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# Differential effects of μ-, δ- and κ-opioid receptor agonists on the discriminative stimulus properties of cocaine in rats

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**Abstract**

The effects of selective μ-, δ- and κ-opioid receptor agonists on the discriminative stimulus properties of cocaine were examined in rats trained to discriminate between cocaine (10 mg/kg) and saline. Cocaine produced a dose-related increase in cocaine-appropriate responses in all of the rats. In generalization tests, neither morphine (μ-opioid receptor agonist) nor *N*-methyl-*N*-7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-11-4-benzofuranacetamide (U50,488H: κ-opioid receptor agonist) generalized to the discriminative stimulus properties of cocaine. On the other hand, the newly synthesized non-peptide selective δ-opioid receptor agonist 2-methyl-4*a*α-(3-hydroxyphenyl)-1,2,3,4,4*a*,5,12,12*a*α-octahydro-quinolino(2,3,3,–*g*)isoquinoline (TAN-67) partially generalized (56.7% cocaine-appropriate responses) to the discriminative stimulus properties of cocaine. Intracerebroventricular (i.c.v.) administration of [D-Ala$^2$]deltorphin II (peptide $\delta_2$-opioid receptor agonist) completely generalized, while neither [D-Ala$^2$,MePhe$^4$,Gly-ol$^5$]enkephalin (DAMGO; μ-opioid receptor agonist) nor [D-Pen$^2$,D-Pen$^5$]enkephalin (DPDPE; $\delta_1$-opioid receptor agonist) generalized to the discriminative stimulus properties of cocaine. These results suggest that the discriminative stimulus properties of cocaine may be partially mediated by δ-opioid (especially $\delta_2$-opioid) receptors. In combination tests, pretreatment with morphine (3.0 mg/kg) and TAN-67 (3.0 and 10 mg/kg) significantly potentiated the discriminative stimulus properties cocaine. In contrast, pretreatment with U50,488H (2.0 and 4.0 mg/kg) scarcely shifted the discriminative stimulus properties of cocaine. Furthermore, the potentiating effect of 3.0 mg/kg morphine on the discriminative stimulus properties of cocaine was attenuated by 2.0 mg/kg U50,488H. In contrast, the potentiating effect of 10 mg/kg TAN-67 on the discriminative stimulus properties of cocaine was not reversed by either 2.0 or 4.0 mg/kg U50,488H. These results suggest that μ-, δ- and κ-opioid receptor agonists modulate the discriminative stimulus properties of cocaine through different mechanisms, perhaps through different effects on the dopaminergic system. © 1997 Elsevier Science B.V.

*Keywords:* Cocaine; Opioid; Drug discrimination; Drug interaction

## 1. Introduction

Cocaine is a psychomotor stimulant with prominent subjective effects that may induce its abuse (Jaffe, 1990). In addition, the properties of drugs that mediate their discriminative stimulus properties are related to aspects of drug actions that result in their subjective effects in humans (Schuster and Johanson, 1988). Therefore, the drug discrimination procedure has been used to classify psychostimulants according to similarities in their discriminative stimulus properties, and is useful for characterizing the interactions between cocaine and other drugs (Spealman and Bergman, 1992).

Although cocaine inhibits the neuronal uptake of monoamines such as dopamine, norepinephrine and serotonin into presynaptic terminals (Heikkila et al., 1975; Koe, 1976), numerous studies have shown that the dopaminergic, particularly the mesolimbic, system plays an important role in the discriminative stimulus properties of cocaine: dopamine receptor direct/indirect agonists generalize to the discriminative stimulus properties of cocaine, and injection of cocaine into the nucleus accumbens completely generalized to the discriminative stimulus properties of i.p. administration of cocaine (Cunningham et al., 1992).

There is considerable evidence that cocaine and opioids

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(μ-opioid receptor agonists) exert similar behavioral activating and rewarding effects that result from activation of the dopaminergic system. In addition, pharmacological, behavioral and biochemical studies on opioids have shown 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). The activation of opioid receptors may modify the release of dopamine in the nucleus accumbens (Di Chiara and Imperato, 1988; Spanagel et al., 1990; Longoni et al., 1991) and induces behavioral effects (e.g., place preference and locomotion) in rodents (Funada et al., 1993; Longoni et al., 1991; Meyer and Meyer, 1993; Narita et al., 1993a; Suzuki et al., 1991).

Simultaneous intake of several drugs by drug abusers has been reported in recent years. The use of cocaine and μ-opioid receptor agonists is currently in vogue; this particular combination is commonly referred to as 'speedball' by street abusers (Kosten et al., 1986; Kreek, 1987). Therefore, many investigators have sought to characterize the interaction of these drugs. The combination of cocaine and morphine produces a mutual enhancement of their reinforcing effects (Masukawa et al., 1993). μ-Opioid receptor agonists can potentiate the discriminative stimulus properties of cocaine in monkeys (Spealman and Bergman, 1992, 1994) and in rats (Suzuki et al., 1995a). Conversely, κ-opioid receptor agonists attenuate cocaine's behavioral effects, such as place preference (Suzuki et al., 1992), stereotypies (Ukai et al., 1992) and discriminative stimulus properties (Spealman and Bergman, 1992, 1994). These investigators suggested that these effects of μ- or κ-opioid receptor agonists on the behavioral effects of cocaine may be mediated by the dopaminergic system, since μ- and κ-opioid receptor agonists can enhance and reduce dopamine release (Di Chiara and Imperato, 1988; Spanagel et al., 1990), respectively, and since the dopaminergic system plays an important role in some behavioral effects of cocaine. Furthermore, morphine's behavioral effects, such as its reinforcing effects, Straub tail and hyperlocomotion, are also reduced by κ-opioid receptor agonists (Suzuki et al., 1992; Funada et al., 1993; Narita et al., 1993a,b).

Like μ-opioid receptor agonists, δ-opioid receptor agonists induce self-administration, place preference and hyperlocomotion (Goeders et al., 1984; Suzuki et al., 1991, 1994a; Meyer and Meyer, 1993; Johnson and Stellar, 1994). In addition, although δ- as well as μ-opioid receptor agonists increase the release of dopamine (Di Chiara and Imperato, 1988; Spanagel et al., 1990), the δ-opioid receptor agonist [D-Pen$^2$,L-Pen$^5$]enkephalin, but not μ-opioid receptor agonists, generalizes to the discriminative stimulus properties of cocaine (Ukai et al., 1993). These results suggest that the discriminative stimulus properties of cocaine may be partially mediated by δ-opioid receptors. Nevertheless, very few studies have shown that δ-opioid receptor agonists could modify the behavioral effects of cocaine (Ukai et al., 1994; Spealman and Bergman, 1994).

Recently, Nagase et al. (1994) synthesized a non-peptide selective δ-opioid receptor agonist, TAN-67, which shows a high affinity for δ-opioid receptors ($K_i = 1.12$ nM) and a low affinity for μ-opioid receptors ($K_i = 2320$ nM) and κ-opioid receptors ($K_i = 1790$ nM). Unlike peptide δ-opioid receptor agonists, TAN-67 easily crosses the blood-brain barrier and can be administered peripherally. In addition, TAN-67 does not bind to dopamine receptors, and does not affect dopamine or norepinephrine uptake. The major aim of the present study was to examine whether TAN-67 (δ-opioid receptor agonist), morphine (μ-opioid receptor agonist) and U-50,488H (κ-opioid receptor agonist) generalize to the discriminative stimulus properties of cocaine, and modify the discriminative stimulus properties of cocaine in rats. Furthermore, the effects of U50,488H on the potentiation of cocaine-induced discriminative stimulus properties by morphine (Suzuki et al., 1995a) and TAN-67 (if TAN-67 potentiates the discriminative stimulus properties of cocaine) were also examined. In addition, generalizations of the prototypic peptide opioid receptor agonists DAMGO (for μ-opioid receptors), DPDPE (for $\delta_1$-opioid receptors) and [D-Ala$^2$]deltorphin II (for $\delta_2$-opioid receptors), which were administered i.c.v., to the discriminative stimulus properties of cocaine were also examined.

We as well as others recently demonstrated that the discriminative stimulus properties of cocaine were attenuated by δ-opioid receptor antagonists in rats (Suzuki et al., 1994b) and in monkeys (Negus et al., 1995). To elucidate the involvement of endogenous opioid ligands in the behavioral effects of cocaine, it may be necessary to examine the effects of μ- and κ-opioid receptor antagonists on the discriminative stimulus properties of cocaine. Therefore, the effects of μ- (β-funaltrexamine) and κ- (nor-binaltorphimine) opioid receptor antagonists on the discriminative stimulus properties of cocaine were also examined.

## 2. Materials and methods

### 2.1. Animals

The 14 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 $22 \pm 1$°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 two levers, with a reinforcement 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. Reinforcement consisted of a 20-mg food pellet (O'Hara).

### 2.3. Discrimination training

Before they were trained to discriminate between cocaine and saline, all of the rats were trained to press a lever. Rats were trained to press either the right or left lever in the daily sequence LRRLLRRLLR (R = right, L = left). Training began under a fixed-ratio (FR 1) reinforcement schedule in which the rat was presented with a food pellet each time it pressed a lever. When reinforcement was provided, the lamp above the lever was illuminated. After the response rates had stabilized, the FR requirement was increased steadily to a reinforcement schedule of FR 10. After the response rates had stabilized under FR 10 and the rat received 40 reinforcements during four consecutive sessions, both levers were presented in the chamber. Rats were trained to discriminate between cocaine (10 mg/kg) and saline. Cocaine or saline was administered i.p. 15 min before each session in a daily sequence of SDDSSDDSSD (D = drug, S = saline). Rats were required to respond on the stimulus-appropriate lever to obtain reinforcement; there were no programmed consequences for responding on the incorrect lever. Training sessions were 15 min in duration and this phase of training continued until all of the rats performed up to the required criterion (accuracies of at least 83% (first food pellet $\leq 12$ responses) for five consecutive sessions). After the rats attained the criterion, the rats were divided into two groups. One group of rats ($n = 6$) was implanted with an i.c.v. cannula. Another group of rats ($n = 8$) was tested according to the following procedure. Moreover, discrimination training was continued even after the criterion was attained.

### 2.4. Testing procedure

After the animals attained the criterion, dose-response, generalization, and combination tests were initiated. Test sessions were conducted after the discrimination criterion described above had been satisfied for at least three consecutive sessions. In the dose-response and generalization tests, rats were placed in the operant box until either they had made ten responses on either lever or 5 min had elapsed after the drugs were administered. The combination test sessions consisted of four FR components to determine four-point cumulative dose-response curves for cocaine. The cumulative dosing procedure used has been described elsewhere (Suzuki et al., 1994b). Briefly, in each component, rats were placed in the operant box until either they had made ten responses on either lever or 5 min (component time) had elapsed without reinforcement. After the first component was finished (5 min had elapsed), drugs were administered again. This procedure was repeated three times. Thus, the entire procedure required 80 min ([15 min + 5 min] × 4). In the combination test, doses of opioid receptor agonists that produced less than 20% drug-appropriate responses in the generalization tests were used.

The pretreatment times and doses of drugs in the present study were: 30 min for 0.3–10 mg/kg morphine (s.c.) and 1.0–8.0 mg/kg U50,488H (i.p.); 60 min for 1.0–56 mg/kg TAN-67 (i.p.); 80 min for 3.0 mg/kg naltrindole (i.p.); 35 min for 0.5 mg/kg naltriben (i.p.); 4 h for 10 mg/kg nor-binaltorphimine (i.p.) and 24 h for 9.0 mg/kg β-funaltrexamine (i.p.). If the rats did not make ten responses during each component, the response was judged to have been disrupted.

### 2.5. I.c.v. cannulation

Rats were anesthetized i.p. with sodium pentobarbital (50 mg/kg) and then placed in a stereotactic apparatus. A unilateral guide cannula was implanted into the left lateral ventricle according to the atlas of Paxinos and Watson (1986). From the bregma, the coordinates used to position the guide cannula above the lateral ventricle were A = −0.8, L = 1.4, V = 3.1. All rats were given at least 7 days postsurgical recovery time before the onset of testing.

### 2.6. Generalization test by i.c.v. injection

Cocaine, DAMGO, DPDPE or [D-Ala$^2$]deltorphin II was injected unilaterally into the left lateral ventricle via a guide cannula (0.6 mm o.d., 0.3 mm i.d.). The drugs were injected over 30 s in a volume of 5 μl and the injection needle was left for 10 s after drug injection. The injection needle, 31-gauge stainless steel, was exactly 1.0 mm longer than the implanted guide cannula. The pretreatment times of the drugs were: 10 min for cocaine, 15 min for DAMGO (0.03–0.56 nmol/rat), DPDPE (3.0–30 nmol/rat) and [D-Ala$^2$]deltorphin II (1.0–10 nmol/rat). The doses and the pretreatment time were based on the papers of Shearman and Herz (1982), Ukai et al. (1993) and Suzuki et al. (1994a).

### 2.7. Drugs

The drugs used in the present study were cocaine hydrochloride (Takeda, Osaka, Japan), morphine hydrochloride (Sankyo, Tokyo, Japan), *N*-methyl-*N*-7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-11-4-benzofuranacetamide (U50,488H) hydrochloride, 2-methyl-4*aα*-(3-hydroxyphenyl)-1,2,3,4,4*a*,5,12,12*aα*-octahydro-quinoline methanesulfonate (TAN-67), DPDPE (Peninsula Laboratories, Irvine, CA, USA), [D-Ala$^2$]deltorphin II and DAMGO (Peninsula Laboratories, CA, USA), naltrindole hydrochloride, naltriben methanesulfonate hydrate, β-funaltrexamine

hydrochloride (Research Biochemicals International, Natick, MA, USA) and nor-binaltorphimine hydrochloride. U50,488H, TAN-67, naltrindole, naltriben and nor-binaltorphimine were synthesized by us. All drugs were dissolved in saline. All doses refer to the salt forms of the drugs.

### 2.8. Data analysis

During the training sessions, accuracy was defined as the number of correct responses as a percentage of the total responses before the first food pellet. During the test sessions, performance was expressed as the number of drug-appropriate responses as a percentage of the total responses on completion of FR 10. Drugs were considered to have generalized to the discriminative stimulus properties of cocaine if more than 80% of the responses were on the drug-appropriate lever. Response rate was calculated as the total number of responses before the completion of ten responses on either lever divided by the time (minutes) taken to complete the first ratio. Results with pretreatment with saline and drugs were compared using a two-factor (groups × cumulative dose) repeated measures analysis of variance (ANOVA). The paired Student's *t*-test was used to compare the percentage of drug-lever responding or response rates during the combination test.

## 3. Results

Rats required approximately 21 sessions for the cocaine-saline discrimination. Once rats attained the criterion, drug-saline discrimination stabilized and was maintained with a high degree of accuracy. During the dose-response tests, cocaine (1.25–10 mg/kg) produced a dose-related increase in cocaine-appropriate responses in all of the rats (Fig. 1).

In the generalization test, 0.3–10 mg/kg morphine and 1.0–8.0 mg/kg U50,488H did not engender cocaine-appropriate responding and decreased response rates as the dose of morphine and U50,488H increased, and no rats generalized to the discriminative stimulus properties of cocaine (Fig. 1). Two of the six rats showed a disrupted response at the highest dose of U50,488H. On the other hand, 3.0–56 mg/kg TAN-67 partially (56.7% responses on the cocaine-appropriate lever at the highest dose (three of six rats completely generalized to the discriminative stimulus properties of cocaine)) generalized to the discriminative stimulus properties of cocaine and decreased response rates in a dose-dependent manner (Fig. 1). Two of eight rats showed a disrupted response at the highest dose of TAN-67. In addition, this partial generalization of the highest dose of TAN-67 was completely reversed by 3.0 mg/kg naltrindole (δ-opioid receptor antagonist; 20 min before TAN-67 treatment) (10.0 ± 3.16% responses on the cocaine-appropriate lever, $n = 5$).

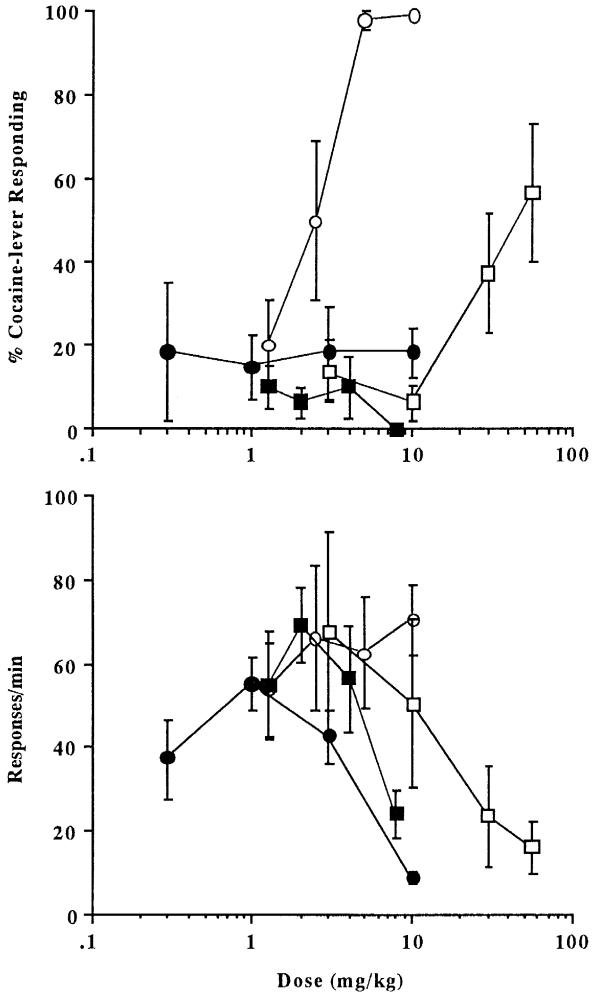


Fig. 1. Dose–response of cocaine (open circles) and generalization of morphine (closed circles), TAN-67 (open squares) and U50,488H (closed squares) to the discriminative stimulus properties of cocaine in rats trained to discriminate between 10.0 mg/kg cocaine and saline. Each point represents the mean percentage of cocaine-appropriate responding and the mean response rates with S.E.M. of 6–8 animals. The percentage of cocaine-appropriate responding and the response rates were not calculated in cases where a rat made fewer than ten responses.

I.c.v. administration of cocaine (10–100 μg/rat) produced a dose-related increase in cocaine-appropriate responding. The dose range of cocaine (30–100 μg/rat) produced more than 80% cocaine-appropriate responding in all of the rats (Table 1), while saline did not engender cocaine-appropriate responding. [D-Ala$^2$]Deltorphin II (10 nmol/rat) completely generalized, while DPDPE (3.0–30 nmol/rat) partially generalized to the discriminative stimulus properties of cocaine (Table 1). Furthermore, the generalization of [D-Ala$^2$]deltorphin II (10 nmol/rat) to the discriminative stimulus properties of cocaine was completely antagonized by 0.5 mg/kg naltriben (a $\delta_2$-opioid receptor antagonist; 20 min before [D-Ala$^2$]deltorphin II treatment) (Table 1). On the other hand, DAMGO (0.1–0.56 nmol/rat) engendered less than 40% cocaine-appropriate responding (Table 1).

Table 1
Effects of i.c.v. administration of cocaine and opioid receptor agonists in rats trained to discriminate cocaine from saline

| Drug | Dose | % Cocaine-lever responding (S.E.M.) | $n/N$ |
|---|---|---|---|
| Saline | | 10.0 (5.0) | 0/6 |
| Cocaine | 10 | 35.0 (15.0) | 1/6 |
| (μg/rat) | 30 | 60.0 (12.4) | 2/6 |
| | 100 | 86.7 (7.6) | 5/6 |
| DAMGO | 0.1 | 30.0 (19.0) | 1/5 |
| (nmol/rat) | 0.3 | 22.0 (12.0) | 0/5 |
| | 0.56 | 38.0 (15.9) | 1/5 |
| DPDPE | 3 | 20.0 (9.1) | 0/4 |
| (nmol/rat) | 10 | 57.5 (13.8) | 1/4 |
| | 30 | 66.0 (16.1) | 3/5 |
| Deltorphin II | 1 | 32.5 (13.1) | 0/4 |
| (nmol/rat) | 3 | 60.0 (11.8) | 1/5 |
| | 10 | 90.0 (4.5) | 5/5 |
| +0.5 mg/kg naltriben | 10 | 12.0 (8.0) | 0/5 |

$n/N$, number of subjects that generalized to the discriminative stimulus properties of cocaine ($n$) out of the total number of subjects tested ($N$).

In the combination tests, 3.0 mg/kg morphine significantly shifted the dose-response curve for cocaine to the left as compared to pretreatment with saline ($F(1,48) = 8.77$, $P < 0.01$), and significantly potentiated the discriminative stimulus properties of cocaine at a dose of 1.25 mg/kg compared to pretreatment with saline ($P < 0.05$) (Fig. 2 ). Furthermore, the potentiating effect of 3.0 mg/kg morphine on the discriminative stimulus properties of cocaine was significantly attenuated by 2.0 mg/kg U50,488H ($F(1,48) = 6.63$, $P < 0.05$) ($P < 0.05$ by the paired Student's $t$-test) (Fig. 2). The dose of U50,488H was based on our previous reports that this dose significantly attenuated the reinforcing effects of morphine (Funada et al., 1993),

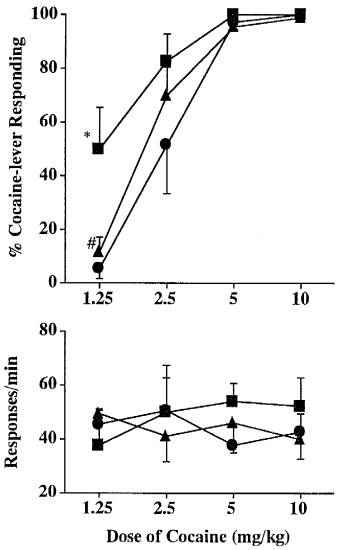


Fig. 2. Effects of U50,488H on the potentiating effects of 3.0 mg/kg morphine on the discriminative stimulus properties of cocaine in rats trained to discriminate between 10.0 mg/kg cocaine and saline. Rats were injected with saline plus saline (circles), saline plus morphine (squares) or 2.0 mg/kg U50,488H plus morphine (triangles) before treatment with cocaine. Each point represents the mean percentage of cocaine-appropriate responding and the mean response rates with S.E.M. of seven animals. * $P < 0.05$ vs. saline control. # $P < 0.05$ vs. morphine control.

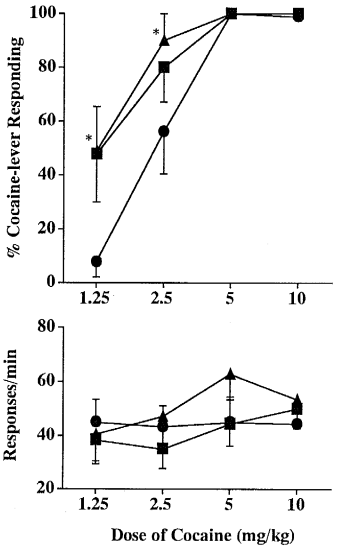


Fig. 3. Effects of TAN-67 on the discriminative stimulus properties of cocaine in rats trained to discriminate between 10.0 mg/kg cocaine and saline. Rats were injected with saline (circles), or 3.0 (squares) or 10.0 (triangles) mg/kg TAN-67 before treatment with cocaine. Each point represents the mean percentage of cocaine-appropriate responding and the mean response rates with S.E.M. of seven animals. * $P < 0.05$ vs. saline control.

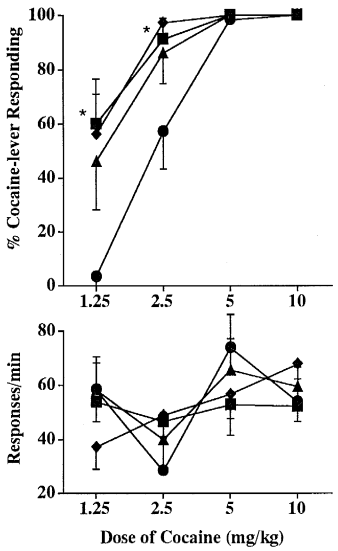


Fig. 4. Effects of U50,488H on the potentiating effects of 10.0 mg/kg TAN-67 on the discriminative stimulus properties of cocaine in rats trained to discriminate between 10.0 mg/kg cocaine and saline. Rats were injected with saline plus saline (circles), saline plus TAN-67 (squares), 2.0 mg/kg U50,488H plus TAN-67 (triangles) or 4.0 mg/kg U50,488H plus TAN-67 (diamonds) before treatment with cocaine. Each point represents the mean percentage of cocaine-appropriate responding and the mean response rates with S.E.M. of seven animals.

Table 2
Effects of opioidergic agents on the percentage cocaine-lever responding (S.E.M.) in rats trained to discriminate cocaine from saline

| | Dose of cocaine (mg/kg) | | | | *N* |
|---|---|---|---|---|---|
| | 1.25 | 2.5 | 5.0 | 10 | |
| Saline + cocaine | 10.0 (3.2) | 58.0 (10.7) | 96.0 (2.5) | 98.0 (2.0) | 5 |
| 2 mg/kg U50,488H + cocaine | 12.0 (8.0) | 54.0 (16.0) | 86.0 (7.5) | 100 (0) | |
| Saline + cocaine | 10.0 (2.6) | 65.0 (11.2) | 96.7 (2.1) | 98.3 (1.7) | 6 |
| 4 mg/kg U50,488H + cocaine | 10.0 (6.8) | 46.7 (15.0) | 85.0 (6.2) | 100 (0) | |
| Saline + cocaine | 6.0 (2.5) | 40.0 (12.3) | 84.0 (16.0) | 100 (0) | 5 |
| β-Funaltrexamine + cocaine | 14.0 (11.7) | 34.0 (19.9) | 88.0 (12.0) | 100 (0) | |
| Saline + cocaine | 20.0 (8.9) | 64.0 (16.9) | 98.0 (2.0) | 100 (0) | 5 |
| Nor-binaltorphimine + cocaine | 26.0 (12.9) | 76.0 (12.1) | 100 (0) | 98.0 (2.0) | |

β-Funaltrexamine, 9 mg/kg; nor-binaltorphimine, 10 mg/kg.

but not of cocaine (Suzuki et al., 1992). On the other hand, 3.0 and 10 mg/kg TAN-67 significantly shifted the dose-response curve for cocaine to the left as compared to pretreatment with saline ($F(1,56) = 5.69$, $P < 0.05$ and $F(1,56) = 9.0$, $P < 0.01$, respectively), and significantly potentiated the discriminative stimulus properties of cocaine at doses of both 1.25 and 2.5 mg/kg compared to pretreatment with saline (both $P < 0.05$ by the paired Student's *t*-test) (Fig. 3). In contrast to the results with morphine, the potentiating effect of 10 mg/kg TAN-67 ($F(1,56) = 15.2$, $P < 0.01$) (both $P < 0.05$ at doses of both 1.25 and 2.5 mg/kg by the paired Student's *t*-test) on the discriminative stimulus properties of cocaine was not reversed by 2.0 or 4.0 mg/kg U50,488H (Fig. 4). Moreover, pretreatment with 2.0 or 4.0 mg/kg U50,488H did not significantly shift the dose-response curve for cocaine (Table 2). The discriminative stimulus properties of cocaine were attenuated in three rats and potentiated in three other rats by 8.0 mg/kg U50,488H, while two of eight rats showed a disrupted response with the combination of 8.0 mg/kg U50,488H and cocaine (data not shown). Furthermore, neither β-funaltrexamine nor nor-binaltorphimine affected either the discriminative stimulus properties of cocaine or the response rates (Table 2).

## 4. Discussion

In the present study, peptide δ-opioid receptor agonists partially or completely generalized, while the newly synthesized non-peptide δ-opioid receptor agonist TAN-67 (Nagase et al., 1994; Kamei et al., 1995; Suzuki et al., 1995b) partially generalized to the discriminative stimulus properties of cocaine in a naltrindole- (δ-opioid receptor antagonist) reversible manner. Furthermore, a previous report demonstrated that the δ-opioid receptor agonist [D-Pen$^2$,L-Pen$^5$]enkephalin (Ukai et al., 1993) generalized to the discriminative stimulus properties of cocaine. On the other hand, neither μ- nor κ-opioid receptor agonists generalize to the discriminative stimulus properties of psychostimulants such as cocaine and amphetamine in animals (Schechter, 1978; Jarbe, 1981, 1982; Evans and Johanson, 1987; Spealman and Bergman, 1992; Suzuki et al., 1995a; present study).

It is unclear why only δ-opioid receptor agonists partially or completely generalized (Ukai et al., 1993, present results) to the discriminative stimulus properties of cocaine. Numerous studies have shown that activation of μ- and δ-opioid receptors can enhance the release of dopamine from presynaptic terminals (Di Chiara and Imperato, 1988; Spanagel et al., 1990; Longoni et al., 1991) and activation of the dopaminergic system plays an important role in the discriminative stimulus properties of cocaine (Cunningham et al., 1992). With regard to these discrepant results, Druhan et al. (1993) showed that amphetamine-like discriminative stimulus properties are produced by morphine injection into the ventral tegmental area, which contains cell bodies of the mesolimbic dopaminergic system, but not by systemic administration of morphine. These results suggest that dopaminergic action on the discriminative stimulus properties of systemically or i.c.v. administered morphine may be masked by other actions (e.g., sedation or antinociception). On the other hand, we as well as others demonstrated that δ-opioid receptor antagonists can attenuate the discriminative stimulus properties and reinforcing effects of cocaine in rats (Menkens et al., 1992; Suzuki et al., 1994b,c) and in monkeys (Negus et al., 1995), while neither naloxone, at a dose which could preferentially antagonize μ-opioid receptors (Suzuki et al., 1995a), the μ-opioid receptor antagonist β-funaltrexamine nor the κ-opioid receptor antagonist nor-binaltorphimine affected the discriminative stimulus properties of cocaine (present results). These findings may support our present results that δ-opioid receptor agonists partially or completely generalize to the discriminative stimulus properties of cocaine.

There are at least two δ-opioid receptor subtypes: $\delta_1$ and $\delta_2$ (Jiang et al., 1990; Mattia et al., 1991). In the present study, the $\delta_2$-opioid receptor agonist [D-Ala$^2$]deltorphin II (10 nmol/rat) completely, and the $\delta_1$-opioid receptor agonist DPDPE (3.0–30 nmol/rat) partially, generalized to the discriminative stimulus properties of cocaine. These results may support our previous results that

the discriminative stimulus properties of cocaine were attenuated by the $\delta_2$-opioid receptor antagonist naltriben, but not by the $\delta_1$-opioid receptor antagonist 7-benzylidenenaltrexone (Suzuki et al., 1994b), suggesting that the discriminative stimulus properties of cocaine may be partially mediated by δ- (especially $\delta_2$-) opioid receptors. With regard to these results, previous reports demonstrated that motor response to intra-accumbens microinjection of the $\delta_2$-opioid receptor agonist [D-Ala$^2$]deltorphin I was augmented after dopamine depletion; in contrast the response to DPDPE was not (Churchill and Kalivas, 1992; Churchill et al., 1995). Furthermore, dopamine receptor antagonists abolished DPDPE- but not [D-Ala$^2$]deltorphin II-induced rewarding effects (Suzuki et al., 1996a). Thus, the effects of $\delta_2$-opioid receptor agonists on the dopaminergic system are different from those of $\delta_1$-opioid receptor agonists. However, we should expect that higher doses of DPDPE would generalize to the discriminative stimulus properties of cocaine, since DPDPE can interact with both $\delta_1$- and $\delta_2$-opioid receptors (Vanderah et al., 1994) and [D-Pen$^2$,L-Pen$^5$]enkephalin generalized to the discriminative stimulus properties of cocaine (Ukai et al., 1993).

In combination tests, morphine potentiated the discriminative stimulus properties of cocaine. These results are consistent with previous results in monkeys (Spealman and Bergman, 1992, 1994) and our recent results in rats (Suzuki et al., 1995a). With regard to these results, microinjection of cocaine into the nucleus accumbens, which is the terminal region of the mesolimbic dopaminergic system, generalized to the discriminative stimulus properties of systemically administered cocaine (Wood and Emmett-Oglesby, 1989). Conversely, 6-hydroxy dopamine lesion of the nucleus accumbens or intra-accumbens administration of the dopamine $D_1$ receptor antagonist SCH23390 attenuates the discriminative stimulus properties of amphetamine or cocaine, respectively (Dworkin and Bimle, 1989; Callahan et al., 1994). Direct injection of morphine into the ventral tegmental area generalized to the discriminative stimulus properties of amphetamine, which may induce a release of dopamine from the nucleus accumbens (Druhan et al., 1993). Thus, morphine and cocaine interact at the same point in the dopaminergic system. In addition, dopamine-releasing effects of μ-opioid receptor agonists might be expected to augment the dopamine uptake-inhibiting effects of cocaine (Heikkila et al., 1975; Koe, 1976). Furthermore, Masukawa et al. (1993) suggested that the combination of a dopamine releaser (opioids) and a dopamine-uptake inhibitor (cocaine) could potentiate their reinforcing effects. These findings suggest that morphine might potentiate the discriminative stimulus properties of cocaine.

The potentiating effects of morphine on the discriminative stimulus properties of cocaine were attenuated by co-administration of 2.0 mg/kg U50,488H. It is known that several μ- and κ-opioid receptor agonists have opposite pharmacological effects. For example, μ-opioid receptor agonists increase locomotor activity (Narita et al., 1993a) and induce place preference (Funada et al., 1993), while κ-opioid receptor agonists decrease locomotor activity and induce place aversion (Funada et al., 1993). On the other hand, it has been demonstrated that some of morphine's behavioral effects (reinforcing effects, locomotor enhancing effects and Straub tail) are reduced by several κ-opioid receptor agonists (Narita et al., 1993a,b; Funada et al., 1993), and κ-opioid receptor agonists abolished the increase in dopamine metabolites produced by morphine in the limbic forebrain (including the nucleus accumbens) (Funada et al., 1993). Therefore, the above mechanisms may be involved in the attenuation of the potentiating effects of morphine on the discriminative stimulus properties of cocaine.

Spealman and Bergman (1992, 1994) recently demonstrated that U50,488H attenuates the discriminative stimulus properties of cocaine in monkeys. In the present study, 2.0 and 4.0 mg/kg U50,488H scarcely modify the discriminative stimulus properties of morphine, while 8.0 mg/kg U50,488H attenuated the discriminative stimulus properties of cocaine in some rats. With regard to these discrepancies, cocaine dramatically increases synaptic dopamine concentration, while the inhibitory effects of U50,488H on dopamine release are relatively weak in the nucleus accumbens, as measured by a microdialysis technique (Di Chiara and Imperato, 1988). The morphine-induced place preference is attenuated by a low dose of U50,488H (1.0 mg/kg), while a high dose (10.0 mg/kg) of U50,488H is required to attenuate the cocaine-induced place preference (Funada et al., 1993; Suzuki et al., 1992). Thus, these findings may explain why the discriminative stimulus properties of cocaine were scarcely attenuated by U50,488H in rats trained to discriminate between cocaine and saline.

In the present study, the δ-opioid receptor agonist TAN-67 potentiated the discriminative stimulus properties of cocaine. Our present results are consistent with the finding that [D-Pen$^2$,L-Pen$^5$]enkephalin potentiates cocaine-induced stereotypies (Ukai et al., 1994). Central administration of the δ-opioid receptor agonist DPDPE or [D-Ala$^2$]deltorphin II increases dopamine release in the nucleus accumbens, based on microdialysis techniques (Spanagel et al., 1990; Longoni et al., 1991). However, 10.0 mg/kg of TAN-67 did not increase the release of dopamine in the nucleus accumbens using a microdialysis procedure (unpublished observation) and a higher dose of TAN-67 (20 mg/kg) did not influence dopamine turnover in the mouse limbic forebrain (Suzuki et al., 1996b), suggesting that TAN-67 hardly affects the dopaminergic system. As would be expected, the potentiating effect of TAN-67, unlike those of morphine, on the discriminative stimulus properties of cocaine was not reduced by U50,488H. These results can be explained by previous reports that microinjection of [D-Ala$^2$,Met$^5$]enkephalinamide (enkephalin analog) into the nucleus accumbens produces an increase in locomotion and rearing independent

of the mesolimbic dopaminergic system (Pert and Sivit, 1977; Kalivas et al., 1983). Furthermore, we recently demonstrated that neither the dopamine receptor antagonist nor U50,488H antagonizes [D-Ala$^2$]deltorphin II-induced rewarding effects (Suzuki et al., 1996a, 1997). Thus, δ-opioid receptor agonists exert behavioral activating effects through a dopamine-independent system, like those of cocaine through the dopaminergic system. These results suggest that a dopamine-independent system that is activated by stimulation of δ-opioid receptor may exist, and this system may explain why the potentiating effect of TAN-67 on the discriminative stimulus properties of cocaine was not attenuated by U50,488H. In addition, this system may play an important role in the complete generalization of [D-Ala$^2$]deltorphin II to the discriminative stimulus properties of cocaine (see above).

In summary, although it is well known that the dopaminergic system plays the primary role in the discriminative stimulus properties of cocaine, among the opioid receptor agonists used in the present study, only the $\delta_2$-opioid receptor agonist [D-Ala$^2$]deltorphin II completely generalized to the discriminative stimulus properties of cocaine. On the other hand, we already demonstrated that naltrindole and naltriben attenuated the discriminative stimulus properties of cocaine (Suzuki et al., 1994b). These results suggest that the discriminative stimulus properties of cocaine may be partially mediated by δ-opioid (especially $\delta_2$-opioid) receptors. Furthermore, not only the μ-opioid receptor agonist morphine, but also the δ-opioid receptor agonist TAN-67 potentiated the discriminative stimulus properties of cocaine. In addition, the κ-opioid receptor agonist U50,488H attenuated the potentiating effects of morphine, but not those of TAN-67, on the discriminative stimulus properties of cocaine. Thus, μ-, δ- and κ-opioid receptor agonists can modulate the discriminative stimulus properties of cocaine through different mechanisms, perhaps through different effects on the dopaminergic system.

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