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ORIGINAL INVESTIGATION

David C. Jewett · Henry I. Mosberg
James H. Woods

Discriminative stimulus effects of a centrally administered, delta-opioid peptide (D-Pen^2-D-Pen^5-enkephalin) in pigeons

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Abstract The present study assessed the discriminative stimulus effects of the delta-opioid agonist [D-Pen^2-D-Pen^5]enkephalin (DPDPE) in pigeons. Food-restricted pigeons were trained to discriminate between ICV injections of 100 μg [D-Pen^2-D-Pen^5]enkephalin (DPDPE) and saline in a two-key operant procedure; acquisition of discriminative control was rapid (14–28 daily sessions). [D-Ser^2, Leu^5, Thr^6]enkephalin (DSLET) and [D-Ala^2]deltorphin II, peptides selective for delta-opioid receptors, produced discriminative stimulus effects similar to DPDPE, and were approximately equipotent to DPDPE. The non-peptidic, delta-opioid agonist BW373U86 (0.032–100 mg/kg, IM) partially generalized to DPDPE. The kappa-opioid agonist U69,593 (0.01–1 mg/kg, IM), and the mu-opioid agonists, DAMGO (0.1–3.2 μg, ICV) and morphine (1–10 mg/kg, IM), did not produce discriminative stimulus effects similar to DPDPE, up to doses that markedly decreased response rates. Naltrindole (0.1 mg/kg, IM), an antagonist selective for delta-opioid receptors, produced approximately a 30-fold reduction in the potency of DPDPE. DPDPE's discriminative stimulus effect in pigeons appears to be mediated through a delta-opioid receptor; this effect may provide a procedure for assessing delta-opioid receptor function in vivo.

Key words [D-Pen^2-D-Pen^5]enkephalin (DPDPE) · [D-Ser^2, Leu^5, Thr^6]enkephalin (DSLET) · [D-Ala^2]deltorphin II · BW373U86 · Drug discrimination · Pigeons · Delta opioids · Operant behavior

D. C. Jewett (✉) · J. H. Woods
Department of Pharmacology,
University of Michigan Medical School, 1301 MSRB III,
Ann Arbor, MI 48109-0632, USA

H. I. Mosberg
Department of Medicinal Chemistry,
University of Michigan Medical School,
Ann Arbor, MI 48109-0632, USA

Introduction

Opioids produce their effects through three major types of opioid receptors, mu, kappa, and delta. Drug discrimination studies using receptor-selective agonists and antagonists have made important contributions in characterizing these receptors. Distinct discriminative stimulus effects of mu- and some kappa-opioid agonists have been characterized in pigeons. For example, bremazocine produced discriminative stimulus effects similar to those of another highly selective kappa agonist, U50,488, but neither produced morphine-like discriminative stimulus effects (Picker and Dykstra 1987; although some kappa-opioid agonists do produce morphine-like discriminative effects, see Herling et al. 1980). A larger dose of naloxone is required to reduce the potency of U50,488 as a discriminative stimulus than is required to reduce morphine's potency (Picker and Dykstra 1987). Discriminative stimulus effects of delta-opioid receptor agonists, however, have not been studied extensively. One possible reason for the paucity of drug discrimination information on delta-opioid agonists is that most agonists at delta-opioid receptors are peptides, have difficulty crossing the blood-brain barrier, and probably need to be administered centrally.

To date, only one study has demonstrated discriminative stimulus effects mediated through a delta-opioid receptor (Comer et al. 1993). The discriminative stimulus effects of IM BW373U86 were antagonized by small doses of naltrindole, which is more potent in antagonizing delta-opioid effects than mu- or kappa-opioid mediated effects. Interestingly, central administration of the prototypic delta-opioid receptor agonists DPDPE and DSLET did not produce a discriminative stimulus similar to that of BW373U86. Additionally, a portion of BW373U86's discriminative stimulus effects were shared with mu-opioid agonists. Systemically administered morphine, alfentanil, and etonitazene all produced partial generalization to the BW373U86 discriminative stimulus, and BW373U86 partially generalized to morphine in pigeons trained to discriminate 5.6 mg/kg morphine from saline.

Few studies have *established* discriminative stimulus effects based on centrally administered compounds (see, however, Jewett et al. 1991, 1993). Some studies have assessed the ability of proposed delta-opioid agonists (e.g. D-Ala^2, D-Leu^5-enkephalin; DADLE) to produce discriminative stimulus effects similar to mu-opioid agonists. In rats, centrally administered DADLE produced discriminative stimulus effects similar to fentanyl, but not ethylketocyclazocine (Shearman and Herz 1982). In rats trained to discriminate morphine from saline, ICV DADLE produced a morphine-like discriminative stimulus but ICV [D-Pen^2-L-Pen^5]enkephalin (DPLPE), which has greater selectivity for delta-opioid receptors than DADLE, did not (Ukai and Holtzman 1988). That DPLPE did not produce its effects through mu- or kappa-opioid receptors does not prove that DPLPE, and agonists more selective than DPLPE for delta-opioid receptors, produce their effects through delta-opioid receptors.

The goals of the present study were to establish a discrimination based on the central administration of DPDPE, a peptide highly selective for delta opioid receptors (Mosberg et al. 1983). The ability of selective agonists for mu- (DAMGO, morphine), kappa- (U69,593) or delta- (BW373U86, DSLET, deltorphin II) opioid receptors and a non-opioid (cocaine) to produce discriminative stimulus effects similar to DPDPE was also assessed. To demonstrate further the receptor selectivity of DPDPE's discriminative stimulus effects, experiments were performed using naltrindole, an antagonist selective for delta-opioid receptors.

Materials and methods

Subjects

Ten experimentally naive white Carneaux pigeons were used in the present studies. All pigeons were maintained at 80% of their free-feeding weight by mixed grain availability during experimental sessions and Purina Pigeon Checkers received post-session in the home cage. All subjects were housed individually with water and grit freely available.

Apparatus

Experimental sessions were conducted in operant chambers (36×28×33 cm high) equipped with three translucent response keys (2.4 cm diameter) that could be illuminated by 7-W red lights located behind each key. Food was presented via a hopper that pivoted into an opening located below the center response key. Operant chambers were located in ventilated, sound-attenuating cubicles. Experimental contingencies were arranged and data were recorded by MED-PC software (MED Associates, East Fairfield, Vt.) and an IBM PC computer, located in an adjacent room.

Surgery

The details of the surgical procedure have been described previously (France et al. 1985). Briefly, pigeons were anaesthetized with 2.5–2.75 ml/kg Chloropent (chloral hydrate and pentobarbital: Fort Dodge Laboratories, Fort Dodge, Iowa) and 8 mg/kg ketamine. A chronic, indwelling cannula (Plastic Products, Roanoke, Va.) was implanted in the right lateral ventricle using stereotaxic procedures and a Rezvin adapter (Karten and Hodos 1967). A 28 g dummy cannula was inserted into the guide cannula except during ICV injections. The patency of the cannula was assessed by ICV injection of radioopaque dye (Conray: Mallinckrodt, St Louis, Mo.) or by catalepsy induced by 17.2 μg 2-amino-5-phosphonovalerate (Koek et al. 1985; AP5; Sigma, St Louis, Mo.).

Procedures

Discrimination training

Pigeons were initially trained to peck a single (center) illuminated key to obtain access to mixed grain by the method of successive approximations. Initially, one key-peck produced food access. This response requirement was gradually increased until 20 key-pecks were required to produce access to mixed grain (FR 20; Ferster and Skinner 1957). When responding was reliable (greater than 1.5 responses/s), pigeons were implanted with cannulae in the right lateral ventricle. Following surgery and a 1-week recovery period, discrimination training began.

Pigeons were trained to discriminate between an ICV injection of 100 μg DPDPE and an equal volume (10 μl) of saline. Daily training sessions consisted of one trial per day. The first three training sessions were preceded by an injection of saline, after which the pigeon was placed in the operant chamber for 10 min. During this time, the chamber was dark, and responses had no programmed consequences. At the end of the pretreatment time, the left key was illuminated, and 20 responses on the key produced 5-s access to mixed grain. The training session continued until 25 reinforcers were earned or 30 min, whichever occurred first. The next three training trials were preceded by an injection of 100 μg DPDPE, and following the 10-min pretreatment period, only the right key was illuminated. Pecks on this key produced access to mixed grain under an FR 20. Following these six sessions, discrimination training began. These training sessions consisted of an injection of either DPDPE (100 μg) or saline, the 10-min pretreatment period, and a 30-min response period. Both response keys were illuminated during the response period. Responses on the injection-appropriate key (right following DPDPE; left following saline administration) were reinforced by 5-s access to mixed grain under an FR 20. Responses on the incorrect key had no programmed consequences. Sessions preceded by DPDPE and saline alternated randomly with the restriction that no more than two consecutive sessions of DPDPE or saline administration occurred.

Discriminative control was defined as 1) greater than 50% of the responses prior to the first reinforcer delivery, and 2) greater than 90% of the responses for the total session, on the injection-appropriate key. Additionally, response rates were required to be greater than one response/s. Before discrimination testing began, subjects were required to meet these criteria for eight consecutive training sessions. Thereafter, tests were conducted whenever criteria were met for two consecutive sessions (a session preceded by DPDPE, and a session preceded by saline administration).

Discrimination testing

A single dosing procedure was used to assess the time course of DPDPE's (100 μg) discriminative stimulus effects in five pigeons. The stimulus effects were evaluated 0, 5, 10, 20, 40, 80, 160, and 320 min after a single injection of 100 μg DPDPE. At each time point, a response period was initiated during which pigeons obtained access to food by for pecking either response key under an FR 20. The response period continued for 5 min, or until ten reinforcers were delivered.

Tests assessing the ability of DPDPE and other drugs to either produce discriminative stimulus effects similar to those of 100 μg DPDPE, or to antagonize the discriminative stimulus effects of DPDPE involved the use of cumulative dosing procedures. The testing procedure consisted of several trials composed of a 10-min time-out period, and a response period. During the response peri-

od, 20 responses on either key resulted in food presentation, and continued for 5 min, or until ten reinforcers were delivered. After each trial, additional drug was administered (in 1/2 or 1/4 log unit increments) and a new trial began. This sequence continued until responding was reduced to less than 0.3 responses/s or until the solubility limit of the test drug precluded additional testing. Two groups of pigeons (n=5 per group) were used in the present studies. In one group, tests were conducted with DPDPE, DSLET, and deltorphin II (all administered ICV). These pigeons also received IM injections of morphine, U69,593 and BW373U86 prior to test sessions. Another group of pigeons were tested with increasing doses of DPDPE (ICV), DAMGO (ICV), and cocaine (IM). Additionally, these pigeons received naltrindole (IM) 15 min prior to increasing doses of DPDPE.

Data analysis

Results are presented as the mean (±SEM) percentage of responses on the DPDPE-appropriate key as a function of dose. Compounds were considered to have partially generalized to DPDPE if they resulted in greater than 10%, but less than 90% DPDPE-appropriate responding. Compounds completely generalized to DPDPE if they resulted in at least 90% responding on the DPDPE-appropriate key. Response rates are expressed as means (±SEM) and are plotted as a function of dose administered. ED_{50}s were calculated using procedure #8 in the Pharmacological Calculation System of Tallarida and Murray (1987). This procedure does not exclude data points less than 20% or greater than 80% effect levels. Reductions in DPDPE's potency by naltrindole are expressed as a dose ratio (DR) between the ED_{50} of DPDPE in the presence of 0.1 mg/kg naltrindole and the ED_{50} of DPDPE alone. ED_{50} values for DPDPE and DPDPE in combination with naltrindole were considered to be significantly different if the 95% confidence limits did not overlap. In vivo apparent pK_B values were determined for naltrindole in combination with DPDPE using the equation pK_B=–log [B/(DR–1)] (Negus et al. 1993). The variable "B" equals the dose of naltrindole in mol/kg.

Drugs

[D-Pen^2, D-Pen^5]enkephalin, [D-Ser^2, Leu^5, Thr^6]enkephalin (DSLET), [D-Ala^2]deltorphin II (all synthesized by H. I. Mosberg and colleagues), U69,593 (Upjohn Co., Kalamazoo, Mich.), morphine sulfate (Mallinckrodt, St Louis, Mo.), [D-Ala^2, NMePhe^4-Met(O)^5-(ol)]enkephalin (DAMGO) (Sigma, St Louis, Mo.), naltrindole and cocaine (National Institute on Drug Abuse, Rockville, Md.) were dissolved in sterile water or saline (0.9%).

Results

DPDPE acquisition and duration of discriminative effects

Pigeons rapidly learned to discriminate DPDPE from saline. Stimulus control was attained in an average of 22 daily sessions (range 14–28) from the beginning of the "choice" procedure to the session immediately preceding the eight consecutive sessions demonstrating stimulus control. During these eight sessions, every pigeon averaged greater than 92% injection-appropriate responding prior to the first reinforcer, and greater than 97% injection-appropriate responding for the entire session. Response rates were unaffected following administration of 100 μg DPDPE (2.0±0.2 r/s) or saline (2.2±0.3 r/s). DPDPE produced dose-dependent increases in DPDPE-appropriate responding (Fig. 1, panel A). Following 32 μg DPDPE, four of five pigeons responded the DPDPE-appropriate key, and complete generalization occurred after 100 μg DPDPE. Subjects responded on the saline-appropriate key following administration of ICV saline (10 μl, ICV).

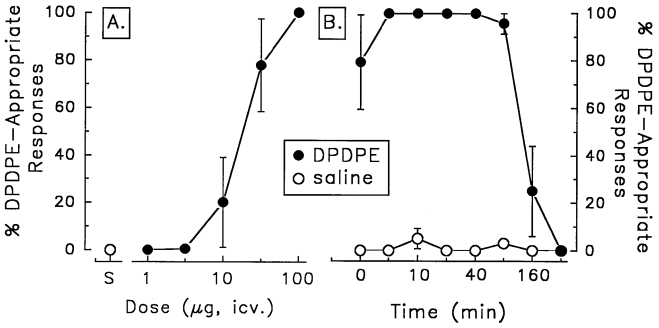

Fig. 1 **A** DPDPE dose-effect curve in pigeons trained to discriminate 100 μg DPDPE from saline. Response rates were not affected by DPDPE administration (data not shown). **B** Time course of the discriminative stimulus effects of 100 μg DPDPE. Points are means (±SEM), n=5

The training dose of DPDPE (100 μg) had a rapid onset and long duration of action (Fig. 1, panel B). Four of five pigeons responded exclusively on the DPDPE-appropriate key immediately after DPDPE administration. All subjects responded on the DPDPE-appropriate key 5 min after administration, and responded on this key up to 80 min after DPDPE administration. After 160 min, only 25% of the responses were emitted on the DPDPE-appropriate key. No DPDPE-appropriate responding was observed 320 min after its administration. Response rates were not affected by this dose of DPDPE (data not shown). Subjects responded on the saline-appropriate key following administration of ICV saline (10 μl, ICV) at all time points tested.

Discrimination tests

DSLET and deltorphin II, administered ICV, caused a dose-dependent increase in DPDPE-appropriate responding (Fig. 2, top panel). DSLET was 10- to 30-fold more potent than deltorphin II and DPDPE in three of the pigeons tested, but DPDPE, DSLET, and deltorphin II resulted in greater than 90% DPDPE-appropriate responding in all pigeons following 100 μg. Response rates were not affected by any doses of DSLET and deltorphin II tested. No DPDPE-appropriate responding was observed following ICV injections of DAMGO, although doses of 1 μg or greater markedly reduced responding (Fig. 2, bottom panel).

The ability of mu- and kappa-opioids and cocaine to produce a discriminative stimulus similar to DPDPE was also assessed. Intramuscularly administered morphine, U69,593, and cocaine did not produce discriminative stimulus effects similar to those of DPDPE (Fig. 3) although these drugs markedly reduced responding. On the other hand, BW373U86, an agonist selective for delta-opioid receptors, produced 30–60% DPDPE-appropriate responding over a wide dose range (0.1–32 mg/kg, IM).

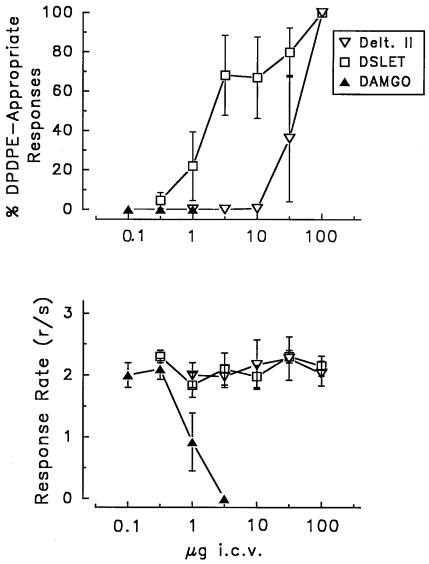

Fig. 2 Dose-effect curves for ICV Deltorphin II (*Delt. II*), DSLET and DAMGO in pigeons trained to discriminate DPDPE (100 μg) from saline. *Top panel*: *ordinate*: percentage of DPDPE-appropriate responses. *Abscissa*: agonist of dose (log scale). *Bottom panel*: response rate expressed in responses/s as a function of dose. Points are means (±SEM), *n*=5

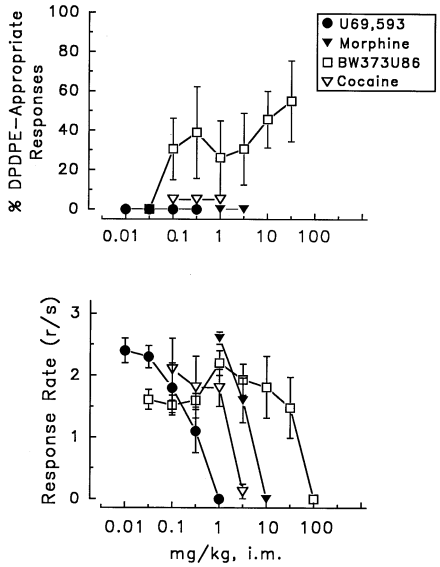

Fig. 3 Dose-effect curves for IM morphine, U69,593, BW373U86 and cocaine in pigeons trained to discriminate ICV DPDPE (100 μg) from saline. *Top panel*: percentage of DPDPE-appropriate responses. *Bottom panel*: response rate (responses/s). Points are means (±SEM), *n*=5

Naltrindole antagonism of DPDPE discriminative stimulus effects

As shown in Fig. 4, administration of increasing doses of DPDPE produced dose-related increases in DPDPE-appropriate responding. Complete generalization (>90% DPDPE-appropriate responding) occurred after administration of 32 μg DPDPE in these pigeons. Response rates

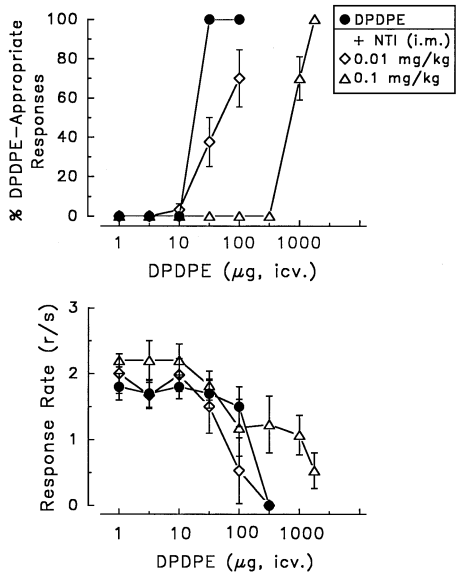

Fig. 4 Effects of naltrindole (0.01 and 0.1 mg/kg) on the discriminative stimulus and rate-decreasing effects of DPDPE. *Top panel*: percentage of DPDPE-appropriate responses. *Bottom panel*: response rate (responses/s). Points are means (±SEM), *n*=5

were unaffected following 1–100 μg DPDPE, but responding was suppressed following 320 μg.

Pretreatment with naltrindole (0.01–0.1 mg/kg IM) produced a dose-dependent shift in the discriminative stimulus effects of DPDPE (Fig. 4). Naltrindole (0.1 mg/kg, IM), produced approximately a 30-fold reduction in the potency of DPDPE to produce its discriminative stimulus and response rate decreasing effects. The apparent pK_B value for naltrindole (0.1 mg/kg) against DPDPE was 8.3.

Discussion

The goals of the present studies were to establish DPDPE as a discriminative stimulus and to determine the opioid receptor type mediating this effect. The present studies demonstrate that DPDPE was discriminable, and that its discriminative stimulus effects were mediated through a delta-opioid receptor. Administration of the peptidic, delta-opioid agonists DSLET and deltorphin II resulted in DPDPE-appropriate behavior. DPDPE, DSLET and deltorphin II were equipotent in producing DPDPE-like discriminative stimulus effects in pigeons, although DSLET was more potent in three of five pigeons tested. In mice, DPDPE and deltorphin II both produced antinociceptive effects, assessed using the warm-water tail-withdrawal assay, and both were antagonized by delta-receptor-selective antagonists (e.g., Jiang et al. 1990). In mice, deltorphin II was 3-fold more potent than DPDPE in producing antinociceptive effects, and tolerance developed to deltorphin II and DPDPE, but no cross-tolerance was found between them, suggesting that these effects were produced through different sub-

types of delta-opioid receptors (Mattia et al. 1991). In the present study, the finding that deltorphin II and DSLET produced discriminative stimulus effects similar to DPDPE suggests that a similar receptor type mediates this effect in pigeons.

Only one previous study has described the acquisition of discriminative stimulus effects mediated through delta-opioid receptors in pigeons (Comer et al. 1993). Although BW373U86's discriminative stimulus effects were antagonized by small doses of naltrindole, its stimulus effects, were partially mediated through mu-opioid receptors. The mu-opioid agonists morphine, alfentanil, and etonitazene produced some BW373U86-appropriate responding. Also, BW373U86 produced some morphine-appropriate responding. These results suggested that mu-opioid receptors are at least partially involved in the discriminative stimulus effects of BW373U86. In pigeons trained to discriminate DPDPE from saline, BW373U86 produced some DPDPE-like discriminative stimulus effects over a wide dose range. Taken together, these findings are consistent with the notion that BW373U86's discriminative stimulus effects are comprised of both a delta-opioid component and mu-opioid component.

Discrimination tests did not provide evidence for other opioid receptor mechanisms or cocaine-related mechanisms modulating the discriminative stimulus effects of DPDPE. Mu-opioid agonists DAMGO (ICV) and morphine (IM) failed to produce a discriminative stimulus effect similar to DPDPE at active doses. The kappa-opioid agonist U69,593 and cocaine (IM) did not produce DPDPE-like discriminative stimulus effects. In rats, some studies have revealed interactions between delta-opioid receptor mechanisms and cocaine related mechanisms. For example, in rats trained to discriminate cocaine from saline, DPLPE produced discriminative stimulus effects similar to those of cocaine (Ukai et al. 1993). In addition, naltrindole and naltriben, antagonists selective for delta-opioid receptors produced a small (2-fold), but significant, reduction in the potency of cocaine to produce its discriminative stimulus effects in rats (Suzuki et al. 1994). Taken together, these studies suggest delta-opioids can modulate the discriminative stimulus effects of cocaine in rats. In the present study, however, we found no evidence for cocaine producing discriminative stimulus similar to those of DPDPE in pigeons.

In order to evaluate further the notion that delta-opioid receptors mediate the discriminative stimulus effects of DPDPE, studies were performed with naltrindole, an antagonist selective for delta-opioid receptors. A small dose of naltrindole (0.1 mg/kg, IM) antagonized the discriminative stimulus and rate decreasing effects of DPDPE by approximately 30-fold. Small doses of naltrindole have previously been found to antagonize the discriminative stimulus of BW373U86, but not those of the mu-opioid agonist morphine (Comer et al. 1993). Also, naltrindole was 32- to 100-fold more potent in antagonizing the discriminative stimulus and rate-decreasing effects of DPDPE than reducing the potency of morphine to produce discriminative stimulus (Comer et al. 1993) and response rate decreasing effects (D.C. Jewett, unpublished observations). The apparent pK_B value for naltrindole with DPDPE (8.3) was similar to the apparent pA_2 value obtained by Comer et al. (1993) for naltrindole with BW373U86 in the pigeon (7.9±0.5).

The discriminative stimulus effects of DPDPE were acquired rapidly. Subjects learned to discriminate DPDPE from saline in 14–28 sessions. Few studies have established discriminative stimulus effects using a centrally administered drug. In those instances, the training drug's discriminative stimulus effects have been rapidly acquired (within 14 daily sessions; Jewett et al. 1991, 1993). At present, it is unclear if discriminative stimulus effects are acquired faster via central administration. Further research with a variety of compounds, especially those that can be established as discriminative stimuli by systemic administration, would be useful to address this issue.

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