Drug and Reinforcement History as Determinants of the Response-Maintaining Effects of Quinpirole in the Rat

Gregory T. Collins and James H. Woods
Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan
Received March 19, 2007; accepted August 2, 2007

ABSTRACT
The present study examined the effect of drug and reinforcement history on quinpirole-maintained responding in rats. Quinpirole (0.01, 0.032, or 0.1 mg/kg per injection) was assessed as a reinforcer in experimentally naive rats, as well as in rats trained to self-administer cocaine, remifentanil, ketamine, or food under a fixed ratio 1 schedule of reinforcement. Quinpirole failed to maintain responding in experimentally naive rats, or in ketamine- or food-trained rats. However, robust responding was maintained in rats with a history of cocaine reinforcement, and modest levels of responding were observed in rats with a history of responding for remifentanil. In a second set of studies, the effects of protracted drug histories on quinpirole-maintained responding in food-trained rats were assessed. Rats were maintained with food reinforcement, and different groups of rats were then allowed to respond for saline, quinpirole, and response-contingent cocaine or were administered noncontingent cocaine; all rats were subsequently allowed to respond for quinpirole. Only rats that previously responded for cocaine showed quinpirole-maintained responding; all other conditions failed to establish quinpirole-maintained responding. Although the high levels of quinpirole-maintained responding observed when quinpirole was substituted for cocaine are suggestive of positive reinforcing effects, these response-maintaining effects were highly dependent upon both drug and reinforcement history, suggesting that quinpirole may only function as a reinforcer under very specific conditions. The behavioral effects of quinpirole under these situations represent a novel constellation of actions relative to other drug reinforcers, and they suggest that the direct effects of self-administered quinpirole may be important in establishing the response-maintaining effects.

Growing evidence suggests that D2 and D3 receptors may play important roles in the mediation of the reinforcing properties of drugs of abuse such as cocaine (e.g., Heidbreder et al., 2005; Newman et al., 2005). Not only are D2 and D3 receptors expressed at high levels within the nucleus accumbens (Lévesque et al., 1992; Gurevich and Joyce, 1999; Stanford et al., 2000) but also in both monkey and human, D2/D3 receptor levels have been found to be inversely correlated with the positive reinforcing effects of psychostimulants. In human subjects asked to rate the subjective effects of methylphenidate, those with lower striatal D2/D3 receptor levels reported a more pleasant effect compared with those with higher striatal D2/D3 receptor levels (Volkow et al., 1999). In addition, monkeys with lower striatal levels of D2/D3 receptors more readily self-administered cocaine compared with monkeys with higher striatal D2/D3 levels, suggesting that the reinforcing effects of cocaine differed between the two groups (Morgan et al., 2002). Furthermore, a history of cocaine exposure has been shown to result in long-lasting decreases in striatal D2/D3 receptor levels (Volkow et al., 1993; Nader et al., 2006), presumably resulting in a strengthening of the reinforcing and enteroceptive effects of cocaine.

Further evidence for the involvement of D2 and D3 receptors in the reinforcing effects of drugs has been provided through the study of D2/D3 agonists and antagonists in a variety of operant procedures in animals. In drug discrimination experiments, D2/D3 agonists often generalize to cocaine-trained cues (Barrett and Appel, 1989; Terry et al., 1994; Barrett et al., 2001), suggesting that the D2 and/or D3 receptors may, at least in part, mediate the enteroceptive effects of cocaine. In addition, in reinstatement procedures, D2/D3 agonists have been shown to induce nonreinforced, drug-appropriate, responding (Khroyan et al., 2000; De Vries et al., 2002). Antagonists at D2/D3 receptors have been shown to inhibit the capacity of drug-paired cues (Gilbert et al., 2005), stress (Xi et al., 2004), and drug “priming” (Andreoli et al., 2003) to reinstate responding that was previously reinforced by a variety of drugs. Furthermore, and of direct relevance to the present study, a variety of D2/D3 agonists have been shown to be self-administered in rats (Caine and

ABBRiEVATIONS: LED, light-emitting diode; inj, injection; FR, fixed ratio; TO, time-out; ANOVA, analysis of variance; GBR 12909, 1-{2-[bis-(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylpropyl)piperazine; MK-801, 5H-dibenz[a,d]cyclohepten-5,10-imine (dizocilpine maleate).
Koob, 1993), mice (Caine et al., 2002), and monkeys (Woolverton et al., 1984; Nader and Mach, 1996; Sinnott et al., 1999) when substituted for cocaine. Taken together, these findings suggest that D2/D3 agonists may possess anteroreceptive and reinforcing properties similar to those of cocaine.

Although the majority of these studies have not examined the influence of drug and/or reinforcement history on the capacity of D2/D3 agonists to maintain responding, evidence in monkeys suggests that the capacity of the D2/D3 agonists to maintain responding is modified by previous cocaine reinforcement. For example, 7-hydroxy-2-dipropylaminotetralin and quinpirole were readily self-administered when substituted in monkeys trained to respond for cocaine, but they failed to maintain responding in experimentally naive monkeys and drug-naive monkeys that were trained to respond for food (Nader and Mach, 1996; Sinnott et al., 1999). Moreover, 7-hydroxy-2-dipropylaminotetralin did not maintain responding in monkeys before a brief period of cocaine self-administration, but it did maintain significant levels of responding after experience with cocaine self-administration (Nader and Mach, 1996). Although these findings suggest that the reinforcing properties of D2/D3 agonists may be influenced by a history of cocaine administration, the influence of different reinforcement and/or drug histories on the capacity of D2/D3 agonists to maintain responding has not been systematically addressed.

The aims of the current study was to examine the influence of both drug and reinforcement history on the capacity of quinpirole to maintain responding in rats. In the current study, a history of cocaine reinforcement was sufficient to establish the response-maintaining effects of quinpirole, whereas, as reported previously in rhesus monkeys (Nader and Mach, 1996; Sinnott et al., 1999), quinpirole failed to maintain responding in experimentally naive and food-trained rats. Therefore, we explored other drug reinforcement histories with drugs from the opioid (remifentanil) or dissociative anesthetic (ketamine) classes of drugs that are known to maintain strong self-administration behavior in rats. Finally, we determined whether noncontingent cocaine administration was sufficient to establish the response-maintaining effects of quinpirole, and whether it was necessary that cocaine reinforcement immediately precede the substitution of quinpirole. Together, these studies suggest that quinpirole functions to maintain responding under a limited set of conditions and that the response-maintaining effects of quinpirole may represent some combination of direct drug effects, along with a weaker, situational, reinforcing effect in the rat.

Materials and Methods

Subjects. Male Sprague-Dawley rats (350–375 g) were obtained from Harlan (Indianapolis, IN), and they were maintained in a temperature- and humidity-controlled environment, on a 12-h dark/ light cycle with lights on at 7:00 AM. Rats were allowed free access to food before the start of experiments, and they were maintained with ~20 g of food per day for the duration of the experiments. All studies were performed in accordance with the Guide for the Care and Use of Laboratory Animals, as adopted and promulgated by the National Institutes of Health, and all experimental procedures were approved by the University of Michigan Committee on the Use and Care of Animals.

Surgery. Rats were surgically prepared with chronic indwelling jugular catheters in both the right and left jugular veins under ketamine/xylazine (100:10 mg/kg i.m.) anesthesia. Catheters were tunneled under the skin and attached to stainless steel tubing, exiting the back through a metal tether button that was sutured to the muscle between the scapula. Rats were allowed 5 to 7 days to recover from surgery before the start of any experiments. Catheters were flushed with 0.2 ml of heparinized saline (100 U/ml) before the start of self-administration sessions as well as after the completion of the session to ensure patency.

Apparatus. All experimental sessions were conducted in operant conditioning chambers (30.5 × 24 × 21 cm [width × depth × height]: MED Associates, St. Albans, VT) placed inside sound-attenuating cubicles. Each chamber was equipped with a single nosepoke device (ENV-114BM; MED Associates) positioned 6 cm above the stainless steel grid floor, and it was illuminated with a yellow stimulus light. Each chamber was also equipped a green LED stimulus light, located above the nosepoke, and a white house light. An air-driven pneumatic syringe pump (ITTC, Woodland Hills, CA) allowed for drug delivery through Tygon tubing connected to a fluid swivel (Instech Laboratories Inc., Plymouth Meeting, PA) and spring tether, which was held in place by a counterbalanced arm. For food self-administration sessions, chambers were also equipped with a liquid food dipper with a 50-μl dipper cup (model E14-05; Coulbourn Instruments, Allentown, PA).

Acquisition of Operant Responding and Determination of Dose-Response Curves. Nosepoke responses were followed by either 0.0032 mg/kg/inj cocaine, 0.0032 mg/kg/inj remifentanil, 1.0 mg/kg/inj ketamine, 0.032 mg/kg/inj quinpirole, saline, or 10-s access to 50 μl of liquid food (100% Ensure) during each session. Allentown, PA.

Nosepoke responses were followed by either 0.0032 mg/kg/inj cocaine, 0.0032 mg/kg/inj remifentanil, 1.0 mg/kg/inj ketamine, 0.032 mg/kg/inj quinpirole, saline, or 10-s access to 50 μl of liquid food (100% Ensure) during daily, 90-min sessions under a fixed ratio (FR) 1 schedule of reinforcement. Illumination of the yellow nosepoke light signaled drug, food, or saline availability, and subsequent nosepokes resulted in an injection (100 μl/kg/0.5 s), or 10-s access to liquid food during which time a green LED above the nosepoke was illuminated. Delivery of liquid food was also paired with the illumination of a light above the dipper to signal food availability. A 5-s time-out (TO) followed drug delivery and food presentation during which time the house light was illuminated and responses were recorded but had no consequence.

Upon acquisition of stable responding, defined as three consecutive sessions with less than 20% difference and no increasing or decreasing trend in responding, the dose was randomly changed to allow for the determination of dose-response curves. Rats were allowed to respond for the new dose until stability criteria were met. Each dose was available for at least five sessions before substitution of the next, randomly assigned dose. Dose-response curves for each reinforcer were obtained in separate groups of rats (n = 6/dose). Each rat responded for at least three doses of either cocaine (saline, 0.001, 0.032, 1.0, 0.32, 0.56, and 1.0 mg/kg/inj), remifentanil (saline, 0.0001, 0.00032, 0.001, 0.0032, and 0.01 mg/kg/inj), or ketamine (saline, 0.032, 0.1, 0.32, 1.0, and 3.2 mg/kg/inj).

Effect of Reinforcement History on the Response-Maintaining Effects of Quinpirole. To assess the influence of reinforcement history on the capacity of quinpirole to maintain responding, rats acquired responding for either drug (0.56 mg/kg/inj cocaine, 0.0032 mg/kg/inj remifentanil, and 1.0 mg/kg/inj ketamine) or nondrug (50 μl of 100% Ensure) reinforcers under an FR1TO5 schedule of reinforcement as described above. Upon acquisition of stable responding, quinpirole (0.01, 0.032, or 0.1 mg/kg/inj) or saline was substituted for a period of 7 days. Rats that were allowed to respond for liquid food acquired stable responding within the first seven sessions, but they were given 14 days of training before substitution of quinpirole to control for the number of sessions required to achieve stable drug responding. Following substitutions, rats were returned to the initial reinforcer for a period of 5 days to assess changes in baseline responding.

Effect of Prior Drug Exposure on the Response-Maintaining Effects of Quinpirole. The influence of drug history on the
capacity of quinpirole to maintain responding was evaluated in five separate groups of rats (n = 6/group). All rats were initially trained to respond for liquid food under an FRIT05 schedule of reinforcement. After a 14-day acquisition period, responses that previously resulted in access to liquid food now resulted in an intravenous injection of saline (group 1), 0.56 mg/kg/inj cocaine (group 2), or 0.032 mg/kg/inj quinpirole (group 3). Rats in groups 4 and 5 received 45 evenly spaced, noncontingent injections of 0.56 mg/kg/inj cocaine. For group 4, the delivery of cocaine was paired with the same stimuli that subsequently accompanied quinpirole delivery (illumination of the green LED followed by the illumination of the house light for 5 s). For group 5, the delivery of cocaine was not paired with any additional stimuli. Each of these conditions was maintained for seven consecutive sessions, and it was followed by five sessions in which rats were returned to liquid food reinforcement. During the next, test phase, all rats were allowed to self-administer 0.032 mg/kg/inj quinpirole for a period of 7 days; subsequently, they were returned to liquid food reinforcement for 5 days to assess changes in baseline responding.

**Drugs.** Cocaine hydrochloride [methyl (1R,2R,3S,5S)-3-benzoxyloxy-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate hydrochloride] was obtained from the National Institute on Drug Abuse (Bethesda, MD). Remifentanil [methyl 1-(3-methoxy-3-oxopropyl)-4-(phenyl-propanoylamino)piperidine-4-carboxylate hydrochloride], purchased as Ultiva (GlaxoSmithKline, Uxbridge, Middlesex, UK), was obtained from the University of Michigan Hospital Pharmacy (Ann Arbor, MI). Ketamine [2-(4-chlorophenyl)-2-methylaminocyclohexan-1-one] was purchased from Henry Schein (Denver, PA). Quinpirole [trans-(-)-(4A)-4,4$\alpha$,9-octahydro-5-propyl-1H-pyrrozolo[3,4-g]quinoline hydrochloride] was purchased from Sigma-Aldrich (St. Louis, MO). All drugs were dissolved in physiological saline, and they were administered in a volume of 0.1 ml/kg over a period of 0.5 s.

**Data Analysis.** Responses represent the mean ± S.E.M. (n = 6) number of responses that resulted in an injection or food delivery, but they do not include responses made during reinforcement or the subsequent time-out period. Response stability was defined as three consecutive sessions with less than 20% difference in responding and no increasing or decreasing trend in the number of injections earned. Dose-response curves represent the mean ± S.E.M. (n = 6) number of completed ratios during the last three sessions for each dose of drug or saline. Analysis of dose-response curves was conducted using a one-way ANOVA with post hoc Dunnett’s tests (GraphPad Prism; GraphPad Software Inc., San Diego, CA) to determine doses of drug that maintained significantly greater levels of responding than saline. Significant differences in baseline responding or responding maintained during substitutions was determined using a two-way ANOVA with repeated measures and post hoc Bonferroni tests (SPSS; SPSS Inc., Chicago, IL) to assess differences in responding between the groups for each session.

**Results**

**Acquisition of Responding and Determination of Dose-Response Curves.** Experimentally naïve rats readily acquired responding for 0.56 mg/kg/inj cocaine, 0.0032 mg/kg/inj remifentanil, 1.0 mg/kg/inj ketamine, and 10-s access to 50 $\mu$l of liquid food (Fig. 1A). Responding maintained by cocaine, remifentanil, ketamine, or food was generally greater than for saline within the first three sessions, and there were no differences in the number of sessions required to achieve stable responding for cocaine (12.6 ± 0.1 sessions), remifentanil (13.7 ± 0.1 sessions), or ketamine (11.8 ± 0.1 sessions). Stability was generally observed within the first seven sessions for liquid food; however, access was provided for 14 days. Quinpirole (0.032 mg/kg/inj) failed to maintain responding that was any different from that maintained by saline at any point during the 10-session acquisition period (Fig. 1A). As shown in Fig. 1B, cocaine, remifentanil, and ketamine all maintained dose-dependent responding under an FRIT05 schedule of reinforcement, resulting in inverted U-shaped dose-response curves typical of drug reinforcers.

**Effect of Reinforcement History on the Response-Maintaining Effects of Quinpirole.** Responding maintained by quinpirole (0.01, 0.032, or 0.1 mg/kg/inj) or saline during the 7-day substitution for cocaine (0.56 mg/kg/inj), remifentanil (0.0032 mg/kg/inj), ketamine (1.0 mg/kg/inj), or liquid food is shown in Fig. 2, A to D. Differences in quinpirole-maintained responding were observed among the cocaine-, remifentanil-, ketamine-, and food-trained rats. When substituted for cocaine, quinpirole maintained robust responding at doses 0.032 and 0.1 mg/kg/inj, whereas responding for 0.01 mg/kg/inj quinpirole was no different from responding maintained by saline (Fig. 2A). Responding maintained by 0.032 and 0.1 mg/kg/inj quinpirole was significantly greater than responding maintained by saline during
sessions 2 to 7 of the substitution, whereas no significant differences were observed during the initial day of substitution. In remifentanil-trained rats, significant levels of quinpirole-maintained responding were observed during sessions 2 to 7 when a dose of 0.1 mg/kg/inj quinpirole was substituted. However, responding for doses of 0.01 and 0.032 mg/kg/inj quinpirole were not significantly different from responding maintained by saline (Fig. 2B). Unlike in rats trained to respond for cocaine or remifentanil, quinpirole failed to maintain significant levels of responding at any dose tested in rats trained to respond for ketamine (Fig. 2C) or liquid food (Fig. 2D). In fact, as shown in the insets to Fig. 2, C and D, responding maintained by quinpirole was significantly lower than responding maintained by saline during the initial day of substitution in both ketamine- (0.032 and 0.1 mg/kg/inj quinpirole) and food (0.01, 0.032, and 0.1 mg/kg/inj quinpirole)-trained rats.

Rates of responding maintained by quinpirole were not related to the rate of responding maintained by the baseline reinforcers. Significant levels of quinpirole-maintained responding were observed in rats that previously responded for cocaine (<50 reinforcers) or remifentanil (>100 reinforcers), whereas quinpirole failed to maintain responding in rats that previously responded for food (>200 reinforcers) or ketamine (<50 reinforcers). Dose-response curves for responding maintained by quinpirole on the last day of substitution for each of the maintenance reinforcers are shown in Fig. 3.

Effect of Prior Drug Exposure on the Response-Maintaining Effects of Quinpirole. The effects of prior contingent saline, quinpirole and cocaine, or noncontingent cocaine on quinpirole-maintained responding in rats trained to respond for liquid food are shown in Fig. 4. Although there were no significant differences in food-maintained responding between any of the groups during the first, second, or third food components of the experimental paradigm, 0.56 mg/kg/inj cocaine maintained significantly greater levels of responding than either saline or 0.032 mg/kg/inj quinpirole throughout the initial 7-day i.v. exposure (Fig. 4). Low levels of responding were observed when quinpirole (0.032 mg/kg/inj) was available. When substituted for food, responding maintained by quinpirole was no different from responding maintained by saline with the exception of the first day, when quinpirole-maintained responding was significantly lower than saline-maintained responding. Rats that received noncontingent cocaine injections also responded at salinelike levels during the initial exposure period. When all rats were allowed to respond for 0.032 mg/kg/inj quinpirole, the previous drug exposure significantly affected behavior. Rats that had previously responded for either saline or quinpirole responded for quinpirole at low levels throughout the second day.
i.v. self-administration period (Fig. 4). Conversely, rats that responded for cocaine during the initial exposure period responded for quinpirole at high rates throughout the second 7-day period (Fig. 4). However, when cocaine was initially delivered noncontingently, responding for quinpirole was low and no different from responding observed in rats that initially responded for either saline or quinpirole (Fig. 4). Furthermore, pairing the accompanying stimuli (i.e., illumination of the green stimulus light during infusion and house light for 5 s thereafter) with the noncontingent administration of cocaine did not increase the capacity of quinpirole to maintain responding; no differences in quinpirole-maintained responding were observed between the rats that received the accompanying stimuli in addition to the noncontingent cocaine injections, and rats that received noncontingent cocaine without these stimuli (Fig. 4).

### Discussion

The results of this study confirm the findings of previous studies and extend them in several ways. Similar to reports in rats (e.g., Caine and Koob, 1993) and monkeys (e.g., Sinnott et al., 1999), quinpirole-maintained dose-dependent responding resulting in an inverted U-shaped dose-response curve when substituted in rats trained to respond for cocaine. These studies also support the findings of Nader and colleagues, who demonstrated that although quinpirole maintained responding in animals with a history of cocaine reinforcement, quinpirole failed to maintain responding in rats that were exposed noncontingently to roughly equivalent doses and patterns of cocaine injection. These findings suggest that both drug and reinforcement histories were important determinants in establishing the response-maintaining effects of quinpirole and that quinpirole was most effective at maintaining responding in rats with a history of cocaine reinforcement.

Although this study is not the first to describe differences in the reinforcing properties of drugs following substitution from different maintenance drugs (e.g., Hoffmeister and Schlichting, 1972; Young and Woods, 1981; Beardsley et al., 1990; Wojnicki and Glowa, 1996), they are the first to address systematically the impact of varying drug and reinforcement histories on the capacity of a D2/D3 agonist to function as a reinforcer. Although the two highest doses of quinpirole were readily self-administered in rats trained to respond for cocaine, only the highest dose of quinpirole maintained significant levels of responding when substituted in remifentanil-trained rats. Differences in drug history (i.e., cocaine and remifentanil) not only altered the potency of quinpirole to maintain responding, but other drug histories (i.e., ketamine) failed to establish the response-maintaining effects of quinpirole altogether. Similar effects of drug history on reinforcing potency have been reported for GBR 12909 in monkeys with a history of responding for high doses of cocaine or GBR 12909 compared with drug-naïve monkeys (Wojnicki and Glowa, 1996). Although these findings suggest that prior exposure to some drugs may sensitize animals to the reinforcing effects of drug reinforcers, it is unlikely that sensitization alone accounts for the differences in quinpirole-maintained responding in the current study, because roughly equivalent amounts of noncontingent cocaine failed to establish the response-maintaining effects of quinpirole, as would have been expected if cocaine exposure had been sufficient to sensitize the rats to the reinforcing effects of quinpirole (e.g., Robinson and Berridge, 1993; Vezina, 2004).

In addition to shifts in the potency of quinpirole to maintain responding, quinpirole failed to maintain responding...
when substituted in rats trained to respond for either ketamine or food, suggesting a selectivity to the effect of reinforcer history. Similar effects of drug history have been reported by Young and Woods (1981), who demonstrated that although phencyclidine, dexoxadrol, and dextrophan all maintained responding when substituted for ketamine, each of these drugs failed to maintain responding when substituted in monkeys maintained on codeine. Similarly, the capacity of MK-801 to maintain responding seems to be dependent upon drug history, because MK-801 maintained responding when substituted in monkeys trained to respond for L-(1-phenylcyclohexyl)piperidine (phencyclidine), but not cocaine (Beardsley et al., 1990). In both of these studies, the capacity of substitute reinforcers to maintain responding was, in large part, attributed to similarities in the discriminative stimulus properties of the substitute and maintenance drugs. Although it is likely that similarities in the discriminative stimulus effects of quinpirole and cocaine (Barrett and Appel, 1989; Terry et al., 1994; Barrett et al., 2001) are at least in part responsible for the capacity of quinpirole to maintain responding when substituted for cocaine, similar explanations do not account for the maintenance of responding when quinpirole was substituted for drugs with dissimilar discriminative stimulus effects, such as the \( \mu \)-opioid agonist remifentanil (Cook and Beardsley, 2004).

In addition to maintaining responding when substituted for cocaine, D2/D3 agonists such as quinpirole have also been shown to possess a variety of direct effects on operant behavior that may influence their capacity to maintain responding when substituted from different drug- and nondrug-reinforced baselines. For example, in addition to dose-dependently increasing cocaine-appropriate responding in drug discrimination studies, D2/D3 agonists, such as quinpirole, have also been shown to increase nonreinforced (cocaine-appropriate), responding in animals trained to respond for cocaine. For example, during sessions when cocaine was unavailable and responding on the injection lever resulted in saline delivery, D2/D3 agonists dose-dependently increased injection lever responding in monkeys trained on a two-lever, cocaine-food choice procedure (Gasior et al., 2004). Similar increases in cocaine-appropriate responding have been observed following quinpirole pretreatment in reinstatement procedures (Khroyan et al., 2000; De Vries et al., 2002), suggesting that quinpirole is capable of inducing cocaine-appropriate responding regardless of whether cocaine was administered as a reinforcer or as a discriminative stimulus. However, quinpirole has also been shown to reinstate responding previously reinforced by heroin (De Vries et al., 2002), suggesting a more general effect of quinpirole on previously reinforced responding.

Similar direct effects of quinpirole on operant behavior have been reported in rats trained to respond for nondrug reinforcers. For example, when administered at doses roughly equivalent to those available for injection in the current study, quinpirole has been shown to suppress food-maintained responding (Franklin and Tang, 1995; Sanger et al., 1996), suggesting that, at relatively low doses, quinpirole possesses response-suppressant effects. Likewise, chronic treatment with higher doses of quinpirole (\( \geq 0.5 \) mg/kg) has been shown to suppress responding for water (Cioli et al., 2000; Kurylo and Tanguay, 2003; Kurylo, 2004; Amato et al., 2006), although this effect seemed to be time-dependent and transitory. Although quinpirole initially suppressed responding for water, tolerance to this effect seemed to develop within the first few days, and it was followed by large increases in reward-appropriate responding when water was subsequently withdrawn (Kurylo and Tanguay, 2003; Kurylo, 2004) or when water was made freely available throughout the experimental session (Cioli et al., 2000; Amato et al., 2006). Although these data suggest that quinpirole may induce perseverative or “compulsive” responding for water, it should be noted that these effects were observed when relatively large (\( \geq 0.5 \) mg/kg) doses of quinpirole were administered over a number of days; furthermore, quinpirole has also been shown to induce hyperdipsia over a similar range of doses (Fraioli et al., 1997). When taken together, these findings suggest that quinpirole can dose-dependently increase or decrease operant behavior that has been maintained by either drug or nondrug reinforcers.

Thus, it is possible that quinpirole-maintained responding may result from a combination of the direct drug effects on previously reinforced responding rather than a more general reinforcing effect of quinpirole. For example, D2/D3 agonists, given as pretreatments, have been shown to increase previously reinforced responding regardless of whether responding had been extinguished or not. Similar to the findings of the current study, quinpirole, administered noncontingently, has been shown to reinstate responding previously reinforced by cocaine or heroin (Khroyan et al., 2000; De Vries et al., 2002), but not food (Dias et al., 2004). However, the extent to which this effect is influenced by the contingent or noncontingent administration of quinpirole remains to be determined. Furthermore, it is likely that the stimuli associated with reinforcer delivery are also controlling responding; moreover, quinpirole may be affecting these stimulus functions as well (Wolterink et al., 1993). Thus, quinpirole, and other D2/D3 agonists, must be studied in animals with a variety of reinforcement histories, and under a variety of contingencies and stimulus conditions, to fully understand their effects on operant responding.

In summary, the results of this study show that although responding was readily acquired for cocaine, remifentanil, ketamine, and food, quinpirole failed to initiate or maintain responding at levels any different from those maintained by saline in experimentally naive rats. However, quinpirole did maintain significant levels of responding in cocaine- and remifentanil-trained rats, but not in rats that were trained to respond for ketamine or food, or in rats that were trained to respond for food and provided a roughly equivalent history of noncontingent cocaine exposure. Together, these findings suggest that the response-maintaining effects of quinpirole are highly dependent upon both drug and reinforcement history, and although quinpirole is capable of maintaining responding under some experimental conditions, this may result from a combination of the direct effects of quinpirole on operant responding and a more provisional reinforcing effect serving to perpetuate operant responding. Further studies are needed to determine the degree to which the direct drug effects and the reinforcing properties of quinpirole are involved in the capacity of quinpirole to maintain responding in animals with a history of cocaine or opioid reinforcement.
Acknowledgments

We acknowledge the excellent editorial assistance of Dr. Gail Winger and exceptional technical assistance of Michelle Baladi.

References


Address correspondence to: Dr. James H. Woods, Department of Pharmacology, 1301 MSRB III, University of Michigan Medical School, Ann Arbor, MI 48109-0632. E-mail: jhwoods@umich.edu