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Cocaine and other indirect-acting monoamine agonists differentially attenuate a naltrexone discriminative stimulus in morphine-treated rhesus monkeys

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ABSTRACT

Monoaminergic drugs can modify opioid withdrawal in non-humans and cocaine is reported to attenuate opioid withdrawal in humans. Drug discrimination was used to examine whether s.c. cocaine or other indirect-acting monoamine agonists attenuate morphine (3.2 mg/kg/day) withdrawal induced by naltrexone and by 27 h of morphine deprivation. Naltrexone-precipitated withdrawal was attenuated not only by morphine, but also by cocaine, amphetamine and imipramine. However, reversal of naltrexone-precipitated withdrawal was greater for morphine than for any of the indirect-acting monoamine agonists. Attenuation of the naltrexone discriminative stimulus by indirect-acting monoamine agonists was pharmacologically selective insofar as drugs lacking affinity for monoamine transporters (ketamine and triazolam) were without effect. Twenty-seven hours of morphine deprivation occasioned naltrexone-lever responding and decreased response rate, and both effects were reversed by morphine, cocaine and amphetamine and not by imipramine, desipramine, ketamine and triazolam. Thus, indirect-acting monoamine agonists attenuate some (e.g. discriminative) aspects of naltrexone-precipitated withdrawal, whereas only indirect-acting agonists with high affinity for dopamine transporters attenuate deprivation-induced withdrawal. These results suggest that dopamine is differentially involved in naltrexone- and deprivation-induced withdrawal and support the notion that opioid-dependent individuals use stimulants, in part, to attenuate withdrawal.

Many opioid-dependent individuals (30-80%) use cocaine (Leri et al., 2003 for review), and this form of polydrug abuse might be related to positive subjective effects that result from co-administration of cocaine and opioids. For example, combined administration of cocaine and μ opioid agonists can increase the positive and decrease the negative subjective ratings of each drug alone (Kosten et al., 1986; 1987; Foltin and Fischman, 1992; Preston et al., 1996; Walsh et al., 1996), though such interactions are not unanimously apparent (Foltin and Fischman, 1996). Interactions between cocaine and μ opioid agonists also have been observed in non-humans. For example, the discriminative stimulus effects of cocaine or a μ opioid agonist are enhanced by their co-administration under some (Negus et al., 1998; Platt et al., 1999; Rowlett et al., 2001; Negus and Mello, 2002) and not other conditions (Mello et al., 1995; Suzuki et al., 1995). Thus, opioid-dependent individuals might combine an opioid with cocaine to enhance some effects of the individual drugs.

Clinical reports suggest opioid-dependent individuals might also use cocaine to specifically attenuate signs (e.g. sweating and tearing) and symptoms of opioid withdrawal (irritability and nausea). For example, cocaine reportedly attenuated opioid withdrawal and, in some cases, was used to achieve abstinence from opioids (Freud, 1887; Hunt et al., 1984; Kosten and Kosten, 1989; Rosen et al., 1992), though cocaine reportedly exacerbated withdrawal from larger doses of opioids (Stine and Kosten, 1994). Studies in rodents also suggest that stimulants (i.e. indirect-acting monoamine agonists) can modify signs of opioid withdrawal (e.g. jumping and teeth chattering). For example, relatively small doses of monoamine uptake inhibitors (e.g. cocaine and desipramine) and releasers (e.g. amphetamine) enhanced signs of opioid withdrawal in rodents, while larger doses of these compounds decreased withdrawal signs (e.g. Herz et al., 1974; Maruyama and Takemori, 1973). Other

studies reported that monoamines attenuated opioid withdrawal, perhaps because larger doses of indirect-acting monoamine agonists induce behaviors (e.g. stereotypy) that are incompatible with the expression of withdrawal. Thus, a definitive role for monoamines in opioid withdrawal has been difficult to establish using observational procedures.

Drug discrimination has been used to examine the consequences of daily opioid treatment in opioid-treated animals trained to discriminate an opioid antagonist. For example, in rhesus monkeys receiving 3.2 mg/kg/day of morphine and discriminating naltrexone (France and Woods, 1989), naltrexone-lever responding occurs not only when naltrexone is administered but also when morphine treatment is temporarily discontinued (27 h). This type of discrimination appears to be related specifically to withdrawal and not to the absence of opioid treatment or a no-drug condition (Easterling and Holtzman, 1999). The discriminative stimulus effects of naltrexone appear to measure aspects of withdrawal that differ from directly-observable signs of withdrawal (e.g. Gellert and Holtzman, 1979); thus, the naltrexone discriminative stimulus might be relatively unaffected by the unconditioned effects of indirect-acting monoamine agonists (stereotypy). In the present study, a naltrexone discrimination assay in morphine-treated monkeys was used to examine whether cocaine and other indirect-acting monoamine agonists (amphetamine, imipramine and desipramine) attenuate withdrawal induced by naltrexone and by acute morphine deprivation. Morphine was included as a positive control and other compounds (ketamine and triazolam) were included to examine the pharmacologic specificity of any effects of cocaine and other indirect-acting monoamine agonists.

Methods

Subjects. Three adult rhesus monkeys (Macaca mulatta, one male and two females, 6.7-7.8 kg) were housed individually in stainless steel cages with free access to water. Monkeys received chow (High Protein Monkey Diet; Harlan Teklad, Madison, WI) twice daily and fresh fruit following experimental sessions. Two subjects were previously trained to respond under fixed-ratio (FR) schedules (stimulus shock termination) and had received opioid agonists and antagonists in previous studies (e.g. Gauthier and France, 1999). A third monkey received morphine (3.2 mg/kg/day) for nine months and was otherwise pharmacologically and experimentally naïve prior to these studies. Monkeys were maintained in accordance with the Institutional Animal Care and Use Committee, The University of Texas Health Science Center at San Antonio, as well as the Guide for the Care and Use of Laboratory Animals [Institute of Laboratory Animal Resources on Life Sciences, National Research Council; Department of Health, Education and Welfare, Publication No. (NIH) 85-23, revised 1996].

Apparatus. Monkeys were seated in primate chairs (Model R001, Primate Products; Miami, FL) that provided restraint at the neck and shoulders. During experimental sessions monkeys were placed in ventilated, sound-attenuating operant chambers containing two response levers and a red light above each lever. Each chair was equipped with a pair of shoes containing brass electrodes for delivering a brief shock (250 ms, 3 mA) from an A/C generator. Experimental procedures were controlled and data collected by a computer and commercially available software (Med Associates, Inc.; St. Albans, VT).

Behavioral Procedure. Monkeys received morphine (3.2 mg/kg) once daily and were trained 3 h later to discriminate naltrexone (0.0178 mg/kg) from saline (France and Woods, 1989). Each session consisted of 2-8 15-min cycles with each cycle beginning with a 10-min

timeout, during which the chamber was dark and lever presses had no programmed consequence. This was followed by a 5-min response period during which monkeys could respond under an FR5 schedule of stimulus-shock termination with shocks scheduled to occur every 15 s. The lights were illuminated at the beginning of the 15-s period and monkeys could postpone scheduled shock for 30 s by completing five consecutive responses on the correct lever. The correct lever was determined by an injection of either saline or naltrexone (0.0178 mg/kg) administered during the first minute of the cycle. The left lever was correct following saline and the right lever was correct following naltrexone for two monkeys, while the lever assignments were reversed for the third monkey. Responses on the incorrect (injection-inappropriate) lever reset the response requirement on the correct (injection-appropriate) lever. Failure to satisfy the FR within 15 s resulted in the delivery of shock. After 5 min or four shocks, the response period ended and the lights were extinguished. One “sham” injection cycle followed a cycle in which naltrexone was administered and 0-6 saline-injection cycles preceded the naltrexone-injection cycle. On some training days monkeys received only saline or “sham” prior to each of 2-8 cycles.

For the experimentally naïve monkey, the criteria for testing was defined as 5 consecutive or 6 of 7 days in which at least 80% of the total responses occurred on the lever designated as correct and fewer than five responses (one FR) occurred on the incorrect lever prior to completion of the FR on the correct lever. For the two monkeys previously trained to discriminate naltrexone, test drugs were administered every third day as long as performance during intervening training sessions satisfied the same criteria as above. Parameters for test sessions were the same as for training sessions except that five consecutive responses on either lever postponed scheduled shock. Naltrexone dose-effect curves were determined 3 h after

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morphine by administering saline at the beginning of the first cycle, followed by increasing doses of naltrexone in 0.5 log U increments at the beginning of subsequent cycles. When a test drug was combined with naltrexone, a dose of the test drug was administered at the beginning of the first cycle, followed by increasing doses of naltrexone in 0.5 log U increments at the beginning of subsequent cycles, up to doses that occasioned at least 80% naltrexone-lever responding or up to a dose of 1.0 mg/kg of naltrexone. Doses of test compounds studied with naltrexone were as follows: cocaine (0.32-1.78 mg/kg), amphetamine (0.1-1.0 mg/kg), imipramine (1.0-17.8 mg/kg), and desipramine (3.2-17.8 mg/kg). Test drugs also were studied in 27-h morphine-deprived monkeys (i.e. saline was administered 3 h before a test session); under these conditions monkeys respond predominantly on the naltrexone lever. Saline or vehicle was administered in the first cycle of these tests followed by increasing doses of a test compound in subsequent cycles up to doses that occasioned less than 20% naltrexone-lever responding, that resulted in delivery of shock, or to the largest doses that could be safely studied. Doses of test compounds studied after 27 h of morphine deprivation were as follows: morphine (0.1-5.6 mg/kg), cocaine (0.01-1.0 mg/kg), amphetamine (0.01-1.78 mg/kg), imipramine (0.32-17.8 mg/kg), desipramine (0.32-17.8 mg/kg), ketamine (0.1-5.6 mg/kg), and triazolam (0.01-0.56 mg/kg).

Drugs. All drugs were administered s.c. in a volume of 0.1-1.0 ml and doses were expressed as the forms indicated below. The compounds studied were morphine sulphate, naltrexone hydrochloride, cocaine hydrochloride, amphetamine hydrochloride (The Research Technology Branch, NIDA, Rockville, MD), imipramine hydrochloride (ICN Biomedical Inc., Aurora, OH), desipramine hydrochloride, haloperidol (Sigma Chemical Co., St Louis, MO), ketamine hydrochloride (Fort Dodge Laboratories, Fort Dodge, IA), and triazolam (Pharmacia

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and Upjohn, Kalamazoo, MI). All drugs were dissolved in sterile distilled water or 0.9% saline, except triazolam, which was dissolved in 50% Emulphor and 50% ethanol. Solutions were heated and sonicated as needed.

Data Analyses. Drug discrimination data were plotted as the percent of total responses on the naltrexone-lever (% drug-responding; % DR) averaged among monkeys (± S.E.M.) and plotted as a function of dose. When a test with a given compound was conducted more than once, the determinations were averaged for an individual subject for further analyses. Attenuation of naltrexone-lever responding in morphine-deprived monkeys was defined as less than or equal to 20% responding on the naltrexone-lever. Doses of naltrexone (during morphine treatment) and morphine, cocaine and amphetamine (during acute morphine withdrawal) to produce 50% drug-appropriate responding (ED_{50}) and the 95% confidence limits (95% CL) were estimated using linear regression by using more than two appropriate data points, otherwise by interpolation. These values were determined first for individual monkeys and then averaged among all monkeys. ED_{50}s determined for naltrexone in combination with other drugs were considered to be significantly different from control when the 95% CLs for the ED_{50}s did not overlap. Doses and 95% CL of morphine, cocaine, amphetamine and imipramine to increase the ED_{50} of naltrexone 2-fold were estimated from the group averaged data using linear regression. Control response rate represents the average of the five saline training sessions immediately preceding a test. Response rate was calculated as a percentage of control for individual animals, then averaged among subjects (± S.E.M.) and plotted as a function of dose.

Results

The effects of morphine, cocaine and other drugs in morphine-treated monkeys. The experimentally naïve monkey treated with 3.2 mg/kg/day of morphine discriminated naltrexone from saline after 137 training sessions. Naltrexone increased responding on the training-drug associated lever in a dose-related manner in all three monkeys with a dose of 0.01 mg/kg occasioning predominantly naltrexone-lever responding in all morphine-treated monkeys (Figs. 1-7, top, closed circles). The naltrexone ED_{50} (95 % CL) was 0.0053 mg/kg (0.0038-0.0070) (Table 1). Administration of saline during the first cycle of these tests occasioned responding predominantly on the saline-lever (Figs. 1-7, top, V). A dose of 0.01 mg/kg of naltrexone decreased response rate to approximately 65% of control (Figs. 1-7, bottom, closed circles). Acute pretreatment with morphine (3.2-32.0 mg/kg), in addition to daily treatment with 3.2 mg/kg of morphine, attenuated the naltrexone discriminative stimulus (Fig. 1); doses of 10.0 and 32.0 mg/kg of morphine increased the ED_{50} of naltrexone 3.5- and 5.8-fold (Table 1). Morphine did not substantially modify response rate when administered alone (Fig. 1, bottom).

Pretreatment with various doses of cocaine or amphetamine 3 h after morphine (3.2 mg/kg) did not occasion naltrexone-lever responding (Figs. 2 and 3, top, V). A dose of 1.0 mg/kg of cocaine attenuated the naltrexone discriminative stimulus (i.e., shifted the naltrexone dose-effect curve rightward; Fig. 2, top) as evidenced by a significant increase in the ED_{50} of naltrexone (2.1-fold; Table 1). The naltrexone dose-effect curve was not shifted further by a larger dose (1.78 mg/kg) of cocaine. Like cocaine, a dose of 1.0 mg/kg of amphetamine shifted the naltrexone dose-effect curve rightward (Fig. 3, top); however, one monkey responded a maximum of 74% on the naltrexone-lever up to a dose of 1.0 mg/kg of naltrexone (data not shown for doses of naltrexone greater than 0.1 mg/kg), and thus, a group average naltrexone

ED_{50} was not calculated following administration of 1.0 mg/kg of amphetamine. Smaller doses (0.1 and 0.32 mg/kg) of amphetamine did not significantly modify the naltrexone ED_{50} (Table 1). Cocaine and amphetamine did not substantially modify response rate when administered alone (Figs. 2 and 3, bottom, V) and slightly attenuated the rate-decreasing effects of larger doses of naltrexone (Figs. 2 and 3, bottom).

Pretreatment with various doses of imipramine 3 h after morphine (3.2 mg/kg) did not occasion naltrexone-lever responding (Fig. 4, top, V). A dose of 17.8 mg/kg of imipramine attenuated the naltrexone discriminative stimulus as evidenced by an increase in the naltrexone ED_{50} (2.2-fold), whereas smaller doses (1.0-10.0 mg/kg) of imipramine did not modify the naltrexone ED_{50} (Table 1). The rank order potency in shifting the naltrexone dose-effect curve 2-fold to the right during morphine treatment was amphetamine = cocaine = morphine = imipramine (Table 2). Although there was a trend for the largest dose (17.8 mg/kg) of desipramine to increase the naltrexone ED_{50} (2.3-fold), no dose of desipramine significantly modified the naltrexone ED_{50} (Fig. 5; Table 1). Imipramine and desipramine did not substantially modify response rate when administered alone or in combination with naltrexone (Figs. 4 and 5, bottom). Larger doses of imipramine and desipramine could not be safely administered.

Pretreatment with various doses of triazolam or ketamine 3 h after morphine (3.2 mg/kg) did not occasion naltrexone-lever responding (Figs. 6 and 7, top, V). Triazolam did not modify the discriminative stimulus effects of naltrexone up to a dose (0.032 mg/kg) that decreased response rate (Fig. 6, bottom; Table 1). In contrast, ketamine enhanced the naltrexone discriminative stimulus as evidenced by 2.1-fold decrease in the naltrexone ED_{50} after a dose of 3.2 mg/kg that also markedly decrease response rate (Fig. 7; Table 1).

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The effects of morphine, cocaine and other drugs in morphine-deprived monkeys. When saline was substituted for the daily injection of 3.2 mg/kg/day of morphine (i.e. 27-h morphine withdrawal), monkeys responded predominantly on the naltrexone lever (Figs. 8 and 9, V, all panels). Morphine dose-dependently attenuated the naltrexone-like discriminative stimulus effects of acute morphine withdrawal, with a dose of 5.6 mg/kg of morphine occasioning an average of 2% responding on the naltrexone lever (Fig. 8, top left). The ED_{50} (95% CL) of morphine was 1.11 (0.52-2.34) mg/kg. Response rate was decreased after 27 h of morphine deprivation and was dose-dependently increased to near control values by morphine (Fig. 8, bottom left). The naltrexone-like discriminative stimulus effects of acute morphine withdrawal also were dose-dependently attenuated by cocaine and amphetamine (Fig. 8, top middle and right). The largest doses of cocaine (1.0 mg/kg) and amphetamine (1.78 mg/kg) occasioned an average of 8% and 5%, respectively, responding on the naltrexone lever. The ED_{50} (95% CLs) of cocaine was 0.36 (0.15-0.65) mg/kg and the ED_{50} of amphetamine was 0.58 (0.13-1.33) mg/kg (Table 2). Decreases in response rate observed after acute morphine withdrawal were reversed by cocaine and amphetamine (Fig. 8, bottom middle and right).

Imipramine decreased naltrexone-lever responding to 65% at a dose of 10 mg/kg (Fig. 9, top left), with one monkey responding 20% on the naltrexone lever and two monkeys responding 76 and 100% on the naltrexone lever. A larger dose (17.8 mg/kg) of imipramine occasioned an average of 94% naltrexone-lever responding in the latter two monkeys. Larger doses of imipramine attenuated the rate-decreasing effects of acute morphine withdrawal (Fig. 9, bottom left). Desipramine, up to a dose of 10.0 mg/kg, decreased naltrexone-lever responding to 72% and did not alter the rate-decreasing effects of acute morphine withdrawal (Fig. 9, second from left). Triazolam (0.032 mg/kg) decreased naltrexone-lever responding to 74%; larger doses of

triazolam, including a dose (0.32 mg/kg) that decreased response rate to 23% of control, did not further decrease naltrexone-lever responding (Fig. 9, second from right). Ketamine, up to a dose of 3.2 mg/kg, decreased naltrexone-lever responding to 77% and decreased response rate to 20% of control; the next larger dose (5.6 mg/kg) of ketamine suppressed responding (Fig. 9, right).

Discussion

Cocaine and other indirect-acting monoamine agonists reportedly modify signs of opioid withdrawal, though it is not clear from observational procedures whether indirect-acting monoamine agonists attenuate opioid withdrawal or induce behaviors (e.g. stereotypy) that are incompatible with the expression of withdrawal. The present study used a naltrexone discrimination procedure to examine the effects of indirect-acting monoamine agonists on morphine withdrawal induced by naltrexone or by acute deprivation of morphine. In contrast to observational procedures, the naltrexone discrimination procedure appears to be specifically sensitive to interoceptive (e.g. subjective) effects of drugs and physiologic state. The naltrexone discriminative stimulus in morphine-treated monkeys was attenuated not only by morphine but also by cocaine, amphetamine and imipramine. Deprivation-induced withdrawal from morphine was fully attenuated by morphine, cocaine and amphetamine and not by imipramine or desipramine. The effects of cocaine and amphetamine were pharmacologically selective insofar as withdrawal was not attenuated by drugs that do not act at monoamine transporters (e.g. ketamine and triazolam). These results suggest that cocaine and amphetamine can attenuate some (e.g. discriminative stimulus) aspects of morphine withdrawal and are consistent with clinical observations in opioid-dependent subjects (Freud, 1887; Hunt et al., 1984; Stine and Kosten, 1994; Kosten and Kosten, 1989; Rosen et al., 1992).

Supplemental administration of morphine after daily treatment with 3.2 mg/kg of morphine markedly attenuated the naltrexone discriminative stimulus and produced orderly, parallel rightward shifts in the naltrexone dose-effect curve, consistent with a competitive interaction between morphine and naltrexone. Monoamine uptake inhibitors (cocaine and imipramine) and a releaser (amphetamine) also attenuated the naltrexone discriminative

stimulus, though their effects were quantitatively less than morphine. For example, a dose of 32.0 mg/kg of morphine fully attenuated the effects of naltrexone (0.01 mg/kg), whereas large doses of the indirect-acting monoamine agonists only partially decreased the effects of naltrexone (0.01 mg/kg), to approximately 50%. In contrast to morphine and indirect-acting monoamine agonists, a benzodiazepine (triazolam) did not modify the naltrexone discriminative stimulus, while an *N*-methyl-D-aspartate antagonist (ketamine) enhanced the naltrexone discriminative stimulus. It is not clear whether the latter result is due to pharmacologically selective interactions between ketamine and naltrexone in morphine-treated monkeys or to general disruption of stimulus control (Koek, 1999). Collectively, these results suggest that increasing monoamine transmission attenuates some features of antagonist-precipitated opioid withdrawal, though the attenuation of withdrawal by indirect-acting monoamine agonists is more limited than the attenuation of withdrawal by morphine.

In morphine-treated monkeys, the discriminative stimulus effects of naltrexone were qualitatively similar to 27 h of morphine deprivation. The naltrexone-like discriminative stimulus effects of acute morphine withdrawal were fully attenuated not only by morphine, but also by cocaine and amphetamine, demonstrating that cocaine and amphetamine were qualitatively similar to morphine under conditions of morphine deprivation. In contrast, cocaine and amphetamine did not fully substitute for the morphine-like agonist nalbuphine in untreated rhesus monkeys (Gerak and France, 1996), suggesting that attenuation of withdrawal was responsible for the morphine-like effects of cocaine and amphetamine. Cocaine and amphetamine had similar potency in reversing deprivation-induced withdrawal, whereas amphetamine was five times more potent than cocaine in shifting the naltrexone dose-effect curve to the right in morphine-treated monkeys (Table 2). It is not clear whether differences in

selectivity at monoamine transporters or differences in mechanism for increasing monoamine transmission are responsible for the quantitatively different effects of cocaine and amphetamine across the two conditions of withdrawal.

The naltrexone-like discriminative stimulus effects of acute morphine withdrawal were not attenuated by imipramine, desipramine, triazolam or ketamine up to doses that markedly decreased responding (triazolam and ketamine), that attenuated the naltrexone discriminative stimulus (imipramine), or that could be safely studied in morphine-treated monkeys (desipramine). Thus, even though acute morphine withdrawal mimics the discriminative stimulus effects of naltrexone, the two conditions might not be identical insofar as indirect-acting monoamine agonists with relatively low affinity for dopamine transporters (imipramine and desipramine) did not attenuate the naltrexone-like effects of acute morphine withdrawal. These results suggest that various monoamines are differentially involved in antagonist- and deprivation-induced opioid withdrawal. Dopamine has been shown to be altered under both conditions of withdrawal, e.g., dopamine efflux decreases in the ventral striatum and increases in the medial prefrontal cortex during both antagonist- and deprivation-induced opioid withdrawal in rats (Acquas et al., 1991; Pothos et al., 1991; Bassareo et al., 1995). Norepinephrine and serotonin also are altered during opioid withdrawal, e.g., norepinephrine efflux and locus coeruleus activity increase (Maldonado, 1997 for review) and serotonin efflux and turnover decrease (Yarbrough et al., 1973; Tao et al., 1998). However, it is not clear whether antagonist- and deprivation-induced opioid withdrawal differentially alter monoamine transmission.

Temporary discontinuation of drug treatment can decrease rate of responding and resumption of drug treatment can reverse this decrease in responding (e.g. Thompson and

Schuster, 1964), and thus, rate of responding can be a reliable index of drug withdrawal. In 27-h morphine-deprived monkeys, response rate was decreased to 50% of control (3 h after the last morphine injection); this decrease was reversed by re-administration of morphine (Fig. 3, bottom left). Cocaine and amphetamine, and not other drugs (e.g. desipramine, triazolam, and ketamine), also attenuated the rate-decreasing of acute morphine withdrawal. Thus, both naltrexone-lever responding and rate of responding appear to be sensitive to the withdrawal-reversing effects of a μ-opioid agonist and indirect-acting monoamine agonists. However, these results also might be influenced by the rate-increasing effects of cocaine, amphetamine, and related stimulants (e.g. Dews, 1958).

Signs of opioid withdrawal include jumping in rodents, abdominal rigidity and pupil dilation in primates, and sweating and tearing in humans, and many of these signs are attenuated not only by opioid agonists but also by other drugs such as the α_2-adrenoceptor agonist clonidine (Gellert and Holtzman, 1979; Jasinski et al., 1985; Woods and Gmerek, 1985; Katz, 1986; Fukase et al., 1994). Clonidine does not, however, attenuate the subjective ratings of opioid withdrawal (Jasinski et al., 1985), nor does clonidine attenuate the discriminative stimulus effects of naltrexone in morphine-dependent rats and monkeys (Gellert and Holtzman, 1979; France and Woods, 1989). Smaller doses of cocaine and amphetamine increase opioid withdrawal in rodents, whereas larger doses appear to decrease opioid withdrawal, perhaps because cocaine and amphetamine induce stereotypy and therefore prevent the normal expression of withdrawal (e.g. Herz et al., 1974). In contrast, cocaine and amphetamine attenuate a naltrexone discriminative stimulus in *l*-α-acetylmethadol-treated monkeys without decreasing signs induced by naltrexone in the same monkeys (Sell and France, 2002; Sell et al., unpublished observations). Collectively, these studies demonstrate that signs and subjective

ratings of withdrawal are differentially modified by drugs. The results of the present study suggest that cocaine and amphetamine attenuate opioid withdrawal by attenuating the discriminative stimulus, and perhaps subjective, effects of opioid withdrawal, a possible factor underlying cocaine use by opioid-dependent individuals.

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Footnotes

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[2]Recipient of a Research Career Award (DA00211).

Legends for figures

Fig. 1 **Discriminative stimulus and rate effects of naltrexone in morphine-treated monkeys that received supplemental morphine.** Abscissae: dose in milligrams per kilogram body weight; vehicle (V) or a dose of morphine was administered in the first cycle. Ordinates: mean (± S.E.M.) percentage of responding on the drug-appropriate lever (%DR = drug responding, top) and mean response rate expressed as percentage of control (saline training days) rate [rate (% of control), bottom].

Fig. 2 **Discriminative stimulus and rate effects of naltrexone in morphine-treated monkeys that received cocaine.** The control data are from Fig.1. See Fig. 1 for other details.

Fig. 3 **Discriminative stimulus and rate effects of naltrexone in morphine-treated monkeys that received amphetamine.** The triangle above 0.1 mg/kg of naltrexone represents responding from one monkey; all other points are averaged from three monkeys. The control data are from Fig.1. See Fig. 1 for other details.

Fig. 4 **Discriminative stimulus and rate effects of naltrexone in morphine-treated monkeys that received imipramine.** The control data are from Fig.1. See Fig. 1 for other details.

Fig. 5 **Discriminative stimulus and rate effects of naltrexone in morphine-treated monkeys that received desipramine.** The control data are from Fig.1. See Fig. 1 for other details.

Fig. 6 **Discriminative stimulus and rate effects of naltrexone in morphine-treated monkeys that received triazolam.** The control data are from Fig.1. See Fig. 1 for other details.

Fig. 7 **Discriminative stimulus and rate effects of naltrexone in morphine-treated monkeys that received ketamine.** The control data are from Fig.1. See Fig. 1 for other details.

Fig. 8 **Discriminative stimulus and rate effects of morphine, cocaine and amphetamine in monkeys acutely deprived of morphine (27 h).** Vehicle (V) was administered in the first cycle. See Fig. 1 for other details.

Fig. 9 **Effects of imipramine, desipramine, triazolam and ketamine in monkeys acutely deprived of morphine (27 h).** Vehicle (V) was administered in the first cycle. See Fig. 1 for other details.

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Table 1 Mean ED_{50} and 95% CL for the naltrexone discrimination dose-effect curve under control conditions and following pretreatment with cocaine, amphetamine, imipramine and desipramine.

Drug Dose	Naltrexone Discrimination ED_{50} (mg/kg)	95% CL
Control	0.0053	(0.0038-0.0070)
+ Morphine		
3.2 mg/kg	0.00930	(0.0021-0.00084)
10.0 mg/kg	0.0185 [a]	(0.0102-0.0339)
32.0 mg/kg	0.0305 [a]	(0.0158-0.0591)
+ Cocaine		
0.32 mg/kg	0.0053	(0.0048-0.0059)
1.0 mg/kg	0.0113 [a]	(0.0072-0.0162)
1.78 mg/kg	0.0118	(0.0061-0.0193)
+ Amphetamine		
0.1 mg/kg	0.0062	(0.0016-0.0142)
0.32 mg/kg	0.0073	(0.0043-0.0109)
1.0 mg/kg	ND [b]	
+ Imipramine		
1.0 mg/kg	0.0051	(0.0043-0.0060)
3.2 mg/kg	0.0101	(0.0043-0.0239)
10.0 mg/kg	0.0079	(0.0047-0.0133)
17.8 mg/kg	0.0117 [a]	(0.0076-0.0178)
+ Desipramine		
3.2 mg/kg	0.0058	(0.0056-0.0061)
10.0 mg/kg	0.0053	(0.0036-0.0078)
17.8 mg/kg	0.0120	(0.0057-0.0255)
+ Ketamine		
0.32 mg/kg	0.0037	(0.0017-0.0080)
1.0 mg/kg	0.0042	(0.0027-0.0064)
3.2 mg/kg	0.0025 [c]	(0.0017-0.0037)
+ Triazolam		
0.01 mg/kg	0.0068	(0.0044-0.0106)
0.032 mg/kg	0.0042	(0.0027-0.0064)

[a] greater than control ED_{50}

[b] ED_{50} not determined because of a decrease in the maximal effect of naltrexone in one of three monkeys

[c] less than control ED_{50}

Table 2 Mean dose and 95% CL for morphine, cocaine and amphetamine in shifting the naltrexone dose-effect curve 2-fold to the right during morphine treatment and mean ED_{50} and 95% CL for the same drugs in attenuating the naltrexone-like discriminative stimulus effects of acute morphine withdrawal.

	Morphine treatment		**Acute morphine withdrawal**	
	Dose shifting naltrexone dose-effect curve 2-fold rightward		**ED_{50} in attenuating naltrexone-lever responding**	
Drug	**(mg/kg)**	**95% CL**	**(mg/kg)**	**95% CL**
Morphine	3.24	(0.97-10.83)	1.11	(0.97-10.83)
Cocaine	1.04	(0.82-1.34)	0.36	(0.82-1.34)
Amphetamine	0.16	(0.02-1.19)	0.58	(0.02-1.19)
Imipramine	7.34	(0.37-145.51)	NA[a]	

[a] Not applicable; did not decrease naltrexone-lever responding to less than 50% after acute morphine withdrawal

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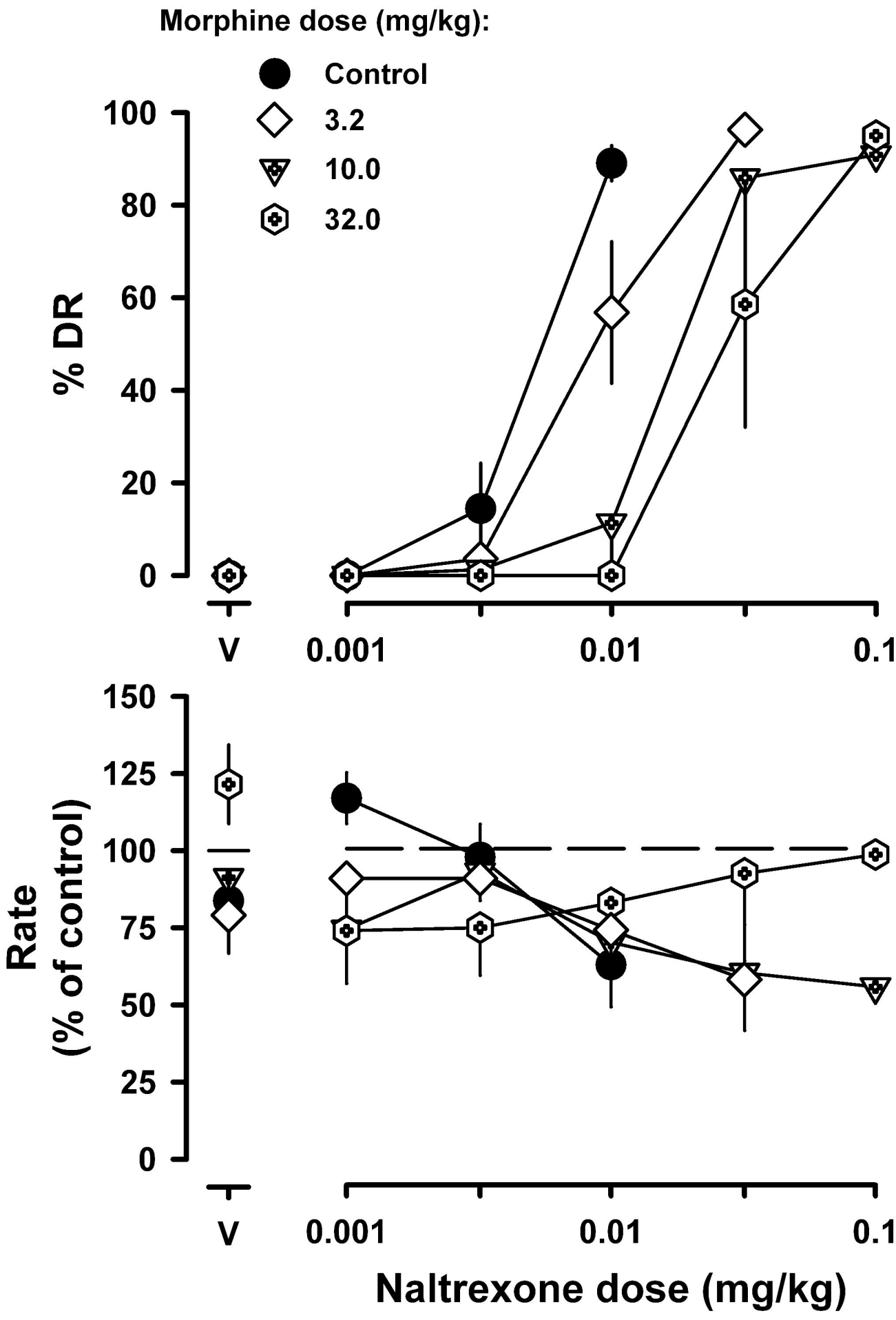

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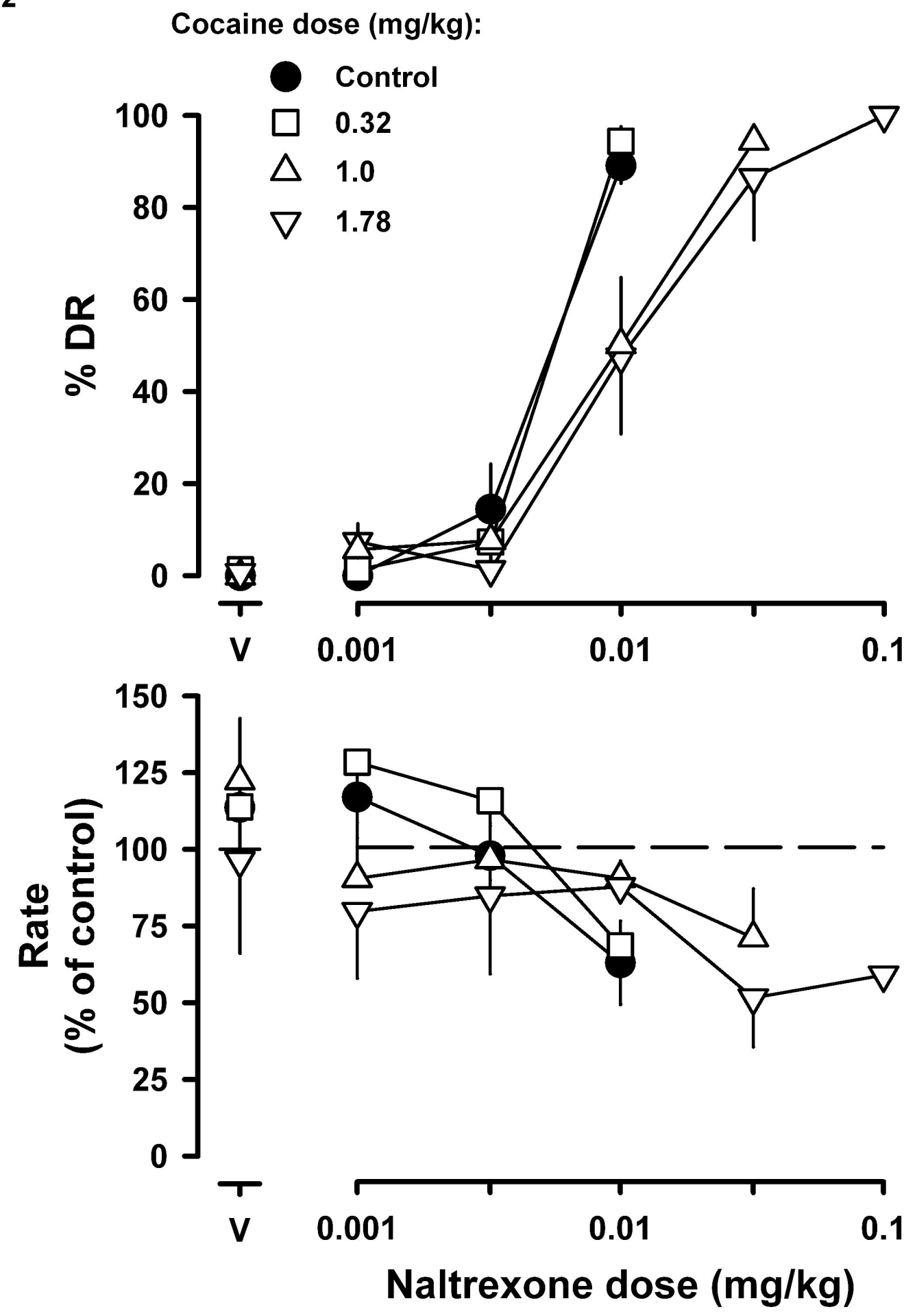

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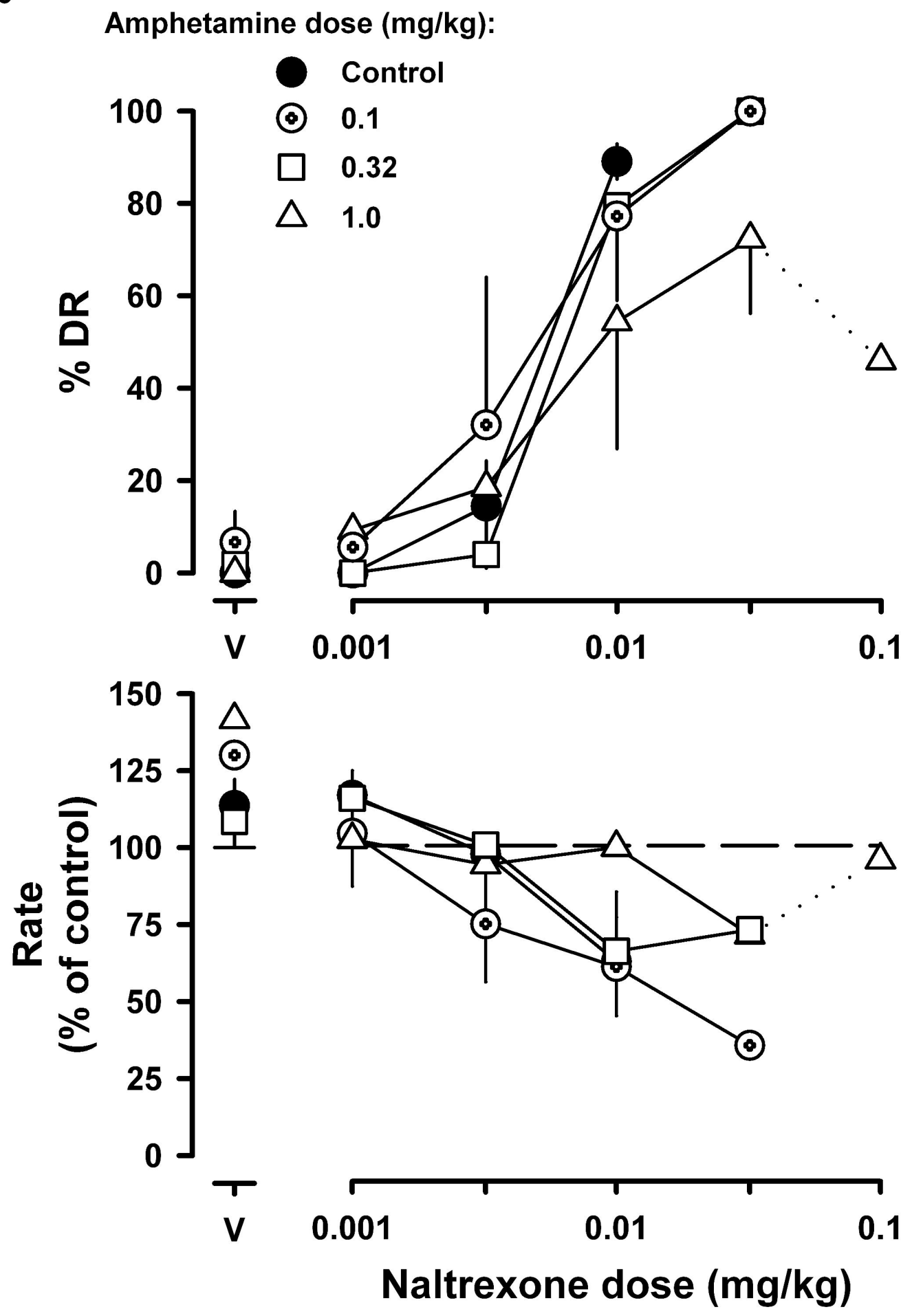

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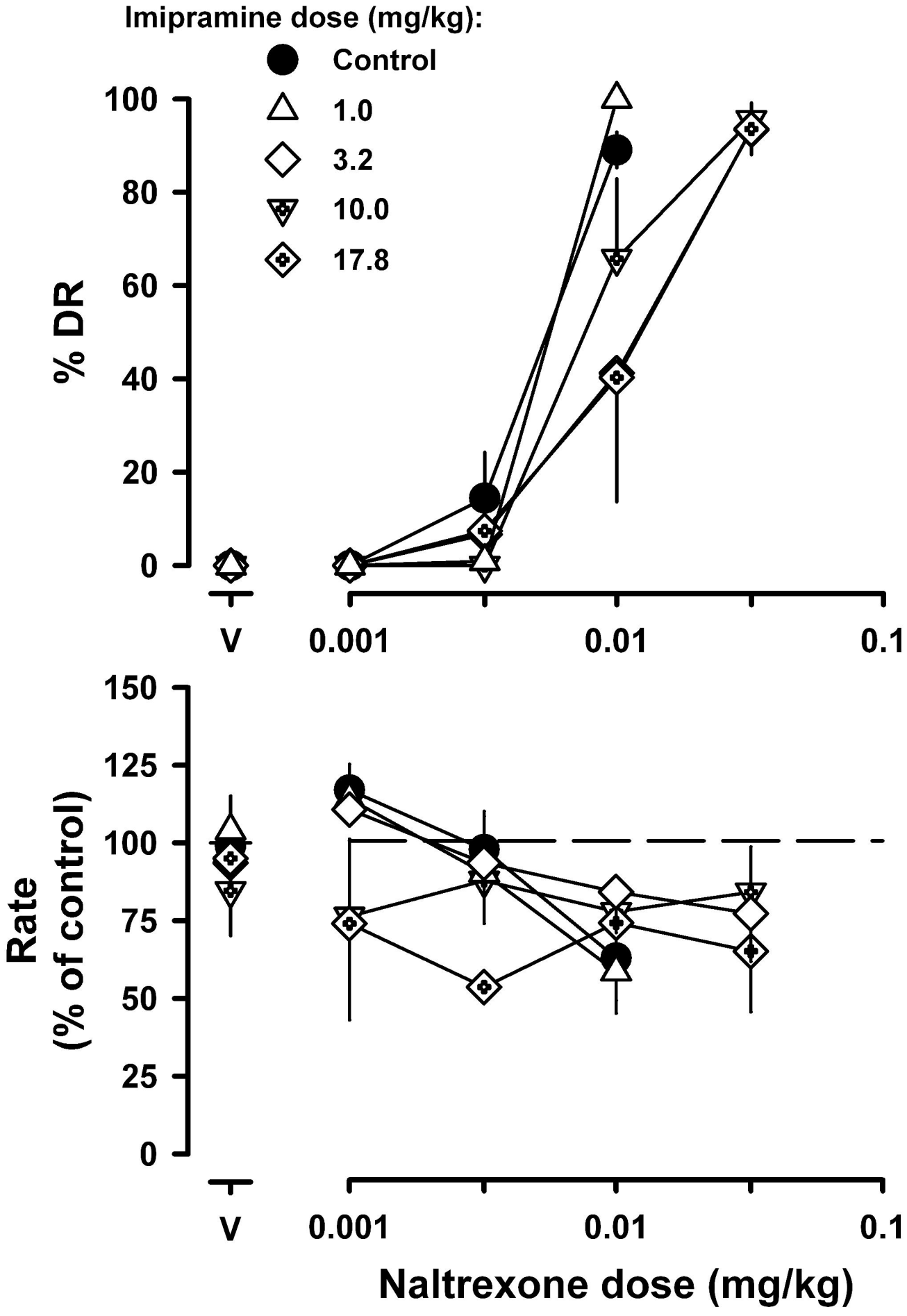

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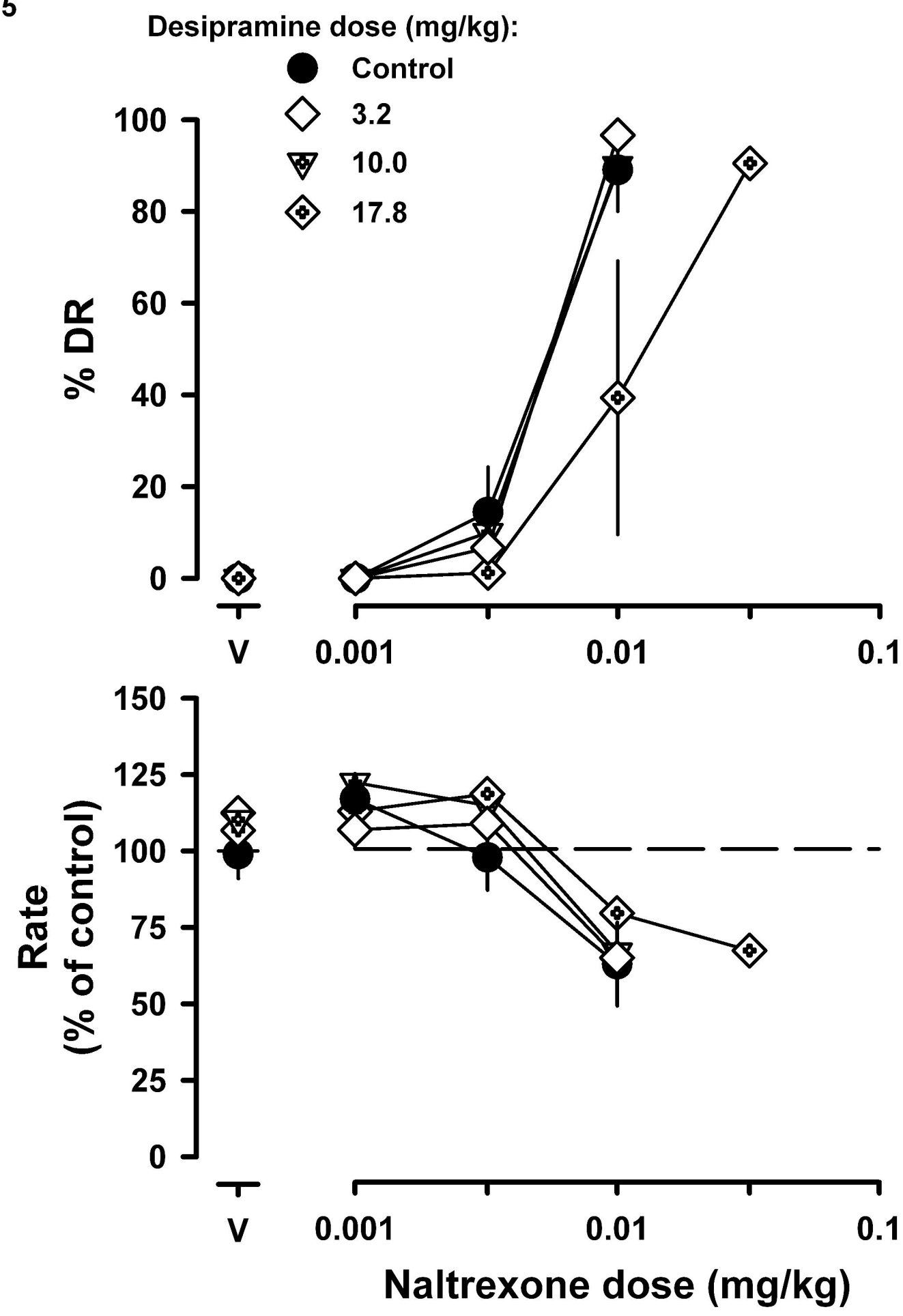

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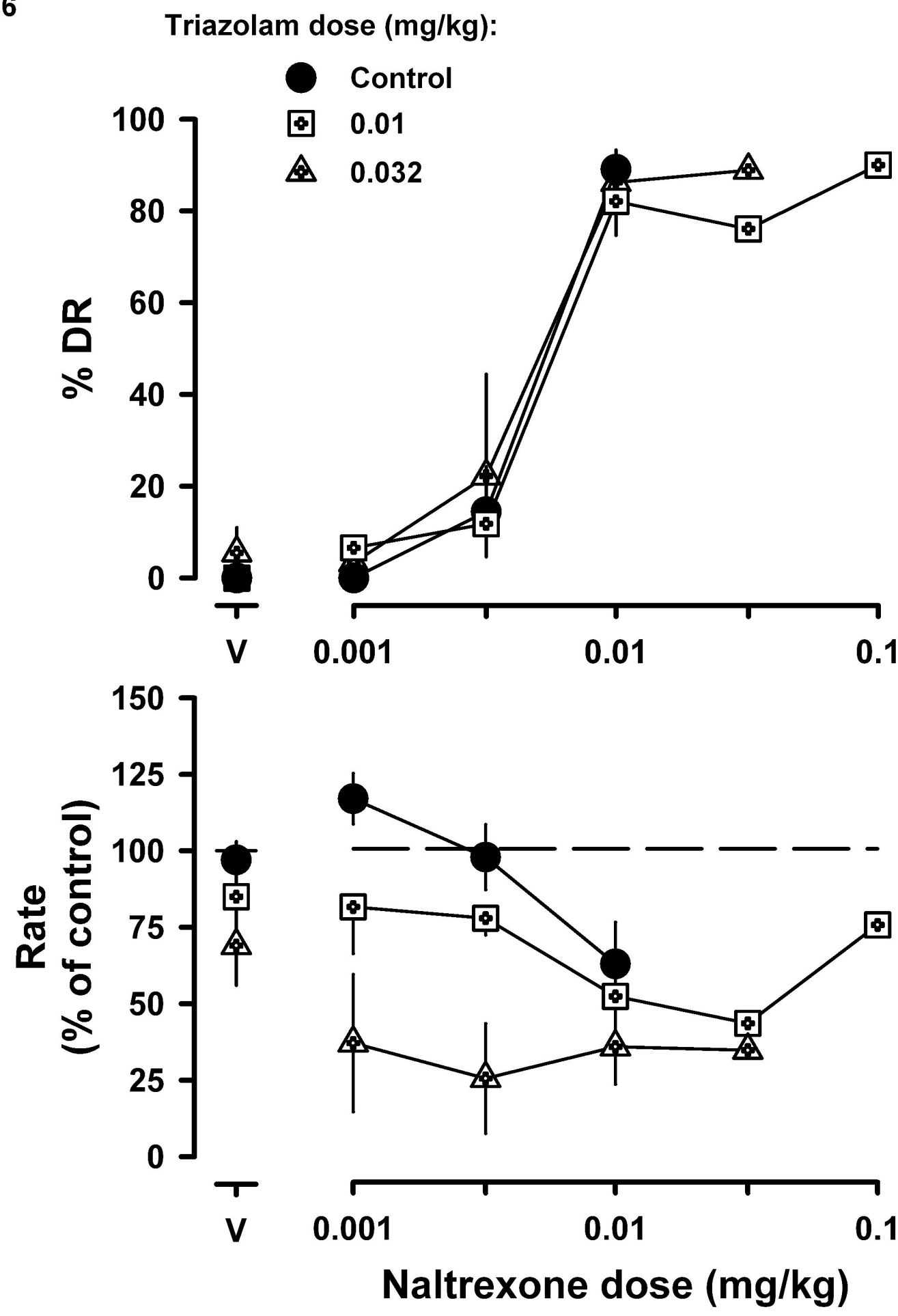

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