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# Comparison of the Stimulus Properties of a Pre- vs. a Putative Postsynaptic Dose of Quinpirole

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CORY-SLECHTA, D. A., C. L. ZUCH AND R. A. V. FOX. *Comparison of the stimulus properties of a pre- vs. a putative postsynaptic dose of quinpirole.* PHARMACOL BIOCHEM BEHAV **55**(3) 423–432, 1996.—Presynaptic $D_2$-like receptors appear to mediate the stimulus properties of a low dose (0.05 mg/kg) of the $D_2$-like agonist quinpirole (QUIN), because treatments decreasing dopamine (DA) release or blocking postsynaptic DA receptor activation produce QUIN-appropriate responding in a drug discrimination context, whereas treatments activating postsynaptic DA receptors evoke saline responding (28). This study examined the hypothesis that training to a presumably postsynaptic dose of QUIN (0.20 mg/kg) would produce the opposite pattern of effects. Using drug discrimination procedures, substitution for 0.05 mg/kg (28), but not 0.20 mg/kg QUIN, was produced by the $D_1$ antagonist SCH23390, the catecholamine depleter alpha-methyl-paratyrosine and low doses of apomorphine (up to 0.25 mg/kg). The $D_2$ agonist NPA substituted fully for 0.05 but only partially for 0.20 mg/kg QUIN. Cocaine and *d*-amphetamine (alone or with SCH 23390) substituted only minimally for either QUIN training dose. The putative $D_3$ agonist 7-OH-DPAT engendered primarily saline responding when substituted for 0.20 QUIN. The 0.20 QUIN stimulus was antagonized by the $D_2$ blocker haloperidol and partially blocked by the $D_1$ antagonist SCH 23390. These data show a clear difference in the mediation of the stimulus properties of a low (0.05 mg/kg) vs. a high (0.20 mg/kg) dose of QUIN and are suggestive of a preferential postsynaptic $D_2$ mediation of the 0.20 mg/kg QUIN dose. 

Quinpirole $D_1$ $D_2$ $D_3$ Dopamine 7-OH-DPAT Stimulus properties Drug discrimination

DOPAMINE receptors have been classified into two major families, $D_1$like ($D_1$, $D_5$) and $D_2$-like ($D_2$, $D_3$, $D_4$), based on differences in their pharmacological profiles and nucleotide sequences and their effects on adenylate cyclase activity (6). Further, $D_2$ dopamine receptors may be either presynaptic or postsynaptic. Presynaptic $D_2$ receptor activation is associated with direct inhibition of DA cell functioning through inhibition of impulse flow, dopamine synthesis, or dopamine release. Postsynaptic $D_2$ receptor activation, in contrast, results in changes in electrical and biochemical function in target neurons, such as altered release of acetylcholine and gamma-aminobutyric acid and modulation of electrical activity of striatal neurons (30).

It is commonly held that dopamine agonists acting on $D_2$ receptors show preferential activation of presynaptic receptors at low concentrations, with stimulation of postsynaptic receptors occurring only at higher concentrations (19,27). Doses of the $D_2$-like dopamine agonist quinpirole (QUIN) that are effective for autoreceptor-mediated inhibition of dopamine cell firing, for example, are consistently 6- to 10-fold lower than those required to alter the firing of postsynaptic cells (5,27) See and colleagues (16) noted significant reductions in striatal extracellular dopamine levels at QUIN doses as low as 0.03 mg/kg IP, whereas Wong et al. (31) observed minor elevations in striatal acetylcholine levels only at much higher doses of 0.10 mg/kg and with an $ED_{50}$ of approximately 0.20 mg/kg.

Autoreceptor and postsynaptic $D_2$ receptor activation can likewise be distinguished behaviorally. Biphasic dose effect curves (inverse U-shaped) for dopamine agonists such as APO

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and pergolide have been described for drug-induced yawning, immobility, and suppression of exploratory behavior (1,4,22). Several findings suggest that presynaptic doses of $D_2$ agonists are associated with effects characteristic of reduced dopaminergic transmission, such as reduced activity and climbing, and sedation, whereas postsynaptic doses engender locomotor activation, stereotypy, and increased climbing behavior (1,30). Eilam and Szechtman(11), for example, reported that a dose of 0.03 mg/kg of QUIN decreased locomotion, whereas doses of 0.125 mg/kg and above increased it. Overall response rates on a fixed interval schedule of reinforcement were recently noted to be decreased by low doses of QUIN (0.033–0.067 mg/kg) but increased by higher (0.10 mg/kg) doses (7a).

Further support for this presynaptic vs. postsynaptic $D_2$ distinction comes from a recent study in rats exploring the stimulus properties of a low dose (0.05 mg/kg) of the $D_2$-like agonist QUIN (28). In concert with a presynaptic mediation of its effects at low doses, compounds engendering decreased dopamine release and availability, such as the catecholamine depleter alpha-methyl-paratyrosine (AMPT) and the $D_1$ antagonist SCH23390, substituted for QUIN in a drug discrimination paradigm. Coadministration of AMPT with QUIN, moreover, significantly shifted the QUIN dose–effect curve to the left. Apomorphine actually produced an inverse U-shaped dose–effect curve, with low doses increasing QUIN lever responding, whereas higher doses, previously shown to substitute for $D_1$ agonists (10), actually decreased drug lever responding. In contrast, compounds directly or indirectly activating postsynaptic receptors, including the $D_1$ agonist SKF38393, *d*-amphetamine, and *d*-amphetamine coadministered with the $D_1$ antagonist SCH23390 (to produce postsynaptic $D_2$ specificity) evoked primarily saline-appropriate responding. Furthermore, administration of direct or indirect postsynaptic agonists such as SKF38393 and *d*-amphetamine partially blocked the QUIN cue.

The current study used a similar strategy to that employed in Widzowski and Cory-Slechta (28) to examine the hypothesis that a higher dose of QUIN would be mediated instead by postsynaptic $D_2$ receptors and produce a profile of effects opposite to that noted after training to 0.05 mg/kg QUIN. A training dose (0.20 mg/kg) was selected based on previous studies suggestive of postsynaptic activity [e.g., (7a, 31)]. In addition, questions related to a $D_1$ "enabling" effect for expression of postsynaptic $D_2$ stimulus properties were addressed using the $D_1$ antagonist SCH23390 (25,26).

## METHOD

### *Animals*

Ten adult male Long–Evans rats (Blue Spruce Farms, Altamont, NY) were used in this study. Rats were maintained at 300 g body weights via regulation of total daily food intake. All rats received a standard rat chow diet and were individually housed in a colony room maintained at 22°C with a 12 L: 12 D cycle. Animal use was conducted in accord with the University of Rochester Institutional Animal Care and Use Committee Regulations and with NIH guidelines.

### *Apparatus*

Behavioral sessions were conducted in operant chambers (Coulbourne Instruments, Inc., Lehigh Valley, PA, model E10-10), each of which was housed in a sound-attenuating enclosure ventilated by a fan. Each chamber contained three response levers; the middle lever was inactive in these experiments. A pellet trough, through which 45 mg food pellets were dispensed, was located below the middle lever. Behavioral contingencies and data collection were executed using SKED 11 systems and programming. Other details of this apparatus have been described elsewhere (7).

### *Drug Discrimination Procedures*

Rats were trained to discriminate 0.20 mg/kg of QUIN from saline. Animals were first trained, in separate overnight sessions, to respond on each of the response levers (8,10). Response shaping was based on a 30-min presentation of a variable time (VT) schedule of reinforcement in which food pellets were delivered independently on responding after a variable period of time averaging 30 s. Any lever press responses that occurred during the 30 min also produced a food pellet delivery, and if 10 such responses occurred, the VT schedule automatically shifted to a fixed ratio (FR) 1 schedule in which each occurrence of a response on the active lever resulted in food pellet delivery, and response-independent food deliveries were no longer provided. If less than 10 lever press responses occurred during the VT schedule, it automatically shifted to a FR1 after 30 min. The FR1 schedule remained in effect until 100 food pellet deliveries occurred or until 0700 h, whichever occurred first.

Subsequently, a drug discrimination procedure was imposed based on a standard two lever (drug vs. saline) food-reinforced operant drug discrimination paradigm. Injections of either QUIN or saline were administered prior to the session according to a randomized sequence with the stipulation of no more than three consecutive QUIN or saline sessions. Responding on one lever was reinforced following injections of QUIN, while responding on the other lever was reinforced following injections of saline. The assignment of QUIN and saline lever was counterbalanced across chambers. Responding on the correct lever was reinforced on a ratio schedule, which was increased from 1 to a final value of 10 (FR10) over the first 10–15 sessions.

Experimental sessions were initiated by the first response on either lever and subsequently lasted 10 min. Sessions were conducted once a day, 5 days a week (M–F). The session accuracy criterion was set at 77% correct in the first ratio (i.e., no more than three incorrect responses before completion of 10 responses on the correct lever), and acquisition of the discrimination was defined as 8 out of 10 consecutive sessions in which the 77% session accuracy criterion was met.

After acquisition of the discrimination, testing sessions (substitution and antagonism tests) were conducted with the pharmacological treatments described below. Test sessions were response initiated and generally lasted 3 min, except for doses of drugs that markedly depressed response rates, in which case the session duration was extended to a maximum time of 10 min. This was done to ensure that measures of response rate could be calculated. During test sessions, responses on either lever had no consequence. Rather, the end of the session was followed by the delivery of three food pellets, each separated by a 0.5 s delay, independently of responding.

To ensure stability of the baseline discriminative performance across time, at least one QUIN and one saline training session with accuracy levels of 77% or greater were required for each rat between all test sessions. In addition, test sessions using the training dose of QUIN and saline were carried out intermittently throughout the duration of the experiment (redeterminations). The order of testing of the various pharmaco-

logical treatments, as well as the dose of each utilized, was pseudorandom.

For the determination of the QUIN dose–effect curve, at least two replications of each QUIN dose were carried out in each rat. For all other pharmacological treatments, rats received at least one replication of each dose of a compound. However, because of the differential rate at which rats progressed through both the training and pharmacological testing phases, not all rats were utilized for tests of all pharmacological compounds. The number of animals contributing to each dose–effect curve is indicated in the corresponding figure legend for each figure.

*Pharmacological Treatments*

In addition to determination of QUIN dose–effect curves, the following pharmacological probes were used to examine the stimulus properties of 0.20 mg/kg QUIN: 1) substitution of other dopamine $D_2$ agonists including NPA (N-n-propylnorapomorphine) and low doses of apomorphine (APO); 2) catecholaminergic depletion produced by substitution with alpha-methyl-para-tyrosine (AMPT); 3) substitution with the putative $D_3$ selective agonist 7-OH-DPAT; 4) postsynaptic dopamine receptor blockade produced by substitution with the $D_1$ antagonist SCH 23390; 5) postsynaptic $D_1$ dopamine receptor activation produced by substitution with the $D_1$ agonist SKF 82958, high doses of APO (mixed direct $D_1/D_2$ agonist), and cocaine and *d*-amphetamine (mixed indirect $D_1/D_2$ agonists); 6) postsynaptic $D_2$ activation produced by coadministration of the $D_1$ antagonist SCH 23390 with *d*-amphetamine; 7) blockade of dopamine $D_2$ receptors produced by the administration of doses of haloperidol before various doses of QUIN; 8) blockade of dopamine $D_1$ receptors produced by the administration of various doses of the $D_1$ antagonist SCH23390 prior to 0.20 mg/kg QUIN or a 0.05 mg/kg dose of SCH23390 prior to various doses of QUIN.

*Drugs*

Quinpirole hydrochloride (LY 171555), alpha methyl-*p*-tyrosine methyl ester (AMPT), SCH23390 hydrochloride (SCH), chloro-APB hydrobromide (SKF 82958), APO hydrochloride (APO), and N-n-propylnorapomorphine hydrochloride (NPA) were obtained from Research Biochemicals Inc. (Natick, MA). Haloperidol (as the lactate; McNeil Pharmaceuticals, Spring House, PA), cocaine hydrochloride and *d*amphetamine sulfate were obtained from the University of Rochester Strong Memorial Hospital Pharmacy. All drugs other than haloperidol were dissolved in 0.9% sterile saline and injected IP; haloperidol was injected SC. QUIN, SKF82958, APO, and *d*-amphetamine were injected 30 min prior to substitution test sessions, SCH23390 45 min, NPA 15 min, cocaine 10 min, and AMPT 3.5 h (to allow for depletion of dopamine) before the test session. Haloperidol and SCH23390 were injected 30 min prior to QUIN for antagonism tests. All drugs were injected in a volume of 1 ml/kg, and doses were calculated based on the salt.

*Data and Statistical Analyses*

The percentage QUIN-lever responding in training sessions was calculated by dividing responses on the QUIN lever during the first ratio by responses on both the QUIN and saline levers during the first ratio and multiplying this quotient by 100. The percentage saline-lever responding in training sessions was calculated similarly using responses on the saline lever during the first ratio as the numerator. Accuracy in test sessions was calculated using data for lever presses up to the point where 10 responses had been emitted on either lever. Response rate was calculated by dividing the total number of responses emitted during the test session by the total duration of the test session in minutes. It was measured to assess the extent to which drug lever response levels in the presence of test drugs might be influenced by very low levels of responding. Because even a single response difference could produce marked changes in levels of drug lever responding in test sessions based on a very small number of responses, only those sessions that resulted in five or more total responses were included in the statistical analyses of drug lever responding. All test results, however, were included in the analysis of response rates to produce the most accurate depiction of drug-induced rate changes.

For the calculation of group mean levels of drug or saline lever responding, median values were used when two or more replications of a particular test had been carried out, because the median value was considered more representative of typical performance. For the calculation of response rates, mean values across replications of a particular test were used. In cases where only a single determination of a test was undertaken, the calculation of response rates and QUIN lever responding represented the group mean of the individual values across rats.

For characterization of the 0.20 mg/kg QUIN stimulus, values of $\leq 23\%$ drug lever responding were defined as saline-appropriate responding, those $\geq 77\%$ were defined as substituting for QUIN; values in between these levels were defined as partial generalization. For comparative purposes, drug lever response data from this study were plotted with results obtained using parallel procedures in rats trained to discriminate a low dose of QUIN, 0.05 mg/kg from saline (28). This was done to permit a more direct assessment of the effects of the two different training doses. Comparisons of the effects of the stimulus properties of 0.05 and 0.20 mg/kg QUIN are based on visual contrasts only. Statistical analyses of drug lever responding was considered unnecessary because effects were either obviously different or overlapped significantly.

To evaluate the effects of antagonism of QUIN drug lever responding by 0.05 mg/kg SCH23390 (Fig. 7, upper right) and QUIN response rates by 0.08 mg/kg haloperidol (Fig. 6, bottom) and 0.05 mg/kg SCH23390 (Fig. 7, bottom right), repeated measures analyses of variance based on two within factors (subject, quinpirole/quinpirole, and antagonist) was used. Because of the rate-suppressing properties of 0.08 mg/kg haloperidol, a sufficient number of complete dose–effect curves were not available to follow this approach for within-rat comparisons of QUIN alone vs. QUIN plus haloperidol (Fig. 6, top). Instead, a one-way analysis of variance with haloperidol as a between-groups factor was employed. Assessment of the effects of varying doses of SCH23390 on 0.20 mg/kg QUIN drug lever responding and response rates (Fig. 7, left) was accomplished using a one factor (SCH23390) repeated measures analyses of variance.

## RESULTS

*Training and Performance Stability*

The mean ± SE number of sessions to criterion averaged 86 ± 15.7 following the imposition of the FR 10 schedule of reinforcement. The relatively long duration required for acquisition of the discrimination was a function of the rate-disrupting properties of the training dose of QUIN. Stability

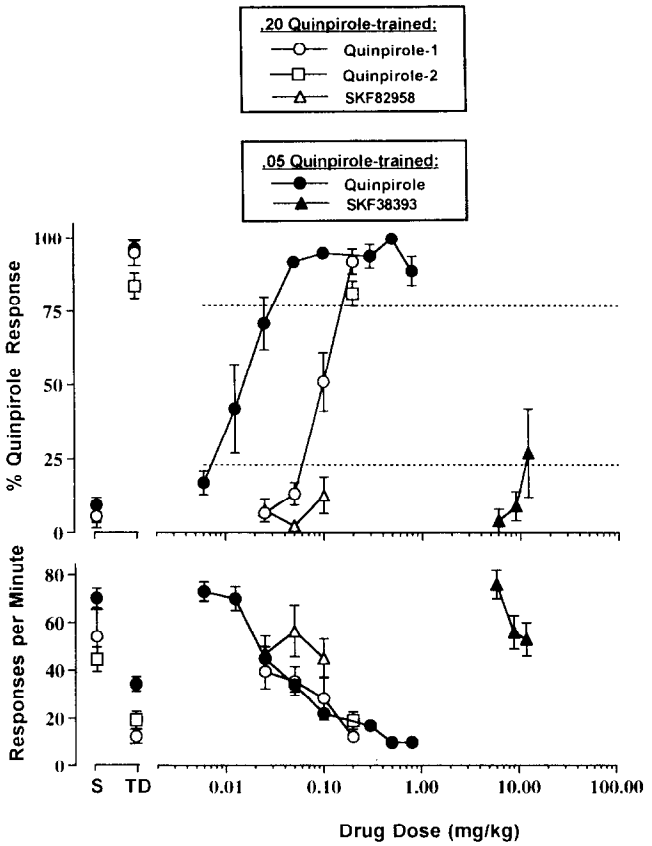


FIG. 1. Top: percent responding on the QUIN lever as a function of dose of QUIN, SKF82958, or SKF38393 in rats trained to discriminate 0.05 mg/kg QUIN [●, QUIN; ▲, SKF38393; from (28)] or 0.20 mg/kg QUIN from saline [○, QUIN original determinations; □, QUIN redeterminations; △, SKF82958). Each data point represents a group mean ± SE value based on the median values derived across replications of each dose for each rat. QUIN dose–effect curves from the 0.05 mg/kg QUIN-trained group were derived from 8–10 rats; curves from the 0.20 mg/kg QUIN-trained group from 10 rats; SKF38393 dose–effect curves derived from seven rats; SKF82958 derived from eight rats. Data were included only if a total of five or more responses occurred during the session. Drug lever response levels greater than or equal to 77% (top dashed line) were defined as full substitution for QUIN; those at or below the bottom dashed line (23%) were defined as saline-appropriate responding and the area between defined as partial substitution. Bottom: responses per minute as a function of mg/kg drug dose as described above. Each data point represents a group mean ± SE based on the mean value derived across replications of each dose for each rat. Sample sizes were the same as described above. Data from all substitution sessions were included. For both top and bottom panels, values labeled "S" show data obtained during saline substitution tests; TD for data obtained during substitution tests with the training dose of QUIN (○ for 0.20 QUIN-trained groups; ● for 0.50 QUIN-trained groups).

of the discrimination was indicated by group mean ± SE QUIN lever response levels of 77.8 ± 5.4% and 4.6 ± 3.2% for 0.20 mg/kg in redeterminations of QUIN and saline generalization test sessions, respectively, carried out over the course of the experiment (Fig. 1, top panel).

### *Substitution Tests*

*Quinpirole.* Increasing doses of QUIN (0.025 to 0.20 mg/kg) resulted in dose-related increases in drug-lever responding in 0.20 mg/kg QUIN-trained rats, as shown in Fig. 1 (top panel), with the training dose engendering drug lever response levels of 92%, and saline producing less than 6% drug lever responding. The dose-effect function for the 0.20 mg/kg QUIN-trained group was shifted to the right of that from the group previously trained to discriminate 0.05 mg/kg QUIN from saline (28).

Relative to rates of responding noted during saline tests, response rates declined as QUIN dose increased [Fig. 1, bottom panel; $F(4, 36) = 7.16$, $p = 0.002$], with the 0.20 mg/kg QUIN dose producing group mean response rates of 12 responses per minute. Response rates in the presence of doses of 0.05, 0.10, and 0.20 mg/kg differed from those of saline. The 0.05 mg/kg QUIN training dose produced a virtually identical pattern of response rate decreases over the corresponding part of the dose–effect curve.

*D1 agonists.* The full $D_1$ agonist SKF 82958 engendered negligible levels of drug lever responding. As Fig. 1 (top panel) shows, doses up to 0.10 mg/kg, a dose that itself serves as an effective training stimulus (Cory-Slechta et al., unpublished data) produced drug lever response levels averaging only 12% in rats trained to 0.20 mg/kg QUIN. Similarly, the partial $D_1$ agonist SKF 38393 evoked minimal levels of QUIN responding in the 0.05 mg/kg-trained rats.

Surprisingly, rates of responding were largely unaffected by either SKF 82958, $F(3, 21) = 0.32$, $p = 0.81$, or SKF 38393 (Fig. 1, bottom panel) when considered relative to saline control levels.

*AMPT.* Percent drug-lever responding when AMPT was substituted for QUIN is depicted in Fig. 2 (top panel). At AMPT doses ranging from 25 to 75 mg/kg, levels of responding on the drug lever reached peak values of only 12.8% after training to 0.20 mg/kg QUIN. This effect stood in sharp contrast to the dose-related increases in drug lever responding with increasing AMPT dose in rats trained to a dose of 0.05 mg/kg QUIN (28), where drug lever responding peaked at almost 70% at the 75 mg/kg dose.

Rates of responding were also differentially influenced in the two different training groups. Group mean rates of responding were only minimally affected by AMPT in the 0.05 mg/kg QUIN-trained group (Fig. 2, bottom panel), whereas the 0.20 mg/kg QUIN-trained group exhibited a decline relative to saline control levels, $F(3, 21) = 5.03$, $p = 0.009$, an effect that derived from a significant difference between the 50 mg/kg dose and saline response rates.

*7-OH-DPAT.* 7-OH-DPAT, reported to be a $D_3$-selective receptor ligand, produced drug-lever response levels consistent with saline lever responding at doses of 0.05–0.10 mg/kg and partial substitution at doses of 0.15–0.20 mg/kg (Fig. 2, top panel).

Virtually all doses of 7-OH-DPAT significantly decreased response rates, $F(4, 32) = 6.31$, $p = 0.0007$, with the highest dose decreasing levels to $< 50\%$ of saline control values (Fig. 2, bottom panel).

*SCH23390.* Substitution with the $D_1$ antagonist SCH23390 at doses ranging from 0.025 to 0.10 mg/kg produced vastly different responses in the two groups (Fig. 2, top panel). Negligible levels of drug lever responding were obtained in rats trained to 0.20 mg/kg QUIN, with peak values of only 11% at the highest SCH 23390 dose. In contrast, doses of 0.05 and 0.10 mg/kg SCH23390 produced levels of drug lever responding $\geq 90\%$ in rats trained to 0.05 mg/kg QUIN.

Rates of responding were also differentially affected in the two groups (Fig. 2, bottom panel). Specifically, all doses of SCH 23390 decreased rates relative to saline control levels in the 0.20 QUIN-trained group, $F(3, 27) = 4.41$, $p = 0.012$,

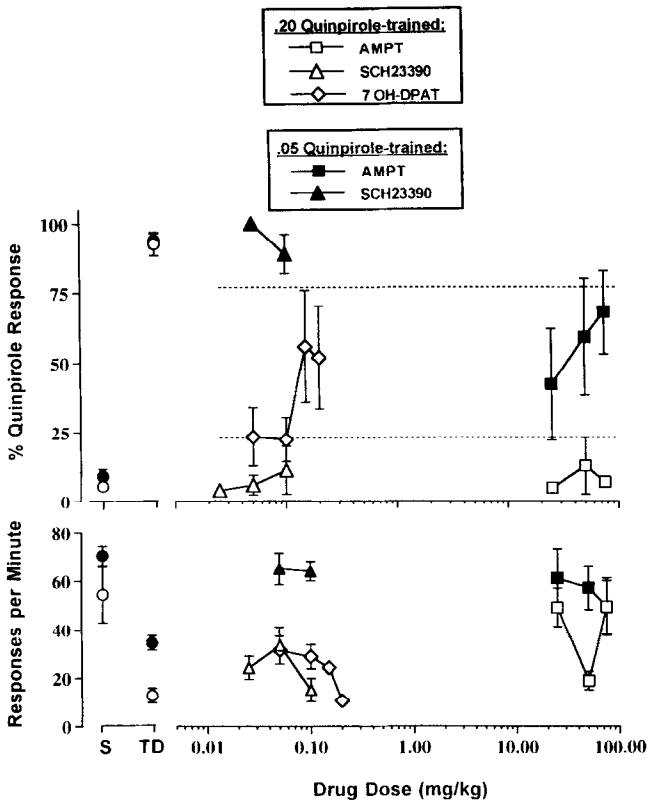


FIG. 2. Top: percent responding on the QUIN lever as a function of dose (25, 50, or 75 mg/kg) of alpha-methyl-paratyrosine (AMPT), 7-OH-DPAT (0.05 or 0.10 mg/kg), or SCH 23390 (0.025, 0.05, or 0.10 mg/kg) in rats trained to discriminate 0.05 mg/kg QUIN [■, ▲ from (28)] or 0.20 mg/kg QUIN from saline (□, △, and ◇). AMPT dose–effect curves from the 0.05 mg/kg QUIN-trained group were derived from seven to eight rats; curves from the 0.20 mg/kg QUIN-trained group from eight rats; SCH23390 dose–effect curves from the 0.05 mg/kg QUIN-trained group were derived from two to six rats; curves from the 0.20 mg/kg QUIN-trained group from 8–10 rats; 7-OH-DPAT dose–effect curves were derived from five to eight rats. Drug lever response levels greater than or equal to 77% (top dashed line) were defined as full substitution for QUIN; those at or below the bottom dashed line (23%) were defined as saline-appropriate responding and the area between defined as partial substitution. Bottom: responses per minute as a function of dose of alpha-methyl-paratyrosine. Sample sizes were as described above. For both top and bottom panels, values labeled "S" show data obtained during saline substitution tests; TD for data obtained during substitution tests with the training dose of QUIN (○ for 0.20 QUIN-trained groups; ● for 0.50 QUIN-trained groups). Other details as in Fig. 1.

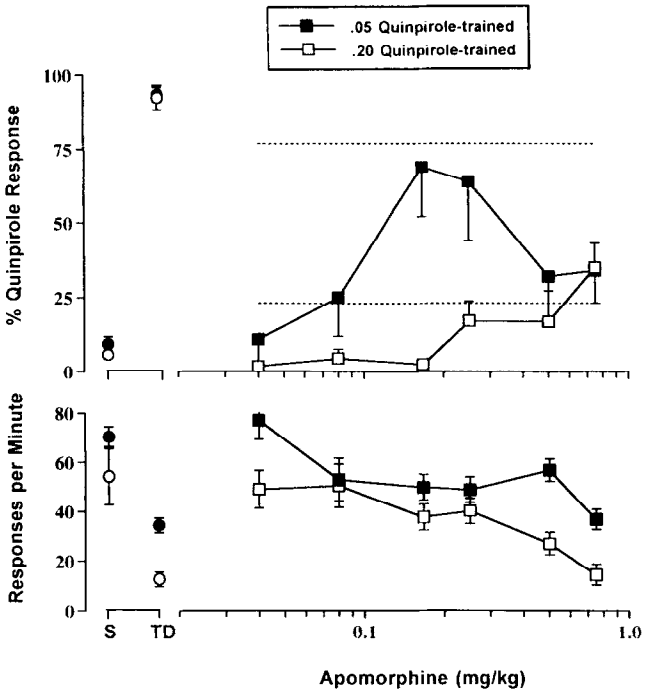


FIG. 3. Top: percent responding on the QUIN lever as a function of dose (0.04, 0.08, 0.167, 0.25, 0.50, and 0.75 mg/kg) of APO in rats trained to discriminate 0.05 mg/kg QUIN [■, from (28)] or 0.20 mg/kg QUIN from saline (□). Dose–effect curves from the 0.05 mg/kg QUIN-trained group were derived from 7–10 rats; curves from the 0.20 mg/kg QUIN-trained group from eight rats. Drug lever response levels greater than or equal to 77% (top dashed line) were defined as full substitution for QUIN; those at or below the bottom dashed line (23%) were defined as saline-appropriate responding and the area between defined as partial substitution. Bottom: responses per minute as a function of dose of APO. Sample sizes were as described above. For both top and bottom panels, values labeled "S" show data obtained during saline substitution tests; TD for data obtained during substitution tests with the training dose of QUIN (○ for 0.20 QUIN-trained groups; ● for 0.50 QUIN-trained groups). Other details as in Fig. 1.

while rates of responding were largely unaffected by either dose tested in the 0.05 group.

*Apomorphine.* Doses of 0.04 to 0.75 mg/kg APO were substituted for QUIN with the results shown in Fig. 3 (top panel). Apomorphine provoked only low levels of drug lever responding in the 0.20 mg/kg QUIN-trained group, with peak levels of QUIN-lever responding reaching only 35% at the highest APO dose. Although this responding showed evidence of being dose related, in fact, only the highest APO dose, 0.75 mg/kg, evoked partial substitution, all lower doses resulted in levels of responding defined as consistent with saline-appropriate response levels. Apomorphine produced a very different dose–effect curve in the 0.05 mg/kg QUIN group (28), with drug lever response levels increasing over the dose range of 0.04 to 0.167 mg/kg to levels of 69%. Drug lever response levels showed a dose-related decline with further increases in APO dose, down to levels of about 35%.

Apomorphine decreased rates of responding in both the 0.20 and 0.05 mg/kg QUIN-trained groups (Fig. 3, bottom panel). Response rates of the 0.20 mg/kg QUIN group decreased from approximately 54 to < 15 responses per minute, a decline of 78%, $F(6, 54) = 3.95$, $p = 0.0002$, as a result of significant differences between saline control response rates and those exhibited at 0.50 and 0.75 mg/kg. The corresponding decline for the 0.05 mg/kg QUIN group was from approximately 70 down to 37 responses per minute, a decrease of about 48%.

*NPA.* Figure 4 (top panel) shows the percent QUIN lever responding following substitution with doses of NPA ranging from 0.02 to 0.24 mg/kg. As can be seen, NPA provoked intermediate levels of drug lever responding of comparable value in the two groups at doses of 0.02–0.04 mg/kg. However, at higher doses of NPA, the two dose–effect curves diverged. In rats trained to 0.20 mg/kg QUIN, peak drug lever response levels were actually obtained at 0.04 mg/kg NPA, with higher

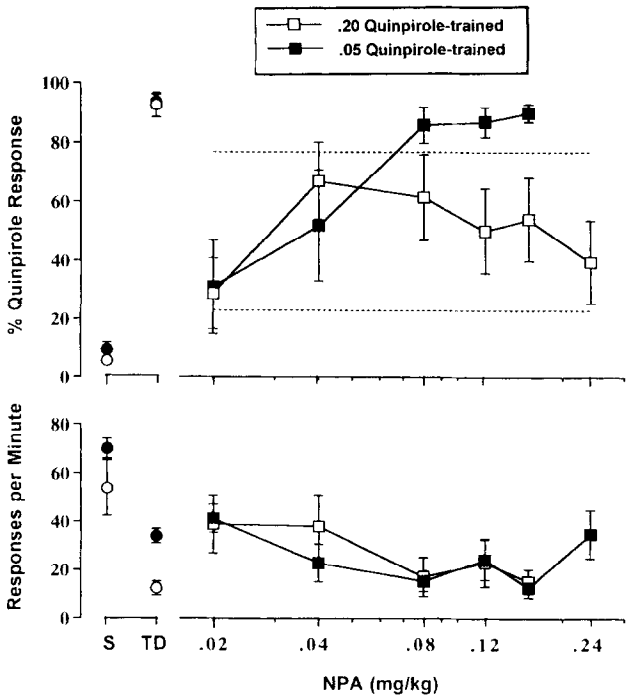


FIG. 4. Top: percent responding on the QUIN lever as a function of dose (0.02, 0.04, 0.08, 0.12, or 0.24 mg/kg) of NPA in rats trained to discriminate 0.05 mg/kg QUIN [■, from (28)] or 0.20 mg/kg QUIN from saline (□). Dose–effect curves from the 0.05 mg/kg QUIN-trained group were derived from six to seven rats; curves from the 0.20 mg/kg QUIN-trained group from six to nine rats. Drug lever response levels greater than or equal to 77% (top dashed line) were defined as full substitution for QUIN; those at or below the bottom dashed line (23%) were defined as saline-appropriate responding and the area between defined as partial substitution. Bottom: responses per minute as a function of dose of NPA. Sample sizes were as described above. For both top and bottom panels, values labeled "S" show data obtained during saline substitution tests; TD for data obtained during substitution tests with the training dose of QUIN (○ for 0.20 QUIN-trained groups; ● for 0.50 QUIN-trained groups). Other details as in Fig. 1.

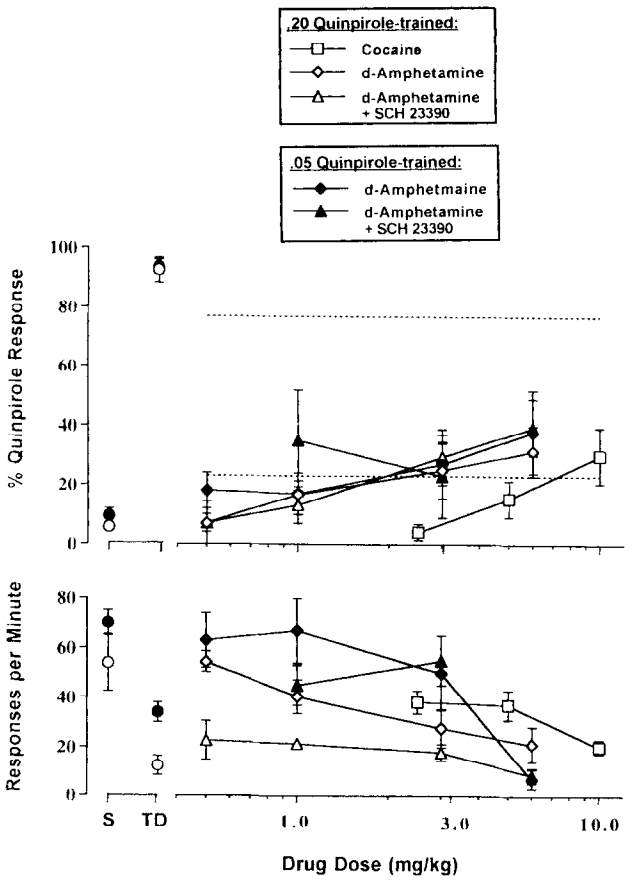


FIG. 5. Top: percent responding on the QUIN lever as a function of dose of *d*-amphetamine (0.5, 1.0, 3.0, or 6.0 mg/kg), cocaine (2.5, 5.0, or 10.0 mg/kg) or *d*-amphetamine (0.5, 1.0, 3.0, or 6.0 mg/kg) coadministered with 0.10 mg/kg SCH 23390 in rats trained to discriminate 0.05 mg/kg QUIN [◆ or ▲, from (28)] or 0.20 mg/kg QUIN from saline (◇, □, or △). Dose–effect curves from the 0.05 mg/kg QUIN-trained group were derived from seven to eight rats; curves from the 0.20 mg/kg QUIN-trained group from 7–10 rats. Drug lever response levels greater than or equal to 77% (top dashed line) were defined as full substitution for QUIN; those at or below the bottom dashed line (23%) were defined as saline-appropriate responding and the area between defined as partial substitution. Bottom: responses per minute as a function of dose of *d*-amphetamine, cocaine or *d*-amphetamine coadministered with 0.10 mg/kg SCH 23390. Sample sizes were as described above. For both top and bottom panels, values labeled "S" show data obtained during saline substitution tests; TD for data obtained during substitution tests with the training dose of QUIN (○ for 0.20 QUIN-trained groups; ● for 0.50 QUIN-trained groups). Other details as in Fig. 1.

doses then producing a gradual decline in QUIN lever responding. In rats trained to 0.05 mg/kg QUIN, however, NPA produced a dose-related increase in QUIN lever responding, with peak levels of > 90% occurring at the highest dose tested, 0.16 mg/kg NPA.

Rates of responding (Fig. 4, bottom panel) were similarly affected by NPA in the two groups. Compared to saline control values, both the 0.05 and 0.20 mg/kg, $F(6, 36) = 3.03$, $p = 0.017$, QUIN-trained groups exhibited comparable decreases in rate across corresponding sections of the NPA dose–effect curve. The effects in the 0.20 mg/kg group were noted at doses of 0.08, 0.12, and 0.16 mg/kg.

*Cocaine, d-Amphetamine, and SCH23390 + d-Amphetamine.* Substitution of either *d*-amphetamine (0.05 to 6.0 mg/kg) or cocaine (2.5 to 10.0 mg/kg), although generally provoking dose-related increases in drug lever responding, produced only partial QUIN substitution in both groups (Fig. 5, top panel). Peak levels of drug lever responding averaged only 30–40% at the highest doses of *d*-amphetamine and cocaine. To block any potential $D_1$ effects of *d*-amphetamine, and direct all dopaminergic activity to $D_2$ receptors, 0.10 mg/kg of the $D_1$ antagonist SCH23390 was coadministered with *d*-amphetamine to determine whether this would elevate levels of QUIN lever responding to amphetamine. However, no substantive increase in QUIN lever responding was achieved by this co-treatment in either group.

Rates of responding generally declined relative to saline control with increasing doses of *d*-amphetamine [Fig. 5, bottom panel; 0.20 mg/kg QUIN, $F(4, 36) = 3.64$, $p = 0.0140$], and cocaine [administered only to the 0.20 mg/kg QUIN-trained group, $F(3, 24) = 3.02$, $p = 0.049$], as did rates following coadministration of *d*-amphetamine and SCH 23390 [0.20 mg/kg QUIN group, $F(4, 36) = 8.58$, $p = 0.0001$].

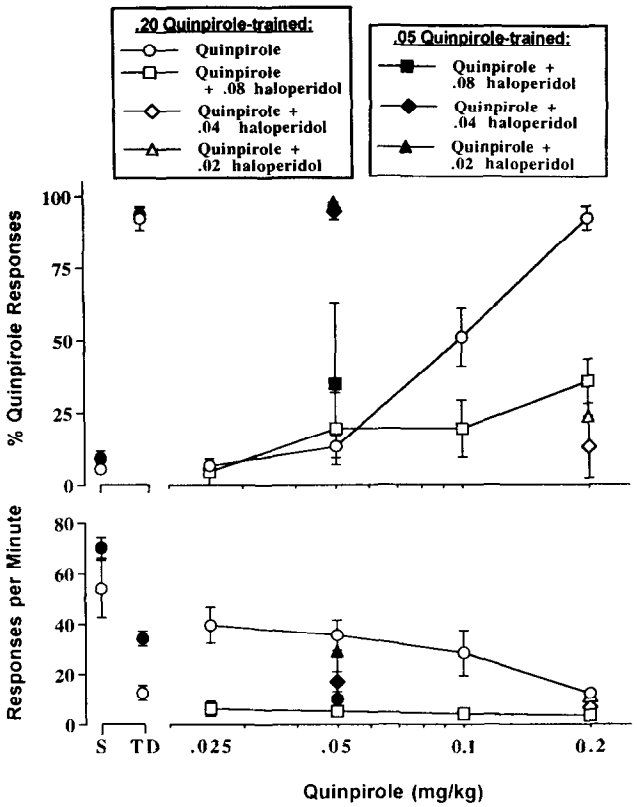


FIG. 6. Top: percent responding on the QUIN lever as a function of dose of QUIN (0.025, 0.05, 0.10, or 0.20 mg/kg) administered alone (○), or in conjunction with 0.08 mg/kg (□), 0.04 mg/kg (◇), or 0.02 mg/kg (△) of haloperidol in rats trained to discriminate 0.20 mg/kg QUIN from saline and percent QUIN responding at 0.05 mg/kg QUIN administered in conjunction with 0.08 mg/kg (■), 0.04 mg/kg (▲), and 0.02 mg/kg (◆) haloperidol in rats trained to discriminate 0.05 QUIN. Dose–effect curves for 0.20 QUIN alone from 10 rats; curves for QUIN coadministered with 0.08 mg/kg from two to five rats, five rats for .20 QUIN coadministered with 0.04 mg/kg haloperidol; eight rats for 0.20 QUIN coadministered with 0.02 mg/kg haloperidol; four rats for 0.05 QUIN coadministered with 0.08 g/kg haloperidol; seven rats for 0.05 QUIN coadministered with 0.04 mg/kg haloperidol, and six rats for 0.05 QUIN administered with 0.02 mg/kg haloperidol. In Widzowski and Cory-Slechta (28), haloperidol was administered 90 min prior to the session, whereas in 60 min pretreatment time was used in the current study. Bottom: responses per minute as a function of dose of QUIN alone or QUIN coadministered with doses of haloperidol as noted above. Sample sizes were 10 for the QUIN-alone dose–effect curve, and seven to eight for QUIN coadministered with 0.08 mg/kg haloperidol. For both top and bottom panels, values labeled "S" show data obtained during saline substitution tests; TD for data obtained during substitution tests with the training dose of QUIN (○ for 0.20 QUIN-trained groups; ● for 0.50 QUIN-trained groups). Other details as in Fig. 1.

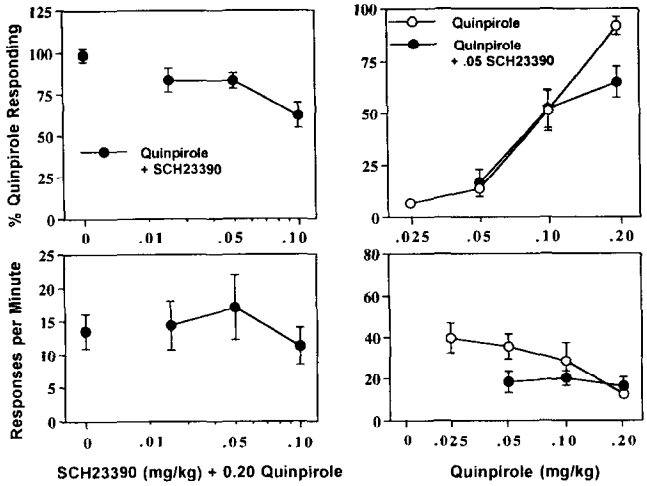


FIG. 7. Top left: percent responding on the QUIN lever as a function of dose of SCH 233390 (0, 0.025, 0.05, or 0.10 mg/kg) coadministered with 0.20 mg/kg QUIN in rats trained to discriminate 0.20 mg/kg QUIN from saline. Data from 7–10 rats. Top right: percent responding on the QUIN lever as a function of dose of QUIN (0, 0.025, 0.05, 0.10, or 0.20 mg/kg) administered alone (○), or coadministered with 0.05 mg/kg SCH 23390 (●) in rats trained to discriminate 0.20 mg/kg QUIN from saline. Dose–effect curves for QUIN alone from 10 rats; curves for QUIN coadministered with 0.05 mg/kg SCH 23390 from 8–10 rats. Bottom: Response rate data corresponding to drug lever responding shown in top panels.

### *Antagonism Tests*

*Haloperidol + Quinpirole.* Pretreatment with 0.08 mg/kg of the $D_2$ antagonist haloperidol produced significant antagonism of 0.20 mg/kg QUIN stimulus properties, as shown in Fig. 6 (top panel) [main effect of haloperidol, $F(1, 18) = 67.6$, $p = 0.0001$; interaction of haloperidol by QUIN dose, $F(3, 54) = 21.0$, $p = 0.0001$]. Drug lever response levels fell from 92% at 0.20 mg/kg QUIN alone, to < 36% with haloperidol pretreatment. Likewise, drug-lever responding declined from 51% at 0.10 mg/kg QUIN to 19% in the presence of 0.08 mg/kg haloperidol. This same dose of haloperidol decreased 0.05 mg/kg-trained QUIN lever responding to about the same extent. Whereas doses of 0.02 and 0.04 mg/kg haloperidol decreased 0.20 mg/kg QUIN lever responding to levels of 13 and 23%, respectively, these doses were not effective in blocking the stimulus properties of 0.05 mg/kg QUIN.

The dose-related decrement in response rates produced by various doses of QUIN alone (Fig. 6, bottom panel), were not antagonized by haloperidol pretreatment. In fact, rates of responding were even further suppressed by coadministration of QUIN and 0.08 mg/kg haloperidol [haloperidol + QUIN vs. QUIN alone, $F(1, 12) = 8.58$, $p = 0.026$].

*SCH 23390 + Quinpirole.* The impact of various doses of the $D_1$ antagonist SCH23390 on the 0.20 mg/kg QUIN cue, and of 0.05 mg/kg SCH23390 on various doses of QUIN in 0.20 mg/kg QUIN-trained rats, are shown in Fig. 7 (top left and right, respectively). As these figures indicate, drug-lever responding in the presence of the 0.020 mg/kg QUIN cue could be modestly attenuated by SCH23390 cotreatment. A repeated measures analysis of variance based only on the seven animals with complete dose–effect curves for QUIN + SCH23390 (top left) indicated a significant main effect of SCH23390, $F(6, 18) = 7.09$, $p = 0.02$. Subsequent post hoc contrasts showed this effect to derive primarily from the 0.10 mg/kg dose of SCH 23390, which differed from 0.20 QUIN alone and from 0.20 QUIN + 0.025 SCH23390 and from 0.20 QUIN + 0.05 SCH23390. This attenuation was further suggested by the differences in the QUIN dose–effect curve alone as compared to that obtained following pretreatment with 0.05 mg/kg SCH 23390 (top right), although this effect did not achieve statistical significance in a two within-factors repeated

measures analysis of variance comparing the QUIN alone curve to the QUIN + 0.05 SCH23390 dose–effect curves.

As shown in Fig. 7 (bottom right), rates of responding did not differ in the presence of 0.20 QUIN alone compared to 0.20 QUIN + 0.05 SCH23390. Nor did the various doses of SCH23390 when coadministered with 0.20 QUIN alter rates of responding (bottom left).

## DISCUSSION

This study was undertaken to determine whether the stimulus properties of a dose of 0.20 mg/kg QUIN would be consistent with dopamine $D_2$ mediation, and whether its stimulus properties would be indicative of postsynaptic $D_2$ mediation, in contrast to the apparent presynaptic $D_2$ mediation engendered by a lower dose of QUIN 0.05 mg/kg as reported by Cory-Slechta and Widzowski (28). As with 0.05 mg/kg QUIN, these data collectively support a predominantly dopaminergic $D_2$ receptor mediation of the stimulus properties of a high dose of QUIN (0.20 mg/kg) when trained against saline using standard operant drug discrimination procedures. This is indicated by the fact that full substitution was produced by increasing doses of QUIN and partial substitution engendered by another $D_2$ agonist, NPA. Furthermore, the full $D_1$ agonist SKF 82958 provoked saline-appropriate responding. Although the doses used were not rate suppressive, they were at levels twice those required to support an SKF 82958 vs. saline discrimination in rats (32). Moreover, the stimulus properties of QUIN were notably attenuated by the $D_2$ antagonist haloperidol, while the $D_1$ antagonist SCH 23390 engendered much more modest effects observed only at the training dose of QUIN.

It is also of interest to note that a $D_2$ rather than $D_3$ mediation of QUIN's stimulus properties is suggested by the fact that the putative $D_3$-selective receptor agonist 7-OH-DPAT did not substitute for QUIN, even at doses known to sustain discriminative performances in rats (15) even up to levels that substantially suppressed responding. This finding might be considered somewhat surprising given reports such as those by Sokoloff and colleagues (14,20,21) that QUIN is significantly more potent at $D_3$ than at $D_2$ receptors, as well as the reports that 7-OH-DPAT is a $D_3$ selective dopamine ligand. However, the relative affinity of 7-OH-DPAT for $D_3$ over $D_2$ sites may be conditional [e.g., see Gobert et al. (13)], and some investigators report that QUIN may be more potent at $D_2$ than $D_3$ receptors (18) and that it binds primarily to the high affinity state of the $D_2$ receptor [e.g., (12,17)]. Furthermore, behavioral and functional distinctions between QUIN and 7-OH-DPAT have been described. Svensson et al. (23), for example, noted a close correspondence between doses that suppressed exploratory activity and those that reduced brain dopamine synthesis and release with QUIN, but not with 7-OH-DPAT. Clearly, additional studies will be warranted to delineate the nature and extent of biochemical and behavioral differences between $D_2$ and $D_3$ receptor agonists.

The stimulus properties of 0.20 mg/kg QUIN differed considerably from those we previously described for a lower dose of QUIN, 0.05 mg/kg, using almost identical behavioral procedures (28). That study assumed that the 0.05 mg/kg QUIN training dose functioned as a $D_2$ presynaptic receptor (autoreceptor), and, thus, any pharmacological treatments that resulted in a decline in dopamine availability or release, or blocked postsynaptic dopamine receptors, should substitute for 0.05 mg/kg QUIN, whereas pharmacological manipulations that activated postsynaptic dopamine receptors should provoke primarily saline-appropriate responding. The current study postulated that the higher dose of 0.20 mg/kg should, instead, be mediated by postsynaptic $D_2$ receptors and, thus, produce a pattern of effects opposite to that observed with the 0.05 mg/kg QUIN stimulus.

The contrasting findings of the two studies are generally in accord with those premises. The most compelling evidence in support of a presynaptic vs. postsynaptic distinction between these two training doses of QUIN derives from the comparative effects of AMPT and SCH 23390 substitution. For example, AMPT, a catecholamine depleter, mimicked the presynaptic stimulus properties of 0.05 mg/kg QUIN and even enhanced these properties when coadministered with 0.05 mg/kg QUIN. However, AMPT produced no notable substitution for the 0.20 mg/kg dose of QUIN. These contrasting effects would be anticipated with a pre- vs. postsynaptic distinction, respectively, because depletion of dopamine should be consistent with autoreceptor activation, but not postsynaptic receptor activation.

Likewise, the $D_1$ antagonist SCH 23390 substituted fully for the 0.05 mg/kg dose of QUIN, but not at all for the 0.20 mg/kg QUIN dose. Again, this pattern is consistent with a presynaptic vs. postsynaptic distinction for these two training stimuli. Blockade of postsynaptic $D_1$ receptors would be functionally achieved by autoreceptor activation by depriving the $D_1$ receptor of its endogenous ligand, dopamine. A $D_1$ antagonist would not be predicted to substitute for a postsynaptic $D_2$ agonist, and virtually no substitution of SCH 23390 for 0.20 mg/kg QUIN was observed in this study.

The contrasting effects of APO are also of interest. In 0.05 mg/kg QUIN-trained rats, APO produced dose-related increases in QUIN responding to levels of almost 70% at doses up to 0.167 mg/kg. However, at higher doses, the percent drug-lever responding exhibited a dose-related decline (28). This pattern was attributed to preferential autoreceptor activation in the rising segment of the curve, with the descending segment probably reflecting postsynaptic mediation, possibly by $D_1$ receptors. This was based on a previous study from this laboratory (10) showing that APO doses in this higher range substituted for SKF 38393, both in rats trained to discriminate 0.167 mg/kg APO from SKF 38393 and those trained to discriminate SKF 38393 from saline. The current study further supports this interpretation. Levels of drug lever responding rose slightly in rats trained to 0.20 mg/kg at the higher doses of APO, i.e., 0.25 mg/kg and above, but even at doses of 0.75 mg/kg never exceeded 36%. In contrast, drug lever response levels of rats trained to discriminate SKF 38393 either from saline or from 0.167 mg/kg APO reached levels of 78 and 65%, respectively, at these higher APO doses. Thus, APO appears to preferentially impact presynaptic $D_2$ receptors at low doses and $D_1$ receptors at higher doses.

Arnt et al. (2) suggested that the stimulus properties of NPA were mediated by postsynaptic $D_2$ receptors. Because NPA produced virtually full substitution for 0.05 mg/kg QUIN, Widzowski and Cory-Slechta (28) posited, instead, that NPA functioned as a presynaptic agonist. The findings of the present study indicated that NPA produced partial substitution for 0.20 mg/kg QUIN, but that these effects were not dose related and actually peaked at 67% drug lever responding at a relatively low NPA dose (0.04 mg/kg) before exhibiting a dose-related decline to $< 40\%$ at 0.24 mg/kg. Over this portion of the dose–effect curve where drug lever responding was declining in 0.20 mg/kg QUIN-trained rats (0.08 to 0.16 mg/kg NPA), percent QUIN responding was $> 80\%$ in the 0.05 mg/kg QUIN-trained group. One possible explanation for par-

tial rather than full substitution of NPA for 0.20 mg/kg QUIN is, of course, that these drugs share some sites of effect, but that they may also impact different postsynaptic $D_2$-like or other sites. Clearly, the use of additional $D_2$-like agonists and antagonists will be required to clarify this issue.

The indirect dopamine agonist *d*-amphetamine evoked comparable levels of responding to both the 0.05 mg/kg QUIN training stimulus (28) and the 0.20 mg/kg training dose, and the levels of substitution engendered were modest at best, even when SCH 23390 was coadministered with *d*-amphetamine to specifically activate $D_2$ receptors. Cocaine, another indirect dopamine agonist, likewise evoked only low levels of drug lever responding even at dose levels that notably suppressed responding. These data are consistent with previous reports of only partial substitution of *d*-amphetamine and cocaine for $D_2$ agonists and with the suggestion that $D_2$ activation per se is not sufficient to mimic these compounds (3,9,24). Perhaps greater success would be achieved in animals trained to a cocktail of potent $D_1$ and $D_2$ agonists.

While, as noted above, many of the observed findings here are consistent with a postsynaptic mediation of 0.20 QUIN as compared to the apparently presynaptic properties of 0.05 QUIN (28), some alternative interpretations of the findings and discrepancies should also be considered. One is the possibility that higher doses of the test drugs would have been required to yield substitution at 0.20 mg/kg, but these doses could not be tested due to rate suppression. Another is that the longer time required for acqusition of the 0.20 QUIN discrimination relative to 0.05 QUIN (86 vs. 52.5 sessions) may have been sufficient to induce tolerance to the higher dose, altering its stimulus properties. A question related to the postsynaptic $D_2$ interpretation is raised by the inverse U-shaped dose–effect curve seen for APO when substituted for 0.05 QUIN, namely, why a similar curve is not evident for quinpirole generalization to 0.05 mg/kg QUIN, in which high doses would likewise yield a decline in drug-lever responding. This question is difficult to answer, given the absence of a clear understanding of the status of autoreceptor function once postsynaptic receptors become activated. Finally, another seeming discrepancy was the fact that doses of 0.02 and 0.04 mg/kg haloperidol antagonized 0.20 QUIN but not 0.05 QUIN drug-lever responding; the opposite might be predicated on the greater sensitivity of presynaptic receptors. However, it should be noted that the effects of haloperidol may not be directly comparable in these two studies, because a 90-min pretreatment time was used in the former study (28) whereas a 60-min pretreatment period was used in this study.

One intriguing aspect of the current study was the finding that the $D_1$ antagonist SCH 23390 was able to partially antagonize the stimulus properties of 0.20 mg/kg QUIN. This effect only achieved statistical significance at a dose of 0.10 mg/kg SCH 23390 and was of modest magnitude, but similar trends were evident at lower doses. Moreover, SCH 23390 itself did not substitute for 0.20 mg/kg QUIN. This effect could not be attributed to response disruption, because response rates in the presence of QUIN alone were comparable to those observed following coadministration of SCH 23390 with QUIN. These data may be suggestive of a "$D_1$-enabling" effect for postsynaptic $D_2$-mediated stimulus properties, as postulated previously for $D_1/D_2$ interactions (25,26). Williams and colleagues (29) studied potential $D_1/D_2$ interaction more systematically, but found that SKF 38393 failed to alter the QUIN dose–effect curve in rats trained to discriminate either 0.012 or 0.05 mg/kg of QUIN from saline. However, based on the findings of Widzowski and Cory-Slechta (28) that 0.05 mg/kg QUIN functions as a presynaptic agonist, the studies of Williams et al. (29) may not have actually examined putative postsynaptic $D_1/D_2$ interactions.

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