus properties of methamphetamine in rats that had been trained to discriminate between 0.4 mg/kg methamphetamine and saline. Each point represents the mean percentage of methamphetamine-appropriate responding and the mean response rates with S.E.M. for 5–8 animals. The percentage of methamphetamine-appropriate responding and the response rates were not calculated when the rat made fewer than 10 responses.

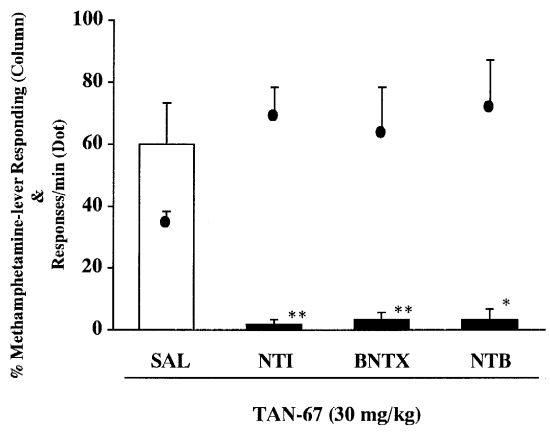

Fig. 3. Effects of naltrindole (NTI), naltriben (NTB) and 7-benzylidenenaltrexone (BNTX) on the partial generalization of TAN-67 (30 mg/kg) to the discriminative stimulus properties of methamphetamine in rats that had been trained to discriminate between 0.4 mg/kg methamphetamine and saline. Each column represents the mean percentage of methamphetamine-appropriate responding and each plot represents the mean response rate with S.E.M. $^{*}P < 0.05$, $^{**}P < 0.01$ versus saline control.

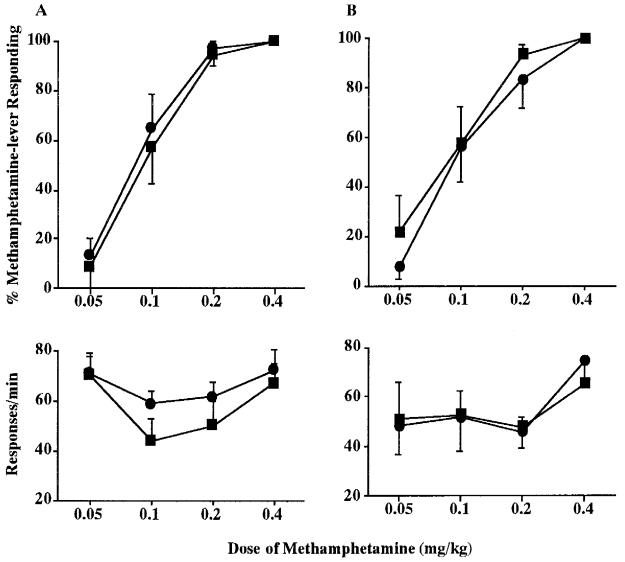

Fig. 4. Effects of 9.0 mg/kg β-funaltrexamine (A) (squares) and 10 mg/kg nor-binaltorphimine (B) (squares) or saline (circles) on the discriminative stimulus properties of methamphetamine (top panel) and on the response rates (bottom panel) in rats that had been trained to discriminate between 0.4 mg/kg methamphetamine and saline. Each point represents the mean percentage of methamphetamine-appropriate responding and the mean response rates with S.E.M. for 7 animals.

trindole on those of methamphetamine in rats trained to discriminate between 1.0 mg/kg methamphetamine and saline, since the training dose of 0.4 mg/kg of metham-

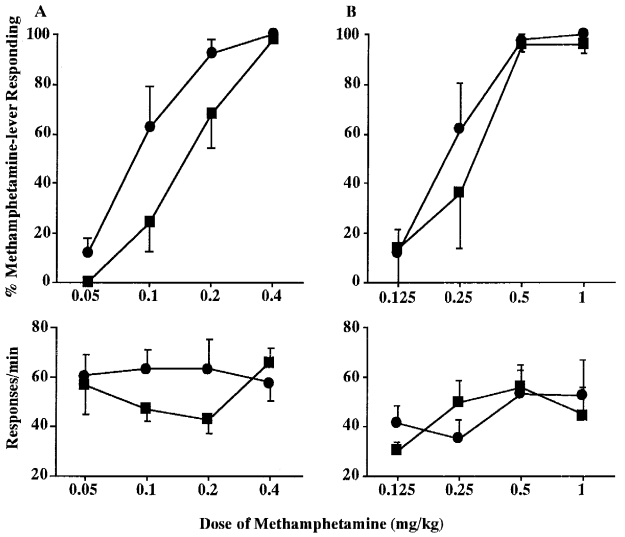

Fig. 5. Effects of 3.0 mg/kg naltrindole (squares) or saline (circles) on the discriminative stimulus properties of methamphetamine (top panel) and on the response rates (bottom panel) in rats trained to discriminate between 0.4 mg/kg (A) or 1.0 mg/kg (B) methamphetamine and saline. Each point represents the mean percentage of methamphetamine-appropriate responding and the mean response rates with S.E.M. for 7 (A) or 5 (B) animals. Naltrindole significantly shifted the dose–response curve for methamphetamine to the right ($F(1,48) = 8.33$, $P < 0.01$) in rats that had been trained to discriminate between 0.4 mg/kg methamphetamine and saline.

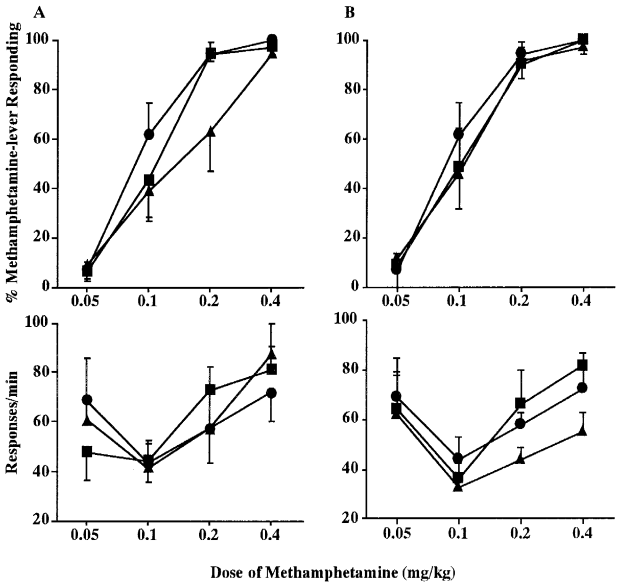

Fig. 6. Effects of 1.0 (squares) and 3.0 (triangles) mg/kg 7-benzylidenenaltrexone (A) and 0.5 (squares) and 1.0 (triangles) mg/kg naltriben (B) or saline (circles) on the discriminative stimulus properties of methamphetamine (top panel) and on the response rates (bottom panel) in rats that had been trained to discriminate between 0.4 mg/kg methamphetamine and saline. Each point represents the mean percentage of methamphetamine-appropriate responding and the mean response rates with S.E.M. for 7 animals. Naltriben (1.0 mg/kg) significantly shifted the dose–response curve for methamphetamine to the right ($F(1,48) = 5.20$, $P < 0.05$).

phetamine is relatively low. In rats that had been trained to discriminate between 1.0 mg/kg methamphetamine and saline, methamphetamine (0.125–1.0 mg/kg) produced a dose-related increase in methamphetamine-appropriate responses to more than 80%, as in rats that had been trained with 0.4 mg/kg methamphetamine (Fig. 1). Pretreatment with 3.0 mg/kg naltrindole slightly shifted the dose–response curve for methamphetamine to the right, but this change was not significant (Fig. 5B).

During the generalization test, naltrindole (3.0 mg/kg), naltriben (0.5 and 1.0 mg/kg) and 7-benzylidenenaltrexone (1.0 and 3.0 mg/kg) engendered methamphetamine-appropriate responses less than 20% of the time; the response rate averaged 45–75 responses/min (data not shown). In the present study, the response rates during the antagonism tests with β-funaltrexamine, nor-binaltorphimine, naltrindole, naltriben and 7-benzylidenenaltrexone did not differ from that with saline.

4. Discussion

In the present study, neither the μ-opioid receptor agonist morphine nor the κ-opioid receptor agonist U50,488H generalized to the discriminative stimulus properties of methamphetamine in rats that had been trained to discriminate between 0.4 mg/kg methamphetamine and saline. These results are consistent with previous results that μ- and κ-opioid receptor agonists do not generalize to the discriminative stimulus properties of other psychostimulants such as cocaine and amphetamine in rats and monkeys (Druhan et al., 1991; Spealman and Bergman, 1992; Suzuki et al., 1995). The newly synthesized non-peptide δ-opioid receptor agonist TAN-67 (Nagase et al., 1994; Kamei et al., 1995; Suzuki et al., 1996a) partially generalized to the discriminative stimulus properties of methamphetamine. Furthermore, this partial generalization of TAN-67 was significantly blocked by δ-opioid receptor antagonists, suggesting that the effects of TAN-67 are mediated by δ-opioid receptors. We found that the δ-opioid receptor antagonist naltrindole attenuated the discriminative stimulus properties of methamphetamine (0.4 mg/kg). In contrast, the μ- and κ-opioid receptor antagonists β-funaltrexamine and nor-binaltorphimine had little or no influence on the discriminative stimulus properties of methamphetamine. These results suggest that the discriminative stimulus properties of methamphetamine may be partially mediated by δ-opioid receptors.

Previous studies have demonstrated that methamphetamine- and cocaine-induced place preference (Menkens et al., 1992; Suzuki et al., 1994b) and cocaine-induced sensitization to locomotor activity (Heidbreder et al., 1993) can be blocked by δ-opioid receptor antagonists. The δ-opioid receptor agonist [D-Pen^2, L-Pen^5]enkephalin generalized to the discriminative stimulus properties of cocaine (Ukai et al., 1993) and the discriminative stimulus properties of cocaine were reduced by δ-opioid receptor antagonists (Suzuki et al., 1994a). These reports, together with the present results, suggest that endogenous δ-opioids may be involved in mediating the behavioral effects of psychostimulants. With regard to the acute effects of psychostimulants, the hyperlocomotion produced by cocaine or methamphetamine was not attenuated by the non-selective opioid receptor antagonists naloxone and/or naltrindole, while that of amphetamine was attenuated (Jones et al., 1993; Jones and Holtzman, 1994). Thus, the acute effects of methamphetamine and cocaine may not be mediated by opioid (especially δ-opioid) receptors, unlike those of amphetamine.

The mechanisms by which δ-opioid receptor antagonists can modify the discriminative stimulus properties of methamphetamine and some behavioral effects of psychostimulants are unclear. Nevertheless, it is well known that a variety of psychostimulant-induced behavioral effects are due to the ability of such drugs to increase the activity of the dopaminergic (especially the mesolimbic) system. Methamphetamine as well as cocaine elevates mRNA levels of enkephalin in the rat brain (Bannon et al., 1989; Hurd and Herkenham, 1992). Enkephalinase inhibitors increase enkephalinergic tone, which increases dopamine release in the nucleus accumbens (Giorgi et al., 1991), and central administration of the δ-opioid receptor agonist [D-Pen^2, D-Pen^5]enkephalin or [D-Ala^2]deltorphin II in-

creases dopamine release in the nucleus accumbens (Spanagel et al., 1990; Longoni et al., 1991). Thus, psychostimulants and enkephalin may interact in the release of dopamine from nerve terminals in the nucleus accumbens. Microinjection of D-Ala^2-Met^5-enkephalinamide (an enkephalin analog) into the nucleus accumbens or i.c.v. administration of [D-Ala^2]deltorphin II produces an increase in locomotion and rearing or an increase in place preference, respectively, which may not be mediated through the dopaminergic system (Kalivas et al., 1983; Suzuki et al., 1994b, 1996c). TAN-67, at the dose which partially generalized to the discriminative stimulus properties of methamphetamine in this study, scarcely affects the release of dopamine in the nucleus accumbens, as demonstrated in microdialysis experiments (unpublished observation). Microinjection of [D-Pen^2, D-Pen^5]enkephalin into the ventral pallidum, the principal efferent projection of the nucleus accumbens, produces a rewarding effect (Johnson and Stellar, 1994). Thus, enkephalin may post-synaptically affect the nucleus accumbens or other brain regions. Both mechanisms can explain why the discriminative stimulus properties of methamphetamine were attenuated by δ-opioid receptor antagonists.

Naltrindole did not significantly attenuate the discriminative stimulus properties of a high dose of methamphetamine (1.0 mg/kg). With regard to this discrepancy, studies using other compounds have often demonstrated qualitative as well as quantitative differences in the drug generalization profiles of different training doses, e.g., for cocaine (Terry et al., 1994), amphetamine (Stolerman and D'Mello, 1981) and morphine (Young et al., 1992). Thus, these phenomena may explain why naltrindole only attenuated the discriminative stimulus properties of a low dose of methamphetamine. A higher dose of naltrindole was required to attenuate the methamphetamine (2.0 mg/kg)-induced rewarding effects than was required for the cocaine (4.0 mg/kg)-rewarding effects (Suzuki et al., 1994b). Amphetamine (like methamphetamine) potently increases the dopamine concentration in nucleus accumbens, which is the terminal region of the mesolimbic dopaminergic system, as compared with cocaine (Di Chiara and Imperato, 1988). Thus, the dopamine concentration in the dopaminergic nerve terminals may explain why a higher dose of naltrindole is required to attenuate the methamphetamine-induced rewarding effects than is needed in the case of cocaine-induced rewarding effects, and similarly naltrindole did not significantly attenuate the discriminative stimulus properties of methamphetamine at higher training dose in the present study.

There are at least two δ-opioid receptor subtypes, δ_1 and δ_2 (Jiang et al., 1990; Mattia et al., 1991). In the present study, to determine whether the attenuating effect of naltrindole on the discriminative stimulus properties of methamphetamine is mediated through δ_1- or δ_2-opioid receptors, we also examined the effects of the δ_2-opioid receptor antagonist naltriben (Portoghese et al., 1991) and the δ_1-opioid receptor antagonist 7-benzylidenenaltrexone (Portoghese et al., 1992) on the discriminative stimulus properties of methamphetamine. Naltriben significantly attenuated the discriminative stimulus properties of methamphetamine, while 7-benzylidenenaltrexone had only a slight, insignificant, attenuating effect. Our findings suggest that blockade of δ_2-opioid receptors rather than δ_1-opioid receptors plays an important role in the attenuation of the discriminative stimulus properties of methamphetamine. Furthermore, these findings may support our previous reports concerning the discriminative stimulus properties of cocaine, and the rewarding effects of cocaine and methamphetamine in rats (Suzuki et al., 1994a,b). In addition, the δ_2-opioid receptor agonist, [D-Ala^2]deltorphin II, generalized to the discriminative stimulus properties of cocaine, while the δ_1-opioid receptor agonist, [D-Pen^2, Pen^5]enkephalin did not (Suzuki et al., 1997). [D-Pen^2, Pen^5]enkephalin-induced rewarding effects are antagonized by a dopamine D_1-receptor antagonist, while dopamine-receptor antagonists do not antagonize [D-Ala^2]deltorphin II-induced rewarding effects (Suzuki et al., 1996b). Thus, the action mechanisms of δ_1- and δ_2-opioid receptors on the dopaminergic system may be different from each other. The partial generalization of TAN-67 to the discriminative stimulus properties of methamphetamine was completely blocked by both naltriben and 7-benzylidenenaltrexone, which suggests that these effects of TAN-67 are mediated by both δ_1- and δ_2-opioid receptors. Furthermore, Jones et al. (1993) demonstrated that the attenuating effects of naltrindole-5′-isothiocyanate (a δ_2-opioid receptor antagonist) on amphetamine-induced hyperlocomotion were potentiated by [D-Ala^2,Leu^5,Cys^6]enkephalin (a δ_1-opioid receptor antagonist). Therefore, further examination is needed to clarify the interaction between δ_1- and δ_2-opioid receptors in the behavioral effects of psychostimulants.

The μ-opioid receptor antagonist β-funaltrexamine and the κ-opioid receptor antagonist nor-binaltorphimine did not affect the discriminative stimulus properties of methamphetamine. μ-Opioid receptor agonists and κ-opioid receptor agonists increase and decrease the release of dopamine in the nucleus accumbens, respectively (Di Chiara and Imperato, 1988; Spanagel et al., 1990) and modify some psychostimulant-induced behavioral effects, such as place preference and discriminative stimulus properties (Spealman and Bergman, 1992; Suzuki et al., 1992; Masukawa et al., 1993; Suzuki et al., 1995). While these previous results raise the possibility that β-funaltrexamine and nor-binaltorphimine may affect the discriminative stimulus properties of methamphetamine, the findings of the present study indicate that the discriminative stimulus properties of methamphetamine are not mediated by μ- or κ-opioid receptors.

In conclusion, the newly synthesized non-peptide δ-opioid receptor agonist TAN-67, but not μ- or κ-opioid receptor agonists, partially generalized to the discrimina-

tive stimulus properties of a low dose of methamphetamine. Furthermore, naltrindole and naltriben attenuated the discriminative stimulus properties of a low dose of methamphetamine. Our findings may have some bearing on the relative importance of δ-opioid (especially δ_2-opioid) receptors in the discriminative stimulus properties of methamphetamine.

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