ELSEVIER

Pharmacology, Biochemistry and Behavior 72 (2002) 803–809

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Comparison of the reinforcing efficacy of two dopamine D2-like receptor agonists in rhesus monkeys using a progressive-ratio schedule of reinforcement

William L. Woolverton*, Robert Ranaldi

Department of Psychiatry and Human Behavior, Division of Neurobiology and Behavior Research, University of Mississippi Medical Center, Guyton Research Building, 2500 North State Street, Jackson, MS 39216-4505, USA

Received 9 November 2001; received in revised form 2 February 2002; accepted 13 February 2002

Abstract

High-efficacy D2-like dopamine (DA) receptor agonists can function as positive reinforcers when made available to animals for intravenous self-administration under a fixed-ratio (FR) schedule of reinforcement. In a previous study, however, low-efficacy D2-like agonists failed to maintain self-administration under an FR schedule, suggesting that agonist efficacy is directly related to efficacy as a positive reinforcer. To examine this hypothesis further, the present study compared two D2-like DA receptor agonists that maintained FR responding, but differ in their D2-like receptor efficacy and selectivity, using a procedure designed to rank-order drugs according to their efficacy as reinforcers. Rhesus monkeys ($n = 5$) were prepared with chronic, indwelling intravenous catheters and allowed to self-administer cocaine (0.1 mg/kg/injection) or saline on different days under a progressive-ratio (PR) schedule. When responding was stable, doses of the full D2-like agonist $R(-)$-propylnorapomorphine (NPA) or the partial D2-like agonist $R(-)$-apomorphine (APO) were made available for self-administration in the test sessions. Both compounds maintained self-administration with sigmoidal or biphasic dose–response functions. Surprisingly, the lower efficacy agonist APO was the more efficacious positive reinforcer. This result fails to support the hypothesis that D2-like receptor efficacy is directly related to efficacy as a reinforcer. It is possible that other pharmacological effects, e.g., D1 receptor activity, influenced self-administration.

Keywords: Cocaine; Self-administration; Progressive-ratio schedule; D2 receptor; Agonist efficacy; Reinforcing effect

1. Introduction

The conclusion that increased dopamine (DA) neurotransmission is involved in the reinforcing effects of psychomotor stimulants is well supported experimentally (Koob, 1992; Wise, 1996; Woolverton and Johnson, 1992). Further, research has implicated both D1- and D2-like DA receptors in this effect. Both D1- and D2-like agonists function as positive reinforcers in rats (Self and Stein, 1982; Yokel and Wise, 1978) and monkeys (Grech et al., 1996; Weed and Woolverton, 1995; Woolverton et al., 1984). Moreover, pretreatment with D1- or D2-like antagonists may reduce the reinforcing effect of stimulants in animal subjects (Corrigall and Coen, 1991; Koob et al., 1987; Wilson and Schuster, 1972; Woolverton, 1986; Yokel and Wise, 1975).

Research with both D1- and D2-like agonists has suggested that efficacy as a positive reinforcer may be directly related to agonist efficacy at DA receptors. Low-efficacy D1-like agonists failed to maintain self-administration by monkeys when substituted for a baseline drug (Grech et al., 1996; Weed and Woolverton, 1995; Woolverton et al., 1984) while high-efficacy D1-like agonists maintained self-administration under these conditions and can be used to establish self-administration in naïve monkeys (Weed and Woolverton, 1995). When a series of D1-like agonists that were reinforcers under a fixed-ratio (FR) schedule were compared under a progressive-ratio (PR) schedule of reinforcement designed to rank-order efficacy as reinforcers, differences between higher efficacy agonists were not obvious (Weed et al., 1997). Thus, although D1-like efficacy appeared to be related to efficacy as a reinforcer, the relationship may

* Corresponding author. Tel.: +1-601-815-1022; fax: +1-601-984-5899.

E-mail address: wwoolverton@psychiatry.umsmed.edu (W.L. Woolverton).

0091-3057/02/$ – see front matter
PII: S0091-3057(02)00749-9

be based upon a "threshold" of efficacy necessary to function as a reinforcer, rather than on a continuum (Ruffolo, 1982).

Previous research with D2 agonists supports the conclusion that D2-like agonists are similar to D1-like agonists in this regard (Pulvirenti et al., 1998; Ranaldi et al., 2001). That is, higher efficacy D2-like agonists [*R*(−)-propylnorapomorphine (NPA); *R*(−)-apomorphine (APO); *R*(+)-3-(3-hydroxyphenyl)-*N*-propylpiperidine] maintained self-administration while lower efficacy agonists [*R*(+)-terguride; *S*(−)-3-(3-hydroxyphenyl)-*N*-propylpiperidine] did not. The present study was designed to extend those findings by using a PR schedule to compare two agonists, NPA and APO, that functioned as reinforcers under an FR schedule but that differ in their agonist efficacies at D2-like receptors. NPA has been reported to be a full D2-like agonist (Arnt and Hyttel, 1990; Lahti et al., 1992; Nilsson and Eriksson, 1992), while APO has generally been reported to be a moderate efficacy agonist, with efficacy measures reported somewhere between 50% and 80% of DA (Lahti et al., 1992; O'Boyle and Lawler, 1996). In addition, NPA appears to be more selective than APO for the D2 receptor (Creese et al., 1979; Euvrard et al., 1979; Herrera-Marschitz and Ungerstedt, 1984). Our hypothesis was that the higher efficacy, more selective D2-like agonist, NPA, would be a more effective reinforcer than the lower efficacy D2-like agonist APO.

2. Methods

All procedures were in compliance with the NIH Guide for the Care and Use of Laboratory Animals.

2.1. Animals and apparatus

The subjects were five male (9.5–12.5 kg) rhesus monkeys (*Macaca mulatta*). Monkeys RMs2 and RIk2 had a history of self-administration of local anesthetics under a PR schedule of reinforcement (Wilcox et al., 2000). Monkeys L500 and Rju2 had a history of self-administration of methamphetamine on a PR schedule of reinforcement and pretreatment with a 3-phenyltropane analog (Ranaldi et al., 2000). Monkey N425 was experimentally naive at the start of the present experiment. All monkeys were provided with sufficient food to maintain stable body weight (150–200 g/day, Teklad 25% Monkey Diet, Harlan/Teklad, Madison, WI). Water was continuously available. A vitamin supplement was provided three times a week.

The monkeys were housed in the experimental cubicles (1.0 m^3, Plaslabs, Lansing, MI). Each monkey was fitted with a stainless steel restraint harness attached by a spring arm to the rear wall of the cubicle. The front door of the cubicle was transparent and the remaining walls were opaque plastics. Two response levers (PRL-001, BRS/LVE, Beltsville, MD) were mounted on the inside of the door, on either side of a food dish. Four jeweled stimulus lights, two red and two white, were mounted above each lever. A peristaltic infusion pump (Cole-Parmer, Chicago, IL) delivered drug injections. A Macintosh computer with custom interface and software controlled all events in an experimental session.

2.2. Procedure

Each monkey had a chronic indwelling venous catheter surgically implanted in a major vein (jugular, femoral, or brachial). Using strict aseptic techniques performed under ketamine and isoflurane anesthesia, a silicone catheter (0.26 cm O.D. × 0.076 cm I.D., Cole-Parmer) was implanted into a jugular (internal or external) or femoral vein. Brachial veins were implanted with a tapered microrenethane catheter (0.08 cm O.D. × 0.04 cm I.D., Braintree Scientific, Braintree, MA). The proximal end was inserted into the vein and threaded to terminate in the vena cava near the right atrium. The distal end of the catheter was passed subcutaneously to exit the monkey between the shoulder blades. After surgery, the catheter was threaded through the spring arm, out the rear of the cubicle, and connected to the peristaltic pump. In the event of catheter failure, surgery was repeated using another vein, after the veterinarian confirmed the health of the monkey.

Experimental sessions began at noon each day and were conducted 7 days/week. The schedule was identical to the PR schedule used previously to study self-administration of BZT analogs (Wilcox et al., 2000; Woolverton et al., 2001). At the beginning of a session, the white lights were illuminated above both levers. Responding on the right lever under a PR schedule of reinforcement resulted in the delivery of an injection. Responding on the left lever was counted but had no other programmed consequence. The PR procedure consisted of five components, each made up of four trials, for a total of 20 trials/day. Under baseline conditions, the response requirement for the first component was 200, and doubled for each successive component. The same response requirement was in effect for each trial in a component, and a trial ended with a 10-s drug injection or the expiration of a 30-min limited hold. During the injection the lights above both levers turned from white to red. There was a 60-s time-out (TO) after each drug injection or the expiration of a limited hold. If the response requirement was not completed for two consecutive trials (i.e., the limited hold expired) or the animal took all 20 injections, the session ended.

In baseline sessions, cocaine (0.05 mg/kg/injection for RMs2 and 0.10 mg/kg/injection for RJu2, RIK2, L500, and N425) or saline were available for injection on alternate days until responding was stable (mean ± 2 injections) for at least three consecutive cocaine and saline sessions. At this point, the session sequence was changed to a double alternation, i.e., two consecutive cocaine sessions were followed by two consecutive saline sessions.

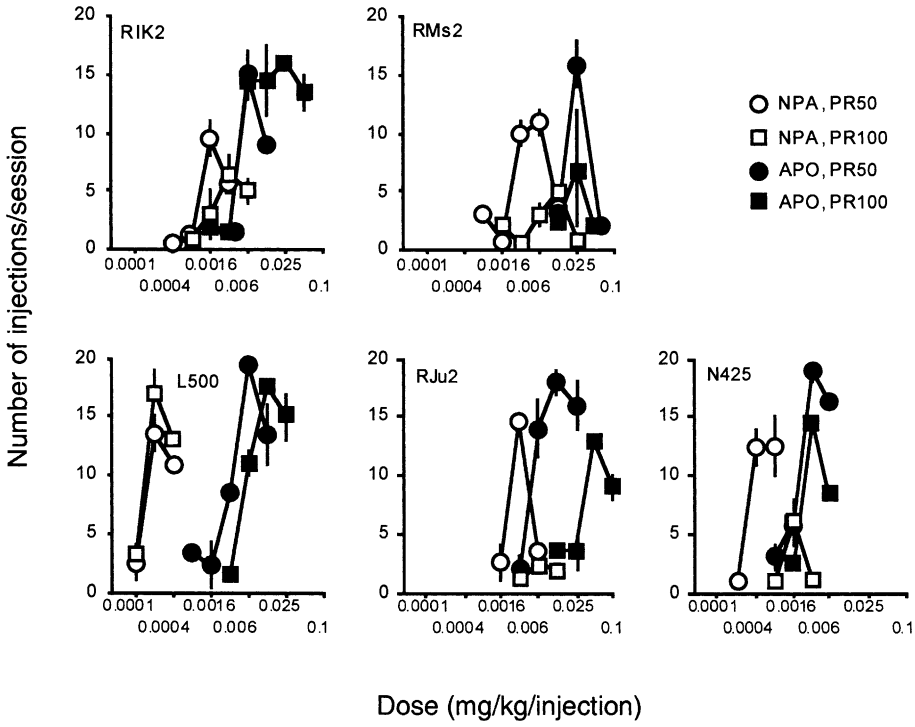

Fig. 1. Self-administration of APO and NPA under PR schedules of reinforcement. Sessions began with response requirements of 50 (PR50) or 100 (PR100) responses that doubled after every fourth injection. Each point represents the total number of injections averaged across two or three test sessions of any particular dose, and vertical lines represent the range of those values. Where vertical lines do not appear, the range is contained within the point. Individual monkeys are identified in the upper left of each panel.

When responding was again stable, test sessions were added to the daily sequence between consecutive saline and consecutive cocaine sessions. Since monkeys occasionally appear to learn this sequence and to anticipate sessions, a randomly determined saline or cocaine session was inserted after a test session at approximately 3-week intervals. During test sessions, the monkeys had available to them one of various doses of NPA or APO. In preliminary studies, responding maintained by NPA or APO at a 30-min TO was investigated in two monkeys (data not shown). Neither NPA (0.0125–0.05 mg/kg/injection) nor APO (0.05 and 0.1 mg/kg/injection) maintained responding above saline levels at starting PR sequences between 25 and 400. Subsequently, NPA or APO was made available under a PR sequence beginning with a randomly determined response requirement of 50 or 100. As in baseline sessions, response requirement doubled for each successive component. The doses of NPA or APO were tested in random order with the first compound or dose for an individual monkey counterbalanced across monkeys. After a test session, a monkey was returned to baseline conditions until responding for cocaine and saline were again stable. All doses of NPA and APO were tested twice on each PR sequence (response requirement 50 or 100 to start) in each monkey. For each PR sequence each dose was tested twice, once between two saline sessions and once between two cocaine sessions.

After each monkey had completed testing of all doses of NPA and APO at each of the PR sequences, the possibility that drug accumulation over a session influenced PR responding was examined by lengthening the TO after injections. The TO was lengthened to 600 s and NPA and APO were tested again, as above, at the PR sequence beginning with 50 responses. Monkey N425 became ill and died, for reasons unrelated to the study, before all conditions could be tested.

2.3. Data analysis

For each monkey the mean number of injections per session was calculated using the data from each test session for each PR sequence. The range of total number of injections in each test session was used as a measure of

Table 1
Mean maximum number of injections and ED50 values for APO and NPA available for self-administration in rhesus monkeys

	Initial PR sequence			
Drug	PR50		PR100	
ED50 (mg/kg)	Max injection	ED50	Max injection	ED50
APO	17.5 ± 1.01	0.009 ± 0.003	14.5 ± 1.88	0.011 ± 0.006
NPA	12.2 ± 1.14	0.001 ± 0.0005	7.4 ± 3.2	0.002 ± 0.001

Values are mean ± S.E.M.

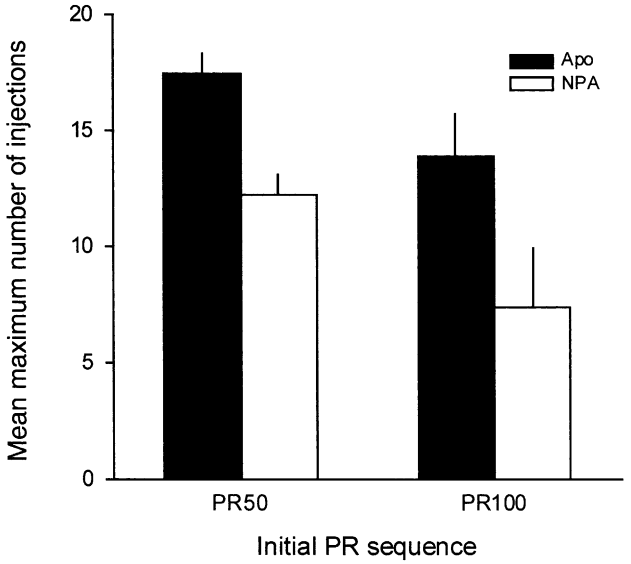

Fig. 2. Mean maximum number of injections of APO and NPA self-administered when either drug was available under the PR schedule of reinforcement starting with 50 or 100 responses. The vertical lines represent the S.E.M.

variability. For each drug under each set of PR and TO conditions, a mean maximum number of injections was calculated by averaging the individual maximum mean number of injections for a particular drug, regardless of dose, across all monkeys. An ED50 was calculated for each drug for each animal in which the drug served as a reinforcer (self-administration in excess of saline rates) at least at one dose, using the visibly linear portion of the dose–response function and least squares linear regression (GraphPad Prism 2.0). Means and S.E.M. were calculated for maximum injections and ED50s for each drug at each starting PR value. Statistical significance of differences between means was examined using a paired *t* test.

2.4. Drugs

Cocaine HCl was provided by the National Institute on Drug Abuse (Rockville, MD). NPA and APO were purchased from Research Biochemicals in Natick, MA. Cocaine was dissolved in saline. NPA and APO were dissolved in distilled water containing 1 mg/ml ascorbic acid. All injections were delivered over 10 s in a volume of approximately 1.0 ml.

3. Results

All monkeys self-administered cocaine (0.05 or 0.1 mg/kg/injection) under baseline conditions. The baseline rates of cocaine self-administration for these monkeys ranged from 12 (L500) to 15 (RIK2) injections per session. The baseline rates of saline self-administration for these monkeys ranged from one to three injections per session for all monkeys. Baseline rates remained stable for an individual monkey over the course of the experiment.

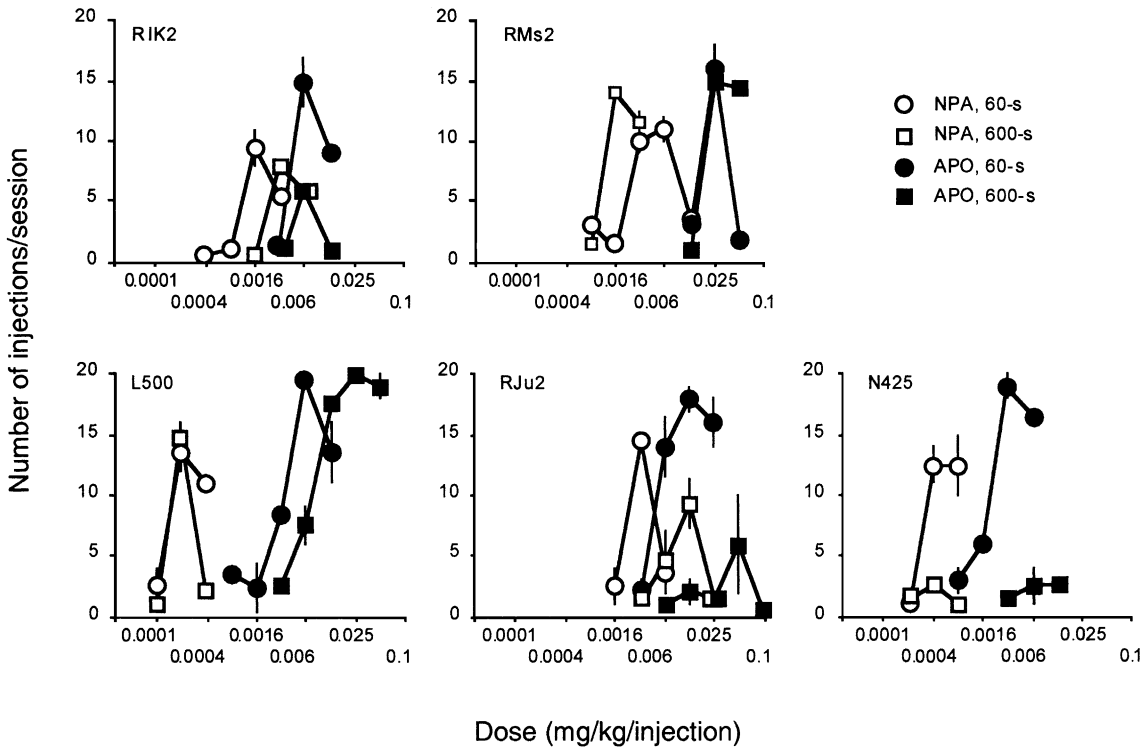

Fig. 3. Self-administration of APO and NPA under PR schedules of reinforcement. Sessions began with response requirements of 50 that doubled after every fourth injection. TO after injections was either 60 or 600 s. Data for the 60-s TO are the same as those in Fig. 1. Other details are as in Fig. 1.

When the PR sequence began at 50, all monkeys self-administered at least one dose of NPA or APO at rates above those observed when saline was available (Fig. 1). Self-administration of these compounds increased over low to moderate doses and, at higher doses, was asymptotic or decreased. The doses of APO or NPA that maintained the greatest number of injections varied somewhat among monkeys. Changing the initial PR sequence from 50 to 100 responses shifted the dose–response functions to the right and/or downward for APO in all monkeys except RIK2. For the group, these changes did not achieve statistical significance (Table 1; $P>.05$). A similar effect was noted for NPA in all monkeys except L500 where the dose–response function shifted upward. NPA was not a reinforcer at PR100 in monkey RJu2 up to 0.012 mg/kg/injection. As with APO, changes in mean ED50s and maxima were not statistically significant (Table 1; $P>.05$) when the PR sequence was changed. For both PR sequences, the mean maximum number of injections per session when APO was available was greater than the mean maximum number of injections per session when NPA was available (Fig. 2, Table 1; PR50: $t=10.3$, $df=4$, $P<.001$; PR100: $t=3.5$, $df=4$, $P=.025$). The calculated ED50 for NPA was 9-fold lower than the ED50 for APO for the PR50 and 5.5-fold lower for the PR100 sequence (Table 1). However, these differences did not achieve statistical significance ($P>.05$). At the highest doses of both drugs, monkeys exhibited psychomotor stimulation during the experimental session.

The dose–response functions for NPA or APO with the 600-s TO were similar to those seen at the 60-s TO in that responding first increased with dose then was asymptotic or decreased (Fig. 3). Although the ED50 appeared to increase when the TO increased from 60 to 600 s, this effect was not statistically significant across the group ($P>.05$). In addition, there were no significant between- or within-drug differences in maximum responding with the change to 600-s TO ($P>.05$).

4. Discussion

Both NPA and APO maintained self-administration under a PR schedule in rhesus monkeys. This finding extends the conditions under which D2-like agonists have been found to function as positive reinforcers. Although NPA was a more potent reinforcer than APO in most monkeys, mean values were not statistically different. In a previous self-administration study with D2-like agonists, we found that both APO and NPA were self-administered under an FR schedule of reinforcement and that NPA was more potent than APO in most monkeys (Ranaldi et al., 2001). Additionally, in radioligand binding studies, NPA has been found to have higher affinity for D2 sites than APO in monkey (Ranaldi et al., 2001) and rat (Arnt et al., 1983; Kula et al., 1985; Valchar et al., 1987) brain tissue. Previous studies of locomotor effects in rodents have found NPA to be as much as 90-fold more potent than APO (Campbell et al., 1986; Martin and Bendesky, 1984). It seems likely that the lack of a statistically significant potency difference in the present study was due variability and a small number of degrees of freedom in the statistical comparison.

When APO and NPA were available under a simple FR schedule of reinforcement, they were indistinguishable in terms of rates of self-administration (Ranaldi et al., 2001). Under the PR schedule used in the present study, there were differences between the drugs in their relative efficacy as reinforcers. When there was a 60-s TO after injections, APO maintained more responding, i.e., was the more effective reinforcer, regardless of initial PR sequence. When there was a 600-s TO after injections, APO was at least as effective as NPA as a reinforcer. Thus, the PR schedule and/or the TO after responding revealed differences between the drugs that were not apparent under a simple FR schedule. This finding supports the longstanding conclusion that rate of self-administration under simple schedules of reinforcement is not a reliable indicator of relative efficacy as a reinforcer (see Johanson, 1978; Young and Herling, 1986).

Clearly, the finding that the lower efficacy D2-like agonist APO was at least as effective a reinforcer as the higher efficacy D2-like agonist NPA is contrary to the hypothesis of the study. A conclusion that reinforcing efficacy is inversely related to agonist efficacy, although consistent with these data, would be both counterintuitive and contrary to existing data with opioids (Winger et al., 1996) and D1 agonists (Weed et al., 1997). However, that the APO < NPA efficacy relationship is based upon in vitro observations from rat brain tissue. It is not clear that this relationship holds in behavioral assays. NPA and APO have also been found to have similar efficacy as locomotor stimulants (Campbell et al., 1986; Martin and Bendesky, 1984). Moreover, APO and the full D2 agonist piribedil have been found to fully cross-substitute as discriminative stimuli in rats (Woolverton et al., 1985; Kamien et al., 1987), suggesting that APO functions as a full D2 agonist in vivo. In monkeys, piribedil fully substituted for APO as a discriminative stimulus, though the reverse has not been tested (Woolverton et al., 1987). It is also possible that the in vitro D2 efficacy relationship reported in rat brain is not the same in the monkey brain. This possibility has not been evaluated, to our knowledge, although substantial efficacy differences were not observed when D1 receptor agonist efficacy was compared in rat and monkey tissue (Weed et al., 1997). On the other hand, behavioral differences between agonists have been reported that may be important in efficacy considerations. NPA has been reported to substitute for D-amphetamine as a discriminative stimulus (Arnt and Hyttel, 1990) while APO substituted for some doses of D-amphetamine but not others (Stolerman and D'Mello, 1981; Woolverton and Cervo, 1986). Additionally, APO has been reported to be a less consistent positive reinforcer than piribedil, suggesting that it is a less efficacious reinforcer (Woolverton et al., 1984).

It is reasonable to also consider that pharmacodynamic mechanism(s) other than D2 receptor efficacy may have contributed to the efficacy of these compounds as positive reinforcers. More specifically, pharmacological actions other than those at D2-like receptors may interact with D2-like actions to contribute to the reinforcing effect. One logical candidate is D1 actions. APO has a relatively high affinity at both D1- and D2-like binding sites (Euvrard et al., 1979; Herrera-Marschitz and Ungerstedt, 1984) while NPA appears to be more selective for the D2 receptor (Creese et al., 1979). Thus, APO may be a more effective reinforcer because of its mix of D1- and D2-like receptor actions, above and beyond its partial D2-like receptor efficacy. Interactions between D1- and D2-like receptor actions have been implicated for other DA-mediated behavioral effects (Walters et al., 1987). Manzardo et al. (2001) have recently reported the combination of a D1 and a D2 agonist is preferred to either type of agonist alone in rats. However, APO is a partial efficacy D1 agonist (Kebabian and Calne, 1979) and partial efficacy D1 agonists have been found not to function as positive reinforcers in rhesus monkeys (Weed and Woolverton, 1995; Weed et al., 1997). Obviously, highly selective agonists allow stronger conclusions in this regard.

In addition to these pharmacodynamic possibilities, pharmacokinetics appear to contribute to the observed differences between these agonists. The relative reinforcing efficacy of the drugs varied with TO. One would expect less drug accumulation with longer TOs after injections. Since drug accumulation over the course of a session generally decreases rate of self-administration (see Johanson, 1978; Young and Herling, 1986), we anticipated that responding would increase with TO. In fact, responding decreased for both drugs. Indeed, to begin the experiment both drugs were briefly made available with a 30-min TO that we have typically used to study cocaine as a reinforcer. As noted, neither NPA (0.0125–0.05 mg/kg/injection) nor APO (0.05 and 0.1 mg/kg/injection) maintained responding above saline levels at starting PR sequences between 25 and 400 at a 30-min TO. Together, these results imply that there is an optimal TO for measuring the efficacy of each of these drugs as a positive reinforcer. When the interinjection interval is shorter than the optimal value, drug accumulates over the session to the point that responding is reduced. Conversely, when the interinjection interval is longer than optimal, responding is reduced as well. The mechanism controlling this effect is unclear. It is possible that insufficient drug accumulates over the session to optimize reinforcement. Alternatively, it may be that there are aversive side effects at the high doses necessary to maintain responding with long TOs that suppress responding. In addition, the higher efficacy agonist could limit self-administration to a greater extent via an aversive side effect. In any case, the general point to be emphasized is that a TO after injection is among the behavioral conditions that can modify the relative efficacy of drugs as reinforcers.

There is an ongoing interest in the relationship between pharmacological mechanism of action and efficacy as a positive reinforcer (e.g., Bergman et al., 1989; Ritz et al., 1987; Wilcox et al., 2000). The hypothesis that agonist efficacy is directly related to efficacy as a reinforcer has intuitive appeal. Indeed, available data tend to support this hypothesis for DA agonists in, at least, a qualitative way (Ranaldi et al., 2001; Weed et al., 1997). However, empirical support for the graded nature of this relationship is, at this point, limited to one experiment with two opioids (Winger et al., 1996). The present experiment underscores the observation that rank-ordering drugs as to relative efficacy as reinforcers is at least a complex undertaking even under the best of circumstances (see Katz, 1990). Clearly, multiple pharmacological and behavioral mechanisms can contribute to a reinforcing effect. Although this is not the first demonstration of that fact, the present experiment emphasizes that there is not a straightforward relationship between in vitro measures of agonist efficacy and efficacy as a reinforcer.

References

Arnt J, Hyttel J. Dopamine D-2 agonists with high and low efficacies: differentiation by behavioral techniques. J Neural Transm 1990;80: 33–50.

Arnt J, Bogeso KP, Christensen AV, Hyttel J, Larsen J-J, Svendsen O. Dopamine receptor agonistic and antagonistic effects of 3-PPP enantiomers. Psychopharmacology 1983;81:199–207.

Bergman J, Madras BK, Johnson SE, Spealman RD. Effects of cocaine and related drugs in nonhuman primates: self-administration by squirrel monkeys. J Pharmacol Exp Ther 1989;251:150–5.

Campbell A, Baldessarini RJ, Teicher MH, Neumeyer JL. Behavioral effects of apomorphine isomers in the rat: selective locomotor-inhibitory effects of *S*(+)*N*-*n*-propylnorapomorphine. Psychopharmacology 1986;88:158–64.

Corrigall WA, Coen KM. Cocaine self-administration is increased by both D1 and D2 dopamine antagonists. Pharmacol, Biochem Behav 1991; 39:799–802.

Creese I, Padgett L, Fazzini E, Lopez F. 3H-*N*-*n*-propylnorapomorphine: a novel agonist ligand for central dopamine receptors. Eur J Pharmacol 1979;56:411–2.

Euvrard C, Premont J, Oberlander C, Boissier JR, Bockaert J. Is dopamine-sensitive adenylate cyclase involved in regulating the activity of striatal cholinergic neurons? Naunyn-Schmiedeberg's Arch Pharmacol 1979; 309:241–5.

Grech DM, Spealman RD, Bergman J. Self-administration of D1 receptor agonists by squirrel monkeys. Psychopharmacology 1996;125:97–104.

Herrera-Marschitz M, Ungerstedt U. Evidence that apomorphine and pergolide induce rotation in rats by different actions on D1 and D2 receptor sites. Eur J Pharmacol 1984;98:165–76.

Johanson CE. Drugs as reinforcers. In: Blackman DE, Sanger DJ, editors. Contemporary research in behavioral pharmacology. New York: Plenum, 1978. pp. 325–90.

Kamien JB, Goldberg LI, Woolverton WL. The discriminative stimulus properties of D1 and D2 dopamine agonists in rats. J Pharmacol Exp Ther 1987;242:804–11.

Katz JL. Models of relative reinforcing efficacy and their predictive utility. Behav Pharmacol 1990;1:30–283.

Kebabian JW, Calne DB. Multiple receptors for dopamine. Nature 1979; 277:93–6.

Koob GF. Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol Sci 1992;13:177–84.

Koob GF, Le HT, Creese I. The D1 dopamine receptor antagonist SCH 23390 increases cocaine self-administration in the rat. Neurosci Lett 1987;79:315–20.

Kula NS, Baldessarini RJ, Bromley S, Neumeyer JL. Effects of isomers of apomorphines on dopamine receptors in striatal and limbic tissue of rat brain. Life Sci 1985;37:1051–7.

Lahti RA, Figur LM, Piercey MF, Ruppel PL, Evans DL. Intrinsic activity determinations at the dopamine D2 guanine nucleotide-binding protein-coupled receptor: utilization of receptor state binding affinities. Mol Pharmacol 1992;42:432–8.

Manzardo AM, Del Rio JA, Stein L, Belluzzi JD. Rats choose cocaine over dopamine agonists in a two-lever self-administration preference test. Pharmacol, Biochem Behav 2001;70:257–65.

Martin GE, Bendesky RJ. Mouse locomotor activity: an in vivo test for dopamine autoreceptor activation. J Pharmacol Exp Ther 1984; 229: 706–11.

Nilsson C, Eriksson E. Partial dopamine D2 receptor agonists antagonize prolactin-regulating D2 receptors in a transfected clonal cell line (GH4ZR7). Eur J Pharmacol 1992;218:205–11.

O'Boyle KM, Lawler M. D2 receptor agonists and partial agonists: relationship between receptor binding measures and functional activity. Biochem Soc Trans 1996;24:183–8.

Pulvirenti L, Balducci C, Piercy M, Koob GF. Characterization of the effects of the partial dopamine agonist terguride on cocaine self-administration in the rat. J Pharmacol Exp Ther 1998;286:1231–8.

Ranaldi R, Anderson KG, Carroll FI, Woolverton WL. Reinforcing and discriminative stimulus effects of RTI 111, a 3-phenyltropane analog, in rhesus monkeys: interaction with methamphetamine. Psychopharmacology 2000;153:103–10.

Ranaldi R, Wang Z, Woolverton WL. Reinforcing effects of D2 dopamine receptor agonists and partial agonists in rhesus monkeys. Drug Alcohol Depend 2001;64:209–17.

Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 1987;237:1219–23.

Ruffolo RR. Important concepts of receptor theory. Physiol Behav 1982; 54:695–700.

Self DW, Stein L. The D1 agonists SKF 82958 and SKF 77434 are self-administered by rats. Brain Res 1982;582:349–52.

Stolerman IP, D'Mello GD. Role of training conditions in discrimination of central nervous system stimulants by rats. Psychopharmacology 1981; 73:295–303.

Valchar M, Vrsecka M, Krejci I, Dlabac A. Binding characteristics of the dopamine agonist/antagonist [3H]terguride (transdihydrolisuride) in the rat striatum. Eur J Pharmacol 1987;136:97–101.

Walters JR, Bergstrom DA, Carlson JH, Chase TN, Braun AR. D1 dopamine receptor activation required for postsynaptic expression of D2 agonist effects. Science 1987;236:719–22.

Weed MR, Woolverton WL. The reinforcing effects of dopamine D1 receptor agonists in rhesus monkeys. J Pharmacol Exp Ther 1995;275: 1367–74.

Weed MR, Paul IA, Dwoskin LP, Moore SE, Woolverton WL. The relationship between reinforcing effects and in vitro effects of D1 agonists in monkeys. J Pharmacol Exp Ther 1997;283:29–38.

Wilcox KM, Rowlett JK, Paul IA, Ordway GA, Woolverton WL. On the relationship between the dopamine transporter and the reinforcing effects of local anesthetics: practical and theoretical concerns. Psychopharmacology 2000;153:139–47.

Wilson MC, Schuster CR. The effects of chlorpromazine on psychomotor stimulant self-administration in the rhesus monkey. Psychopharmacologia 1972;26:115–26.

Winger G, Woods JH, Hursh SR. Behavior maintained by alfentanil or nalbuphine in rhesus monkeys: fixed-ratio and time-out changes to establish demand curves and relative reinforcing effectiveness. Exp Clin Psychopharmacol 1996;4:131–40.

Wise RA. Neurobiology of addiction. Curr Opin Neurobiol 1996;6:243–51.

Woolverton WL. Effects of a D1 and a D2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. Pharmacol, Biochem Behav 1986;24:531–5.

Woolverton WL, Cervo L. Effects of central dopamine depletion on the D-amphetamine discriminative stimulus in rats. Psychopharmacology 1986;88:196–200.

Woolverton WL, Johnson KM. Neurobiology of cocaine abuse. Trends Pharmacol Sci 1992;13:193–200.

Woolverton WL, Goldberg LI, Ginos JZ. Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. J Pharmacol Exp Ther 1984;230:678–83.

Woolverton WL, Kamien JB, Goldberg LI. Effects of selective dopamine receptor agonists in rats trained to discriminate apomorphine from saline. Pharmacol, Biochem Behav 1985;22:577–81.

Woolverton WL, Kamien JB, Goldberg LI. Pharmacological analysis of the apomorphine discriminative stimulus in rhesus monkeys. J Pharmacol Exp Ther 1987;241:213–7.

Woolverton WL, Hecht GS, Agoston GE, Katz JL, Newman AH. Further studies of the reinforcing effects of benztropine analogs in rhesus monkeys. Psychopharmacology 2001;154:375–82.

Yokel RA, Wise RA. Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward. Science 1975;187:547–9.

Yokel RA, Wise RA. Amphetamine-type reinforcement by dopaminergic agonists in the rat. Psychopharmacology 1978;58:289–96.

Young AM, Herling S. Drugs as reinforcers: studies in laboratory animals. In: Goldberg SR, Stolerman IP, editors. Behavioral analysis of drug dependence. New York: Academic Press, 1986. pp. 9–67.