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Full and Partial 5-HT$_{1A}$ Receptor Agonists Disrupt Learning and Performance in Rats

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ABSTRACT

As a means of characterizing the role of 5-hydroxytryptamine (5-HT$_{1A}$) receptors in learning, a full 5-HT$_{1A}$ receptor agonist, 8-hydroxy-dipropylaminotetralin (8-OH-DPAT), was administered both alone and in combination with two partial agonists (buspirone and 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl] piperazine hydrobromide (NAN-190)) and a 5-HT$_{1A}$ receptor antagonist (p-MPPI) to rats responding under a multiple schedule of repeated acquisition and performance of response sequences. In addition, the effects of another 5-HT$_{1A}$ receptor agonist, (LY228729), were also studied under this same procedure. When administered alone, both 8-OH-DPAT (0.1–3.2 mg/kg) and LY228729 (0.32–3.2 mg/kg) dose dependently decreased overall response rate and increased the percentage of errors in the acquisition and performance components. At the doses of each drug tested, both buspirone (0.32 or 1 mg/kg) and NAN-190 (1 or 3.2 mg/kg) also decreased overall response rate and increased the percentage of errors. However, the effects of these drugs differed across behavioral components and dependent measures. The effects of buspirone and NAN-190 on rate and accuracy were also different when they were administered in combination with 8-OH-DPAT. In contrast, p-MPPI (3.2 or 10 mg/kg) had little or no effect when administered alone and antagonized the effects of 8-OH-DPAT; shifting the dose-effect curves for both response rate and the percentage of errors in both components to the right. Taken together, these results indicate that complex behaviors in rats are sensitive to disruption by drugs with both full and partial 5-HT$_{1A}$ receptor agonist properties, and that the effects of partial 5-HT$_{1A}$ receptor agonists on learning may be different depending on their efficacy at pre- and postsynaptic 5-HT$_{1A}$ receptors.

A substantial problem in establishing the functional significance of 5-hydroxytryptamine (5-HT$_{1A}$) receptors in the acquisition of behavior (learning) has been the inability of various animal models to distinguish between the disruptive effects of 5-HT$_{1A}$ receptor agonists on learning and their disruptive effects on other behaviors such as locomotor activity. Winter and Petti (1987), for example, reported that 8-hydroxy-dipropylaminotetralin (8-OH-DPAT) increased the latency for a rat to complete a radial-arm maze, but this increase was accompanied by profound changes in locomotor activity. Similarly, Stanhope et al. (1995) reported that 8-OH-DPAT in rats only disrupted the accuracy of responding in a delayed matching-to-sample task at doses that substantially reduced the rate of trial completion. In contrast, Carli et al. (1992) reported that low doses of 8-OH-DPAT before and immediately after training of a one-trial passive-avoidance task in rats caused memory disruptions without impairment in motor activity. These investigators concluded that relatively low doses of a full 5-HT$_{1A}$ receptor agonist could interfere with learning without affecting other behavioral processes, but that the doses and test were critical for ascertaining the disruptive effects of drugs with 5-HT$_{1A}$ receptor agonist properties. For example, as suggested by Stanhope et al. (1995), many of the passive-avoidance studies in rats may have confounded the memory-disrupting (amnestic) effects of these drugs with their anxiolytic effects or characteristic ability to increase responding suppressed by shock. One effective method for examining the effects of drugs with amnestic effects such as the benzodiazepines has been to utilize appetitive procedures where any decrements in responding might safely be attributed to learning or memory impairment and not to behavioral changes associated with the presentation of shock.

In a repeated acquisition study comparing the disruptive effects of several benzodiazepines with the effects of 8-OH-DPAT and buspirone in rats and monkeys, Winsauer et al. (1996) demonstrated that these 5-HT$_{1A}$ receptor agonists were disruptive to learning in both species. However, the effects obtained with buspirone and 8-OH-DPAT in rats were notably different from the effects obtained in monkeys. In rats, for example, both 8-OH-DPAT and buspirone produced

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ABBREVIATIONS: 5-HT, 5-hydroxytryptamine; LY228729, (−)-4-(dipropylamino)-1,3,4,5-tetrahydrobenz-{c, d,}indole-6-carboxamide; *p*-MPPI, 4-iodo-*N*-[2-[4-(methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-benzamide hydrochloride; NAN-190, 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine hydrobromide; 8-OH-DPAT, 8-hydroxy-dipropylaminotetralin.

rate-increasing effects, and the partial agonist, buspirone, was as disruptive or more disruptive to the accuracy of responding than the full agonist 8-OH-DPAT. In monkeys, neither drug produced rate-increasing effects and 8-OH-DPAT was substantially more disruptive to learning than buspirone. One problem in ascertaining the pharmacological and behavioral variables responsible for these species differences was that the effects of 8-OH-DPAT and buspirone were not directly compared on responding under a multiple schedule in rats. Unlike the experiments in monkeys where a performance task served as a behavioral control for any nonspecific drug effects such as changes in motor activity or deprivation level, the experiments involving rats used only an acquisition task to examine the effects of these 5-HT_{1A} receptor agonists. Furthermore, the role of 5-HT_{1A} receptors in mediating the effects observed in both rats and monkeys remained unclear due to the paucity of 5-HT_{1A} receptor ligands with antagonist properties.

The following experiments were designed to address the issues surrounding the effects of 5-HT_{1A} receptor agonists on learning in rats by administering several drugs with varying degrees of affinity for the 5-HT_{1A} receptor to subjects trained to respond under a multiple schedule of repeated-acquisition and performance of response sequences. The drugs chosen for this particular study were 8-OH-DPAT, (−)-4-(dipropylamino)-1,3,4,5-tetrahydrobenz-{c, d,}indole-6-carboxamide (LY228729), buspirone, 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]-piperazine hydrobromide (NAN-190) and 4-iodo-*N*-[2-[4-(methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-benzamide hydrochloride (*p*-MPPI). Currently, 8-OH-DPAT and LY228729 are considered to be relatively selective full agonists at 5-HT_{1A} receptors (Middlemiss and Fozard, 1983; Foreman et al., 1993); whereas buspirone and NAN-190 are considered to be partial agonists at 5-HT_{1A} receptors (Taylor, 1988; Rydelek-Fitzgerald et al., 1990; Greuel and Glaser, 1992). *p*-MPPI is a putative 5-HT_{1A} receptor antagonist (Kung et al., 1994; Allen et al., 1997). A large part of the present study involved the administration of buspirone and NAN-190 in combination with 8-OH-DPAT to examine the extent to which each partial agonist could block the behavioral effects of the full agonist (Kenakin, 1993). The interaction of NAN-190 and 8-OH-DPAT on responding in this procedure was also of interest because NAN-190 has been reported to antagonize 8-OH-DPAT-induced immobility in the forced swim test (Detke et al., 1995), an 8-OH-DPAT-induced 5-HT behavioral syndrome (Przegalinski et al., 1990), and the discriminative stimulus properties of 8-OH-DPAT (Glennon et al., 1988, 1989). The effects of these drug combinations also served as an experimental comparison for the effects obtained with the combination of *p*-MPPI and 8-OH-DPAT.

Methods

Subjects. Twelve adult male Long-Evans rats maintained at approximately 80% of their free-feeding weights served as subjects. The 80% body weights, which were maintained throughout the experiment, ranged from 318 to 365 g with a mean body weight of 341.8 g. Food was earned during the experimental sessions and, if necessary, was provided in the home cage after the session to maintain subjects at their 80% weight. All subjects were housed individually in plastic cages containing sterilized hardwood-chip bedding. The housing room was maintained at 21 ± 1°C with 50 ± 10% relative humidity on a 12-h light/dark cycle, which began at 6:00 AM each day. Water was available in the home cage.

Apparatus. Six identical modular test chambers (model E10-10TC; Coulbourn Instruments, Inc., Lehigh Valley, PA) configured specifically for rodents were used. The front wall of each chamber contained a houselight, auditory feedback relay, pellet trough (2 cm above the floor and centered), and three response keys aligned horizontally (8 cm apart, center to center, and 11.5 cm above the floor). Each response key could be transilluminated by three Sylvania 28ESB indicator lamps, one with a red plastic cap, one with a yellow plastic cap and one without a colored plastic cap (white). Response keys required a minimum force of 0.15 N for activation, and correct responses on each key produced an audible click of the feedback relay. Each chamber was enclosed within a sound-attenuating cubicle equipped with a fan for ventilation and for masking extraneous sounds. The chambers were connected to a computer (Zenith, model ZBV-2526-EK) programmed in MED-PC/MEDSTATE NOTATION software (MED Associates, Inc. & Thomas Tatham, St. Albans, VT), and to cumulative recorders (Gerbrands Corp., Arlington, MA) located within the room.

Procedure. Preliminary training of the rats was similar to that described for pigeons by Thompson (1973) and included magazine training, shaping of the response (nose press), and reinforcing responses on each of the three keys after shaping. When subjects reliably responded in this single-response sequence, another response (associated with a different colored stimulus) was added until each subject was able to respond in a three-response sequence. The terminal baseline was a multiple schedule with acquisition and performance components. During the acquisition component of this multiple schedule, all three response keys were illuminated at the same time with one of three colors, either white, red, or yellow. The subject's task was to respond (nose press) on the correct key in the presence of each sequentially illuminated set of colors (e.g., keys white, center correct; keys red, left correct; keys yellow, right correct). Completion of this sequence turned off the keylights, produced a 0.4-s presentation of the pellet trough light, and reset the sequence. The same sequence (in this case, center-left-right) was repeated throughout a given session and responding on this sequence was maintained by food presentation under a fixed-ratio 2 schedule (FR2); i.e., every second completion of the sequence produced a 45-mg food pellet. When the subject pressed an incorrect key (in the example, the left or right key when the white keylights were presented), the error was followed by a 5-s timeout. During the timeout, the key lights were turned off and responses had no programmed consequence. An incorrect response did not reset the three-response sequence; that is, the stimuli were the same before and after a timeout.

To establish a steady state of repeated acquisition, the three-response sequence was changed from session to session. An example of a typical set of five sequences (for five different sessions) was as follows: center-left-right, right-center-left, left-right-center, center-right-left, and right-left-center, with the order of the color presentations always white, red, yellow. The sequences were carefully selected to be equivalent in several ways and there were restrictions on their ordering across sessions. More specifically, each sequence was scheduled with equal frequency and adjacent positions within a sequence for a given session were different. Occasionally, a correct sequence position for a given color was the same for two consecutive sessions (as in the above list of sequences, left-right-center and center-right-left).

During the performance component of the multiple schedule, the response keys and the houselight above the keys were illuminated. In this component, the three-response sequence remained the same (right-left-center) from session to session. In all other aspects (colored stimuli for each response in the three-response sequence, fixed ratio 2 schedule of food presentation, timeout duration of 5 s etc.), the performance component was identical with the acquisition component.

Each session began in the acquisition component, which then alternated with the performance component after 40 reinforcers or 20 min, whichever occurred first. Each session was terminated after

TABLE 1
Overall response rate (responses/min) and percentage of errors in the acquisition and performance components of a multiple schedule following 22–24 saline (control) injections in each of the 12 subjects

Subject	Response Rate (A)	% Errors (A)	Response Rate (P)	% Error (P)
1	48.2 ± 0.9[a]	10.9 ± 0.9	46.7 ± 0.9	5.4 ± 0.7
2	63.4 ± 1.4	15.2 ± 1.3	61.6 ± 1.2	5.7 ± 0.9
3	40.1 ± 1.3	20.6 ± 1.7	41 ± 0.9	10.9 ± 0.8
4	54.7 ± 1.4	15.5 ± 0.8	53.5 ± 1.6	8.9 ± 0.5
5	84.7 ± 1.6	15.4 ± 0.9	87.4 ± 1	6.5 ± 0.4
6	65.2 ± 1.4	15.4 ± 0.7	62.9 ± 1.1	6.4 ± 0.7
7	73.8 ± 2.7	17 ± 1.1	71.8 ± 1.6	7.4 ± 1
8	56.4 ± 0.8	12.6 ± 0.8	53.6 ± 0.9	5.6 ± 0.5
9	59.5 ± 2.1	11 ± 0.9	58.3 ± 1.1	5.7 ± 0.7
10	63.6 ± 1.2	14.4 ± 1.3	61.4 ± 1.2	7.9 ± 0.8
11	75.9 ± 1.6	13.2 ± 0.7	71 ± 1.7	6.8 ± 0.5
12	48.9 ± 1.4	14.2 ± 0.9	48.7 ± 1.2	4.7 ± 0.4

[a] Mean ± S.E.M.

200 reinforcers or 100 min, whichever occurred first. When response rates and percentage of errors for each subject no longer showed systematic change from component to component or session to session (i.e., each subject developed a steady state of repeated acquisition and responding in the performance component was stable), drug testing began. Initially, all 12 subjects received 8-OH-DPAT alone. These subjects were then subdivided into two groups of six; one that received 8-OH-DPAT in combination with two doses of buspirone and another that received 8-OH-DPAT in combination with two doses of NAN-190. Then, to evaluate any confounds that might have occurred as a result of drug history, three animals from each of these two groups were used to test combinations of 8-OH-DPAT with *p*-MPPI. Finally, the subjects from this last group were also used to determine the effects of LY228729. Throughout testing, experimental sessions were conducted 5 days per week with drug sessions usually occurring on Tuesdays and Fridays, control (saline or vehicle) sessions occurring on Thursdays, and baseline sessions (no injections) on Mondays and Wednesdays. Higher doses and dose combinations of all of the drugs were administered only once a week. Doses of 8-OH-DPAT alone and all dose combinations of 8-OH-DPAT with buspirone, NAN-190 or *p*-MPPI were tested in a mixed order. The effects of buspirone, NAN-190, and *p*-MPPI alone were always determined before and after various administrations with 8-OH-DPAT. The effects of some doses of 8-OH-DPAT were redetermined after the combination studies and are included in the dose-effect function for 8-OH-DPAT alone. At least 2 weeks of experimental sessions without drug intervened between the end of a series of injections for one drug combination and the start of a series for another.

Drugs. The drugs used were buspirone hydrochloride, LY228729, *p*-MPPI, NAN-190, and 8-OH-DPAT. All of the drugs except LY228729, which was supplied by Eli Lilly and Company (Indianapolis, IN), were obtained from Research Biochemicals International (Natick, MA).

Doses of buspirone, 8-OH-DPAT, and LY228729 were dissolved in sterile saline (0.9%), whereas doses of *p*-MPPI were dissolved in sterile water. NAN-190 was dissolved in a vehicle of propylene glycol (40%), ethyl alcohol (10%), and sterile water (50%). The volume for both control (saline) and drug injections was 0.1 ml/100 g b.wt., and the route of administration was always s.c. Presession administration times, as determined in a previous study (Winsauer et al., 1996) or by preliminary determinations (not shown), were 15 min for buspirone, 8-OH-DPAT, and LY228729, 20 min for *p*-MPPI, and 60 min for NAN-190.

Data Analysis. The data for each session were analyzed in terms of the overall response rate (total responses/minute, excluding timeouts) and the overall accuracy, expressed as percentage of errors [(errors/total responses) × 100]. The grouped data and the individual subject data were generally analyzed by comparing drug sessions with control (saline or vehicle) sessions. Percentage of errors for an individual subject were not included in the data analysis when response rate was less than two responses/min because of the small number of correct and/or incorrect responses involved.

In addition to these measures based on session totals, within-session changes in responding were monitored by a cumulative recorder and a computer. For example, acquisition of a response sequence was indicated by within-session error reduction; i.e., a decrease in the number of errors between food presentations as the session progressed.

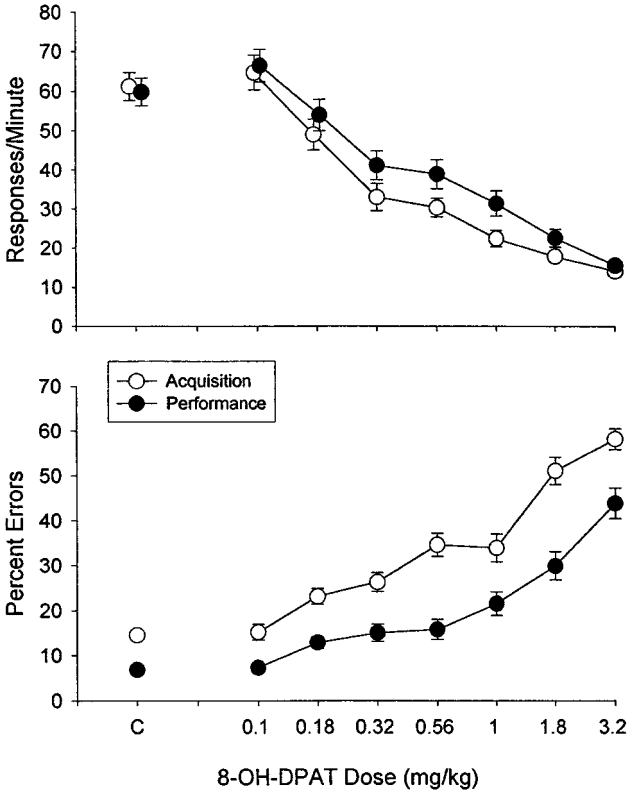

Fig. 1. Effects of 8-OH-DPAT on overall response rates and percentage of errors in 12 rats responding under a multiple schedule with both repeated-acquisition and performance components. Data points at C indicate the mean and S.E.M. for control sessions in which saline was administered, whereas data points in the dose-effect curves indicate the mean and S.E.M. for sessions in which varying doses of 8-OH-DPAT were administered. Any points without error bars indicate instances in which the SEM is encompassed by the data point.

Results

Stable responding by all subjects occurred under both components of the multiple schedule after approximately 110 sessions. Furthermore, measures of both rate and accuracy for each subject remained stable during baseline sessions (no injections) and control sessions when either vehicle or saline was administered (Table 1). Acquisition, which usually occurred a short time after the start of the session (5–10 min), was characterized by a decrease in the number of errors and an increase in consecutive correct completions of the response sequence. This response pattern at the start of the session in acquisition also accounted for the fact that percentage of errors in acquisition were typically larger than percentage of errors in performance under control conditions.

When 8-OH-DPAT (0.18–3.2 mg/kg) was administered to 12 rats responding under the multiple schedule, dose-dependent decreases in overall response rates occurred in both the acquisition and performance components (Fig. 1). Although the rate-decreasing effects obtained in the two components were comparable, the effects on overall response rate in acquisition were quantitatively larger than those obtained in performance at several intermediate doses. For example, the overall decreases in rate obtained with the 0.32- to 1-mg/kg doses of 8-OH-DPAT were slightly larger in acquisition than in performance when compared to their respective control performances.

The effects of 8-OH-DPAT on percentage of errors in both components are shown in the bottom of Fig. 1. In both acquisition and performance, increasing doses of 8-OH-DPAT decreased the accuracy of responding by increasing the percentage of errors. More specifically, when the mean and S.E.M. for control sessions were compared with the mean and S.E.M. for the range of doses of 8-OH-DPAT, doses of 0.18 mg/kg or higher increased errors in both acquisition and performance. Similar to the effects on response rate, the quantitative differences in the error-increasing effects between the two components were quite small (i.e., the curves for the percentage of errors in both components increased monotonically).

Figure 2 shows the effects on overall response rates (top) and percentage of errors (bottom) in the acquisition and performance components for one group of subjects (PR-1 to PR-6) after administration of buspirone alone, and buspirone in combination with 8-OH-DPAT. As shown in the top of Fig. 2, the 0.32-mg/kg dose of buspirone alone had little or no effect on response rate in either component. The 1-mg/kg dose, however, produced a small decrease in rate in acquisition, but had no effect on rate in performance. When these doses of buspirone were tested in combination with 8-OH-DPAT, the 0.32-mg/kg dose tended to shift the 8-OH-DPAT dose-effect curves for response rate in acquisition and performance upward, whereas the dose-effect curves for the 1-mg/kg dose combination were similar to those obtained for 8-OH-DPAT alone. For example, the rate-decreasing effects obtained when the 0.32-mg/kg dose of buspirone was administered with the 0.32-mg/kg dose of 8-OH-DPAT were smaller than those for the 0.32-mg/kg dose of 8-OH-DPAT alone. In contrast, the effects of the 1-mg/kg dose of buspirone in combination with the 0.32-mg/kg dose of 8-OH-DPAT were essentially the same as those for 8-OH-DPAT.

As shown in the bottom of Fig. 2, the 0.32-mg/kg dose of buspirone alone increased the percentage of errors slightly in acquisition but had little or no effect on the percentage of errors in performance. The 1-mg/kg dose of buspirone, however, increased percentage of errors in the acquisition and

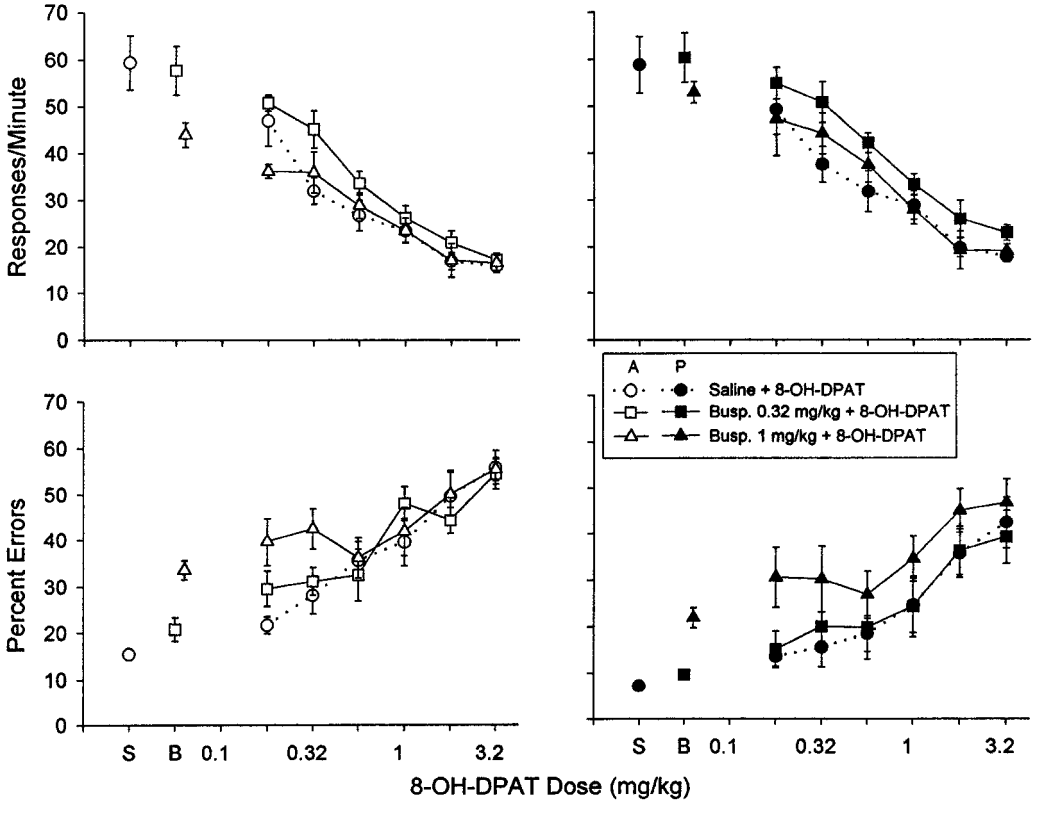

Fig. 2. Effects of buspirone, alone and in combination with 8-OH-DPAT, on overall response rate and percentage of errors in the acquisition (A) and performance (P) components of the multiple schedule. Each data point represents the mean for six subjects (n = 6). Data points at C indicate the mean and S.E.M. for control sessions, whereas data points at B represent the mean and S.E.M. for the effects of the two doses of buspirone alone.

performance components. Administered in combination with 8-OH-DPAT, the effects of buspirone on the percentage of errors varied depending on the dose and component of the multiple schedule. For example, both doses of buspirone in combination with the two lowest doses of 8-OH-DPAT (0.18 and 0.32 mg/kg) produced error-increasing effects in acquisition that were greater than those obtained when these doses of each drug were administered alone. In contrast, when buspirone was combined with higher doses of 8-OH-DPAT, the effects of the two drugs in acquisition were essentially indistinguishable from those obtained for 8-OH-DPAT alone. In the performance component, the 1-mg/kg dose of buspirone in combination with 8-OH-DPAT produced error-increasing effects that were larger than those obtained with 8-OH-DPAT alone and larger than those obtained when the 0.32-mg/kg dose was combined with 8-OH-DPAT. This effect is depicted in the lower righthand panel of Fig. 2 where the dose-effect data for the 1-mg/kg dose of buspirone in combination with 8-OH-DPAT is shifted upward, indicating a relatively uniform increase in errors in performance.

The cumulative records in Fig. 3 depict the effects on the within-session patterns of responding in one subject (PR-2) after the administration of 1 mg/kg 8-OH-DPAT, 1 mg/kg buspirone and the combination of these two doses of drug. For comparison purposes, the top row of Fig. 3 shows the first four components of a control session, which was preceded by two injections of saline. The response pattern in this control record reflects the characteristic decrease in errors and increase in errorless responding that generally occurred during the first acquisition component, and the comparatively errorless responding that occured throughout the session in the performance components. Also, note that the pattern of responding during the second acquisition component was more similar to responding in the performance components in terms of the number of errors and the duration of time spent in that component, indicating that the response sequence had been acquired.

When 1 mg/kg 8-OH-DPAT was administered, the within-session pattern of responding was clearly disrupted. Very little responding occurred during the first acquisition component and there was a substantial increase in the number of errors during both the first and second acquisition components. In the first performance component, there was a substantial decrease in the rate of responding as indicated by the overall time required by this subject to complete the component, but only a relatively small increase in errors. As indicated by the record in the third row, 1 mg/kg buspirone also increased the overall number of errors across the first two acquisition components and decreased the overall response rate in both acquisition and performance. In contrast to 8-OH-DPAT, however, this dose of buspirone also produced a large increase in errors in the first performance component. When the 1-mg/kg doses of each drug were administered together, the pattern of disruption in the acquisition components was similar to or greater than that obtained after the 1-mg/kg dose of 8-OH-DPAT alone, but the pattern of re-

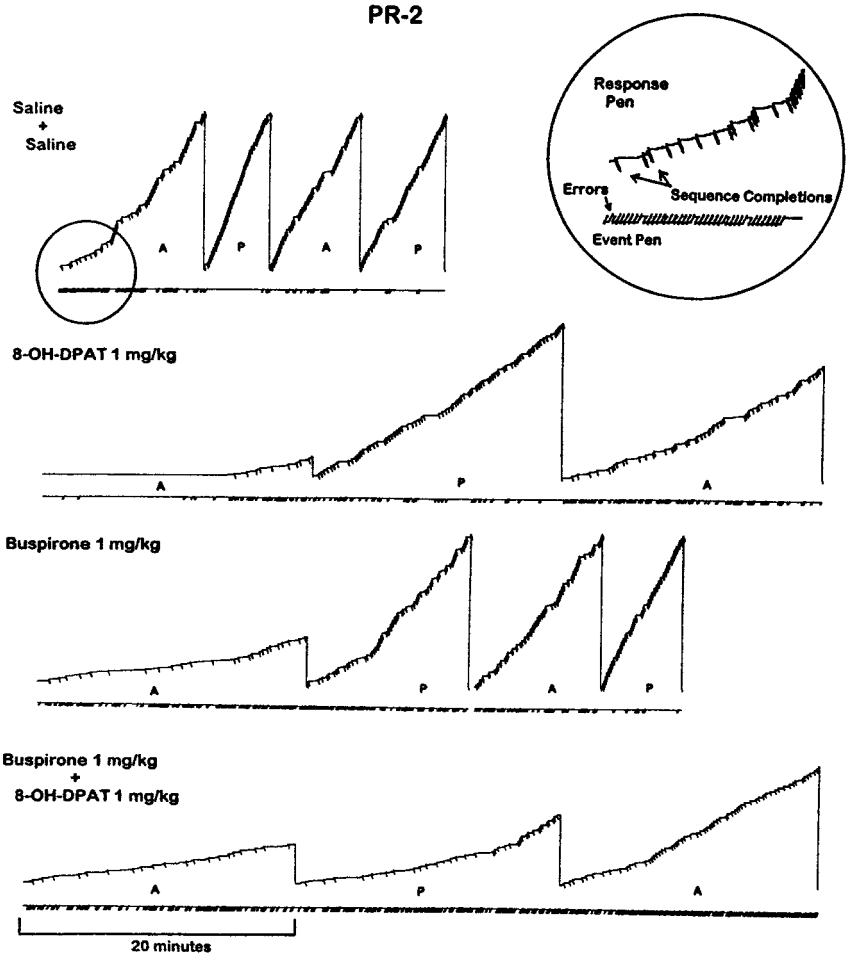

Fig. 3. Cumulative response records for subject PR-2 showing the within-session effects produced in the acquisition (A) and performance (P) components of the multiple schedule by 8-OH-DPAT, buspirone and 8-OH-DPAT in combination with buspirone. As exemplified by the magnified inset, the response pen stepped upward with each correct response and deflected downward each time the three-response sequence was completed. Errors in both components are indicated by the event pen (below each record). A change in components of the multiple schedule, which occurred after 20 min or 40 reinforcements, reset the stepping pen.

sponding in performance was unlike that obtained with either drug alone. In other words, the combination of buspirone and 8-OH-DPAT produced disruptions in acquisition that were similar to those observed with 8-OH-DPAT, but in performance, the disruptions were unlike those obtained with either drug alone because there was a substantial increase in errors.

Figure 4 shows the effects on overall response rates and percentage of errors in both components after administration of NAN-190 alone and NAN-190 in combination with 8-OH-DPAT. Similar to the experiment with buspirone, two doses of NAN-190 (1 and 3.2 mg/kg) were administered both alone and in combination with six doses of 8-OH-DPAT (0.18–3.2 mg/kg). As shown in the top panels of Fig. 4, both doses of NAN-190 alone produced dose-dependent rate-decreasing effects in both components of the multiple schedule. Dose-dependent rate-decreasing effects were also observed when NAN-190 was administered in combination with 8-OH-DPAT and these rate-decreasing effects were larger than those for 8-OH-DPAT alone (i.e., there was a substantial downward shift of the dose-effect data when either dose of NAN-190 was administered with 8-OH-DPAT).

The bottom panels of Fig. 4 show the effects of NAN-190 alone and NAN-190 in combination with 8-OH-DPAT on the percentage of errors. Administered alone, the 1-mg/kg dose produced a small increase in errors in acquisition but produced little or no effect on errors in performance. The 3.2-mg/kg dose of NAN-190 increased errors in both acquisition and performance. When both doses of NAN-190 were administered in combination with 8-OH-DPAT, dose-specific error-increasing effects occurred in both components that were generally larger than those observed with 8-OH-DPAT alone. However, these error-increasing effects were more evident in the performance components where the dose-effect curves for the drug combinations were shifted upward compared to the dose-effect curves for 8-OH-DPAT alone. In acquisition, the error-increasing effects produced by the combinations were more variable.

The within-session effects of 8-OH-DPAT and NAN-190, both alone and in combination, in subject PR-9 are shown in Fig. 5. Each cumulative record in Fig. 5 shows the effects that occurred during an entire session. The record at the top of this figure depicts a representative control session where both vehicle (60 min) and saline (15 min) were administered before the start of the session. As depicted by the record in the second and third row, 1 mg/kg 8-OH-DPAT in this subject produced a large decrease in the overall rate of responding, and a small but noticeable increase in errors in both components. In this same subject, a 1-mg/kg dose NAN-190 (fourth row) did not produce as large a decrease in response rate as that produced by 8-OH-DPAT alone, but produced a comparable increase in errors in both components. When these doses were given together, however, the effects on responding were even greater than those observed with either drug alone. The cumulative record for this dose combination, which is shown in the fifth and sixth rows, shows that responding was virtually eliminated during the first 60 min of the session and that responding during the final 40 min was substantially below control levels (i.e., a large decrease in the rate of responding was still evident, and there was an increase in errors in both components when compared to the number of completions of the response sequence).

Figure 6 shows the overall effects on response rate and percentage of errors for six subjects (i.e., three from each of the previous two combination groups) in each schedule component after administration of *p*-MPPI alone and *p*-MPPI in

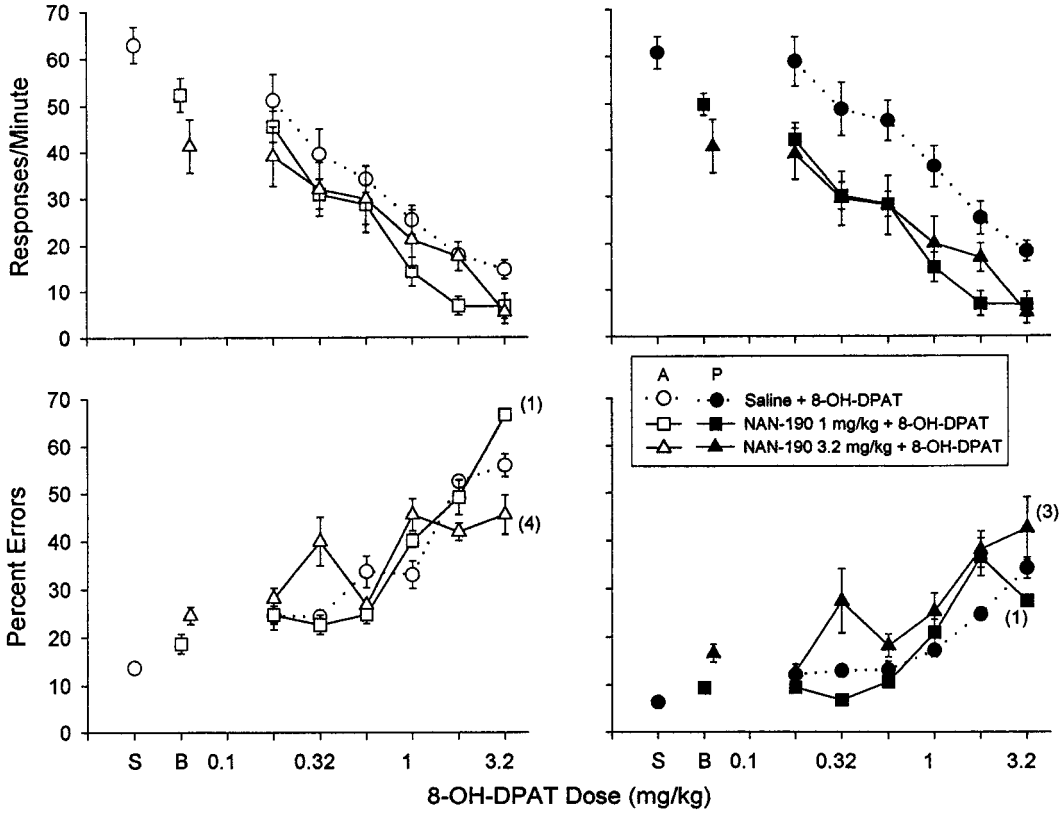

Fig. 4. Effects of NAN-190, alone and in combination with 8-OH-DPAT, on overall response rate and percentage of errors in the acquisition (A) and performance (P) components of the multiple schedule. Each data point represents the mean for six subjects (n = 6). Data points at C indicate the mean and S.E.M. for control sessions, whereas data points at N represent the mean and S.E.M. for the effects of the two doses of NAN-190 alone. The numbers in parentheses adjacent to the data points indicate the number of animals represented by that data point. For additional details, see legend for Fig. 2.

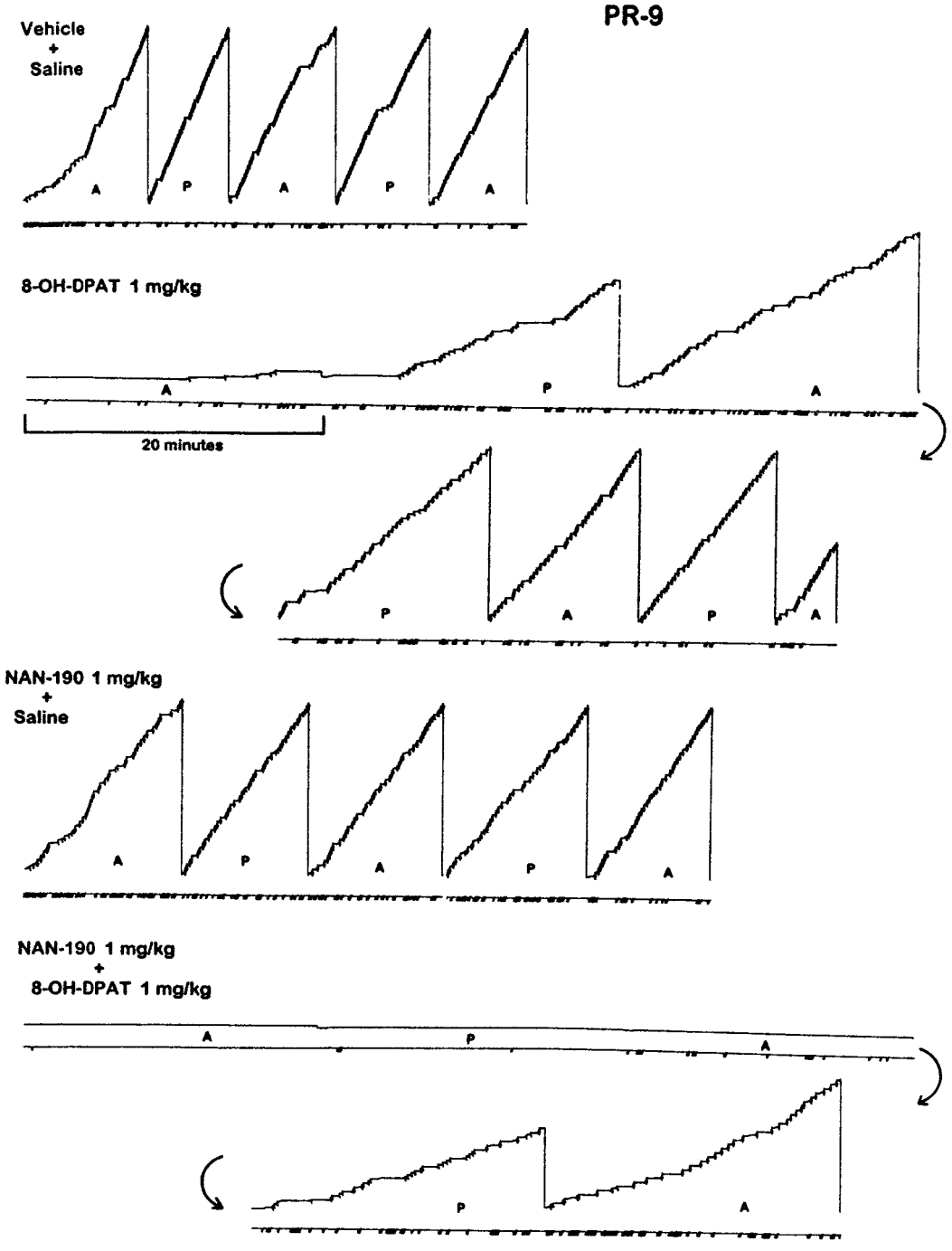

Fig. 5. Cumulative response records showing the within-session effects produced in the acquisition (A) and performance (P) components of the multiple schedule by 8-OH-DPAT, NAN-190 and 8-OH-DPAT in combination with NAN-190. Each record in this figure depicts the effects over an entire session. All sessions terminated after 100 min or 200 reinforcements, whichever occurred first. For additional details, see legend for Fig. 3.

combination with 8-OH-DPAT. The dose-effect curves for 8-OH-DPAT alone in both schedule components represent a combination of the initial determinations and postinteraction redeterminations of 8-OH-DPAT for these six subjects. Unlike either buspirone or NAN-190, the two doses of *p*-MPPI only produced a small disruption in overall response rate in acquisition and performance at the higher dose (10 mg/kg), and had little or no effect on the percentage of errors (bottom) in either component. *p*-MPPI was also different from buspirone and NAN-190 in that both doses of this drug attenuated the rate-decreasing and error-increasing effects of 8-OH-DPAT when the two drugs were administered together. In other words, the dose-effect curves for the combinations of *p*-MPPI and 8-OH-DPAT in both acquisition and performance were shifted approximately ½-¾ log unit to the right by both doses of *p*-MPPI.

Figure 7 shows the effects obtained in PR-1 to PR-3 and PR-7 to PR-9 in the acquisition components after the administration of 8-OH-DPAT and *p*-MPPI. Similar to the grouped data, the individual subject data show the fact that both doses of *p*-MPPI attenuated the disruptive effects of 8-OH-DPAT on overall response rate and percentage of errors in acquisition in each subject while producing only a few small rate-decreasing effects in some subjects when administered alone. The data depicted in Fig. 7 also show that both the 3.2- and 10-mg/kg doses of *p*-MPPI produced approximately the

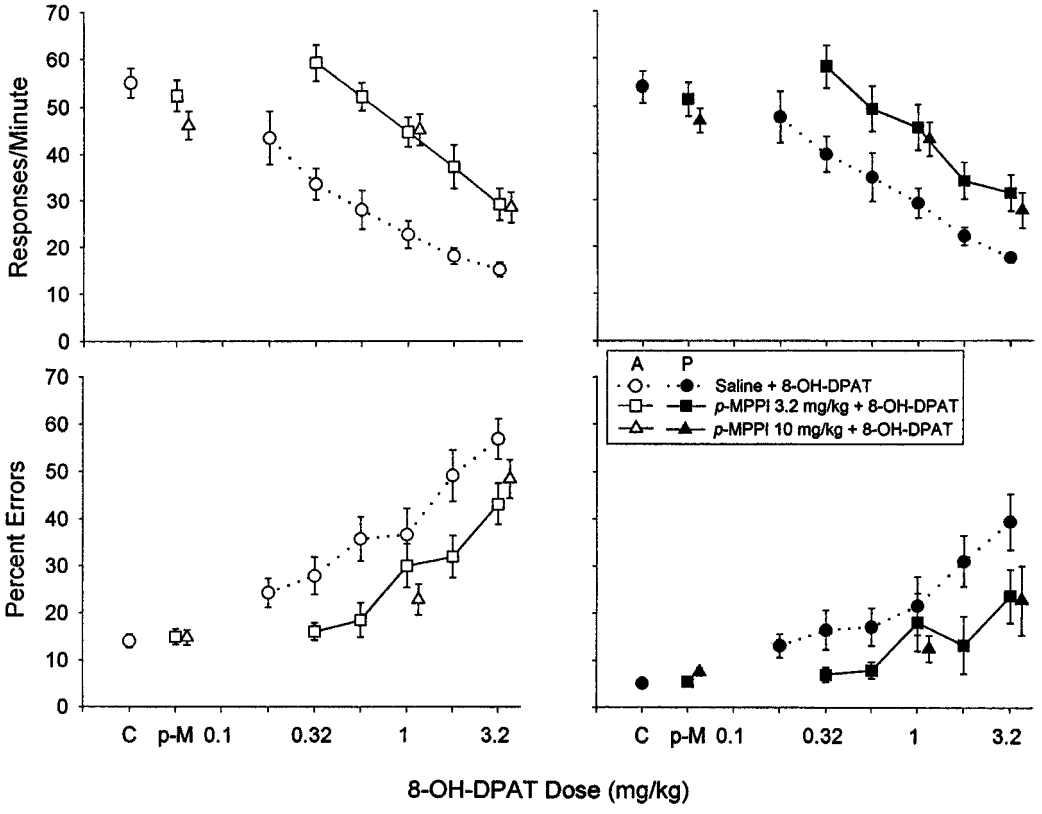

Fig. 6. Effects of *p*-MPPI, alone and in combination with 8-OH-DPAT, on overall response rate and percentage of errors in the acquisition (A) and performance (P) components of the multiple schedule. Data points and vertical lines indicate the mean and S.E.M. for six subjects (n = 6). Data points at C indicate the mean and S.E.M. for control sessions, whereas data points at p-M represent the mean and S.E.M. for the effects of the two doses of *p*-MPPI alone. For additional details, see the legend for Fig. 2.

same degree of antagonism in each subject. Unlike the grouped data, however, the individual subject data more clearly depict the fact that *p*-MPPI attenuated 8-OH-DPAT's rate-decreasing effects to a greater extent than its error-increasing effects. This can clearly be seen in the data for subjects PR-1 and PR-2, where both doses of *p*-MPPI in combination with 8-OH-DPAT shifted the 8-OH-DPAT dose-effect curves for response rate to the right, but had little or no effect on the dose-effect curves for percentage of errors. For example, the 10-mg/kg dose of *p*-MPPI in combination with the 3.2-mg/kg dose of 8-OH-DPAT in subject 8 produced an effect on the percentage of errors that was similar to the effect obtained with 3.2 mg/kg 8-OH-DPAT alone.

The effects of 8-OH-DPAT and *p*-MPPI on the within-session pattern of responding of subject PR-2 are shown in Fig. 8. Cumulative records showing the initial portions of a control session and a session preceded by an injection of 1 mg/kg 8-OH-DPAT are displayed in the first row of Fig. 8. As shown in these records, 1 mg/kg 8-OH-DPAT decreased the overall rate of responding and increased errors when compared to the control session. Moreover, the increase in errors in this subject was larger in the acquisition components than in the performance components. The records depicted in the third row show that the effects of 8-OH-DPAT on the within-session pattern of responding were largely attenuated when either the 3.2- or 10-mg/kg dose of *p*-MPPI was administered with 8-OH-DPAT before the start of the session. That neither dose of *p*-MPPI was able to completely antagonize the effects of the 1-mg/kg dose of 8-OH-DPAT was indicated by the small rate-decreasing and error-increasing effects that appear in these records. The rate-decreasing effects in this subject are apparent, for example, if the time needed to complete three components is compared across drug and control sessions. It should also be noted that neither dose of *p*-MPPI, which attenuated the effects of the 1-mg/kg dose of 8-OH-DPAT, had an effect on the overall response pattern when administered alone (compare records from row 2 with the control record). The cumulative record in the last row Fig. 8 shows the within-session effects obtained after the administration of a 10-mg/kg dose of *p*-MPPI and a 3.2-mg/kg dose of 8-OH-DPAT. This dose combination was interesting in that it produced a pattern of responding that was similar to the pattern observed after the 1-mg/kg dose of 8-OH-DPAT alone.

The effects of LY228729 on overall response rate and the percentage of errors are shown in Fig. 9. Similar to 8-OH-DPAT, increasing doses of LY228729 dose-dependently decreased the overall rate of responding and increased the percentage of errors in both the acquisition and performance components. Unlike 8-OH-DPAT, however, the dose-effect curves for response rate in acquisition and performance overlapped considerably, indicating that there were no quantitative differences in the rate-decreasing effects observed in each component. On the accuracy of responding, LY228729 generally produced larger error-increasing effects in acquisition than in performance.

The rate-decreasing and error-increasing effects produced by LY228729 in the acquisition and performance components are also depicted in the individual subject data shown in Fig. 10. In Fig.10, the effects on overall response rate in each component are shown in the top panels for each of the five subjects, whereas the effects on the percentage of errors are shown in the bottom panels. Similar to the grouped data, the individual subject data indicate that there was virtually no difference in the rate-decreasing effects of LY228729 across the acquisition and performance components of the multiple schedule. However, unlike the grouped data, the individual

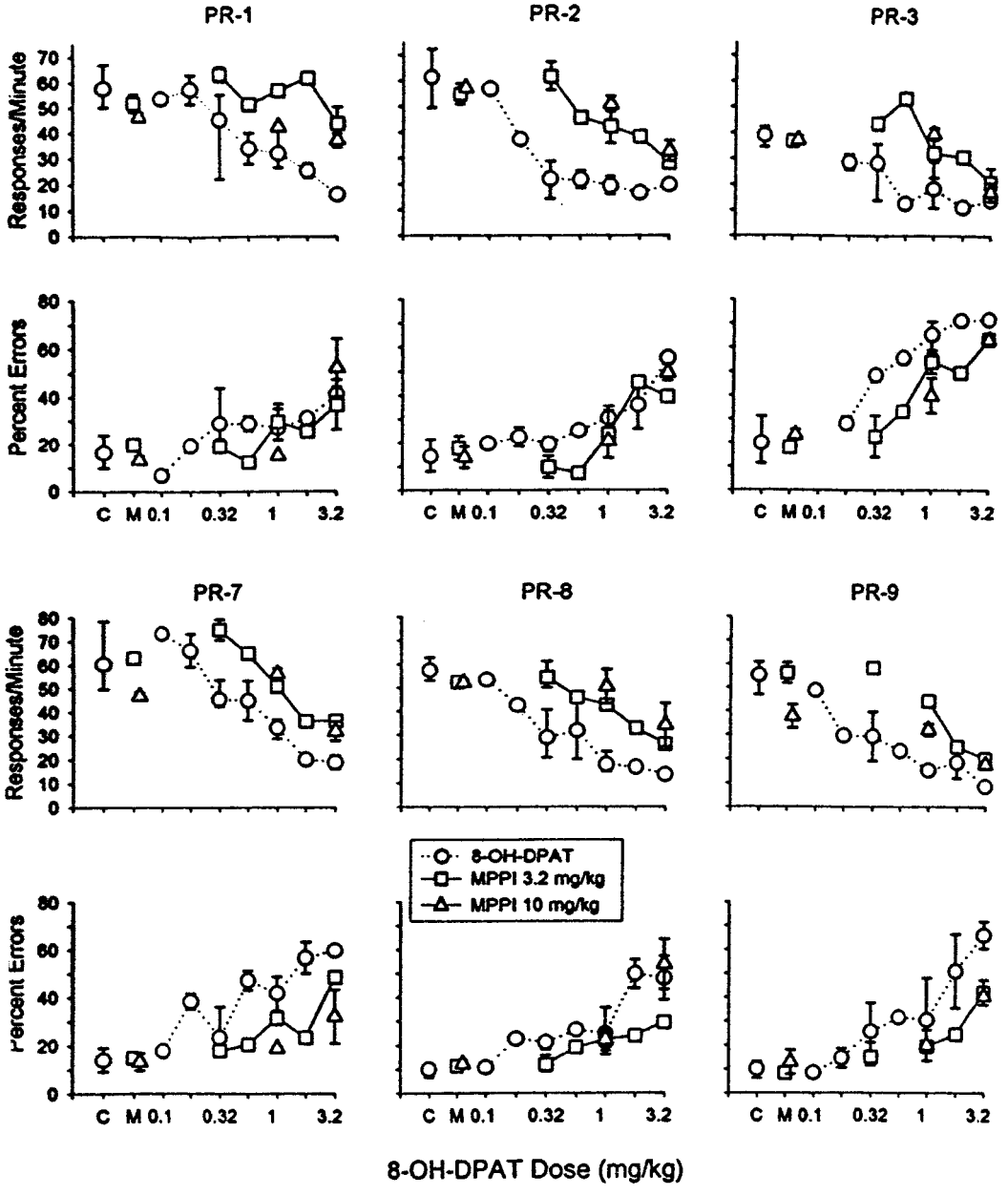

Fig. 7. Individual subject data obtained in the acquisition components after the administration of *p*-MPPI and 8-OH-DPAT. The unconnected points with vertical lines to the left of the dose-effect curves at C indicate the mean and range of eight control (saline) sessions for each subject. Any points at C without vertical lines indicate an instance in which the range is encompassed by the data point. The data points with vertical lines at p-M indicate the mean and range of two determinations of each dose of *p*-MPPI; one before, and one after the dose combinations with 8-OH-DPAT. The data points and vertical lines in the dose-effect curves indicate the mean and range for one to three determinations of that dose combination. Data points without vertical lines in the curves indicate either a single determination of that dose combination or an instance in which the range is encompassed by the point. Note that the 10-mg/kg dose of *p*-MPPI was only given in combination with the 1 and 3.2 mg/kg doses of 8-OH-DPAT.

subject data indicated that the error-increasing effects produced by LY228729 in acquisition were substantially larger than those in performance in three of five rats (PR-1, PR-2, and PR-9).

Discussion

The disruptive effects of 8-OH-DPAT, LY228729, buspirone, and NAN-190 on overall response rate and percentage of errors in this repeated-acquisition study involving rats clearly depended on the dose and the behavioral component of the multiple schedule. This was evident from the data obtained when 8-OH-DPAT and LY228729 were administered alone, and the data obtained when buspirone and NAN-190 were administered alone and in combination with 8-OH-DPAT. These data, therefore, support several suppositions that have been raised in the literature by numerous investigators (e.g., Carli et al., 1992): 1) the specific behavioral task is critical for ascertaining the disruptive effects of 5-HT$_{1A}$ receptor agonists on learning and 2) the extent to which 8-OH-DPAT can disrupt learning in rats without disrupting other behaviors such as locomotor activity may be narrow.

Whether or not the disruptions obtained in learning with this class of drugs are greater or less than those demonstrated by other classes of drugs with similar therapeutic properties (such as the benzodiazepines) needs to be explored further. However, it is clear from the data obtained in this study that the two agonists with selective affinities for the 5-HT$_{1A}$ receptor, 8-OH-DPAT and LY228729, generally produced disruptions in learning at doses that also produced disruptions in other behaviors such as those that are assayed by the performance task. Similar to 8-OH-DPAT, LY228729 has been reported to have potent 5-HT$_{1A}$ receptor agonist properties in several behavioral paradigms including the forced swim paradigm in rodents (Benvenga and Leander, 1993), and to produce responses mediated by both presynap-

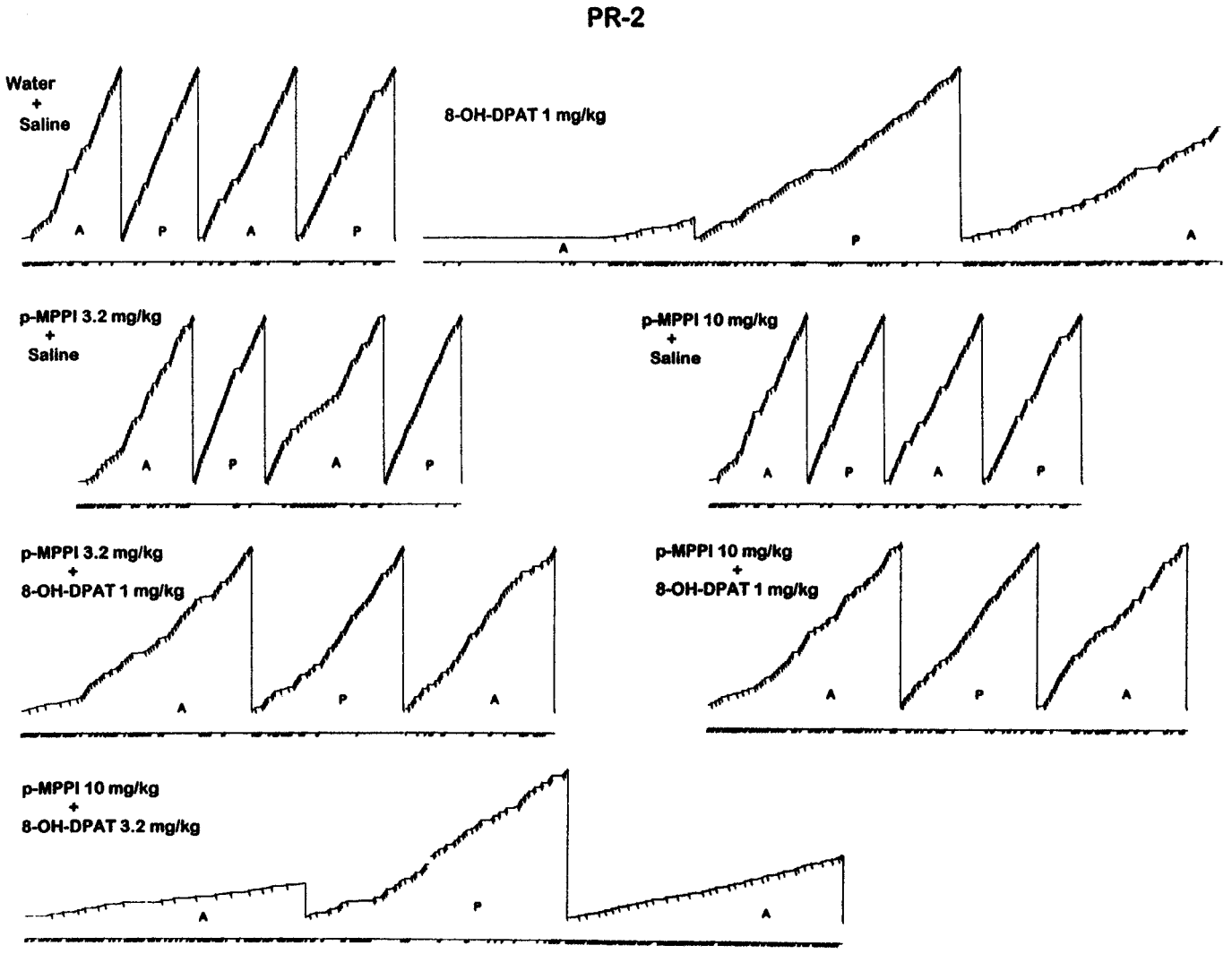

Fig. 8. Cumulative response records showing the within-session effects produced in the acquisition (A) and performance (P) components of the multiple schedule after the administration of 8-OH-DPAT (1 mg/kg), *p*-MPPI (either 3.2 or 10 mg/kg), and 8-OH-DPAT in combination with *p*-MPPI. The first record in row 1 shows a control session in which sterile water and saline were administered before the start of the session. For additional details, see legend for Fig. 3.

tic and postsynaptic 5-HT_{1A} receptors. In a study by Foreman et al. (1993), for example, LY228729 reduced 5-hydroxyindole acetic acid (5-HIAA) levels in hypothalamus (a presynaptic response), increased serum corticosterone levels, and reduced body temperature (two postsynaptic responses). In addition, these authors found that LY228729 produced rate-decreasing effects on unpunished responding in rats at doses comparable to those reported in the present study, and found that a hypothermic effect produced by LY228729 was blocked by (±) pindolol (a 5-HT_{1A} receptor antagonist).

Although there have been relatively few studies in rats that have examined the effects of buspirone on complex learning tasks, or directly compared the effects of buspirone with those of 8-OH-DPAT on a learning task, the majority of the existing data has indicated that it can disrupt these tasks (Rowan et al., 1990; Bass et al., 1992; McNaughton and Morris, 1992; Winsauer et al., 1996). For example, Rowan et al. (1990) reported that a 2-mg/kg dose of buspirone significantly increased the latency to find a submerged or hidden platform in a water maze. Similarly, Bass et al. (1992) found that 1 to 10 mg/kg buspirone, but not 0.5 to 2 mg/kg alprazolam, in rats impaired responses in a three-choice working memory water-escape task. In a study closely related to the present one, Winsauer et al. (1996) found that 1 to 5.6 mg/kg buspirone in rats was as disruptive or more disruptive to the accuracy of responding in a repeated-acquisition task than comparable doses of 8-OH-DPAT. In the present study involving a multiple schedule of acquisition and performance, a 1-mg/kg dose of buspirone produced as large a disruption in the accuracy of responding as a 1-mg/kg dose of either 8-OH-DPAT or LY228729.

Interestingly, the disruptive effects of the 1-mg/kg dose of buspirone on the accuracy of responding were also evident in the performance component when it was administered alone and when it was administered in combination with 8-OH-DPAT. Although this dose of buspirone also potentiated the error-increasing effects of 8-OH-DPAT in acquisition, this effect was only evident when buspirone was combined with lower doses of 8-OH-DPAT (i.e., the error-increasing effect of buspirone combined with higher doses of 8-OH-DPAT was no greater than that for 8-OH-DPAT alone). Thus, the effects obtained in acquisition were more consistent with an interaction between a partial agonist and a full agonist at a single

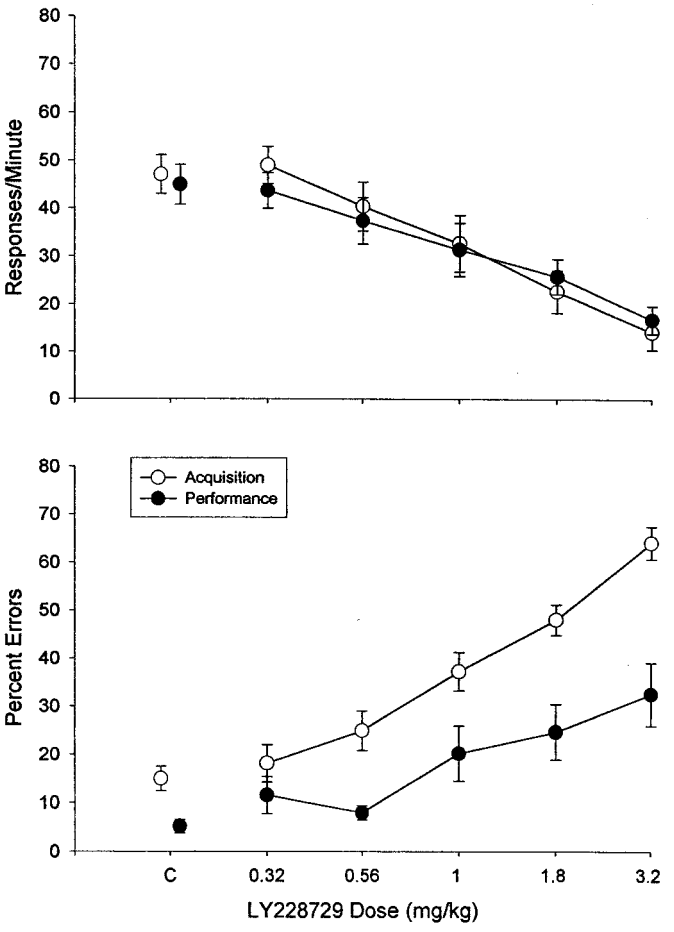

Fig. 9. Effects of LY228729 on overall response rates and percentage of errors in five rats responding under a multiple schedule with acquisition (A) and performance (P) components. Data points at C indicate the mean and S.E.M. for control sessions in which saline was administered. Any points without error bars indicate instances in which the range is encompassed by the data point. For additional details, see legend for Fig. 2.

receptor site (see Kenakin, 1993) than the effects obtained in performance. Explanations for the error-increasing effects obtained in performance might include buspirone's effects at other receptors such as dopamine receptors (Witkin and Barrett, 1986), the possibility of differential mediation by varying numbers of receptors at different brain loci (Meller et al., 1990) or the involvement of behavioral variables such as stimulus control.

In terms of what is known about the effects of NAN-190 on complex behaviors, even fewer studies have been conducted with this compound than with buspirone. Initial reports examining the discriminative stimulus properties of NAN-190 had characterized it as a potential 5-HT$_{1A}$ receptor antagonist (e.g., Glennon et al., 1988,1989), whereas more recent studies have reported effects that were more consistent with a partial agonist at 5-HT$_{1A}$ receptors (Przegalinski et al., 1990; Rydelek-Fitzgerald et al., 1990; Greuel and Glaser, 1992). Przegalinski et al. (1990), for example, reported that NAN-190 could antagonize an 8-OH-DPAT-induced 5-HT behavioral syndrome, but failed to antagonize the hypothermic or corticosterone responses produced by 8-OH-DPAT. These investigators and others who conducted both binding (Rydelek-Fitzgerald et al., 1990) and electrophysiological (Greuel and Glaser, 1992) studies with NAN-190 concluded that it could act as an agonist and sometimes mimic the effects of 8-OH-DPAT.

In the present study, the effects observed with NAN-190 both alone and in combination with 8-OH-DPAT were consistent with this profile and differed from the antagonistic effects previously reported in the literature in studies with a variety of behavioral tasks that did not involve learning (e.g.,Przegalinski et al.,1990; Detke et al., 1995). At doses that had been shown to be effective in blocking the effects of 8-OH-DPAT in other tests such as the forced swim test (Detke et al., 1995), NAN-190 generally produced greater rate-decreasing and error-increasing effects than those obtained with 8-OH-DPAT alone, especially on response rate in the performance component. Additionally, the effects obtained with NAN-190 both alone and in combination with 8-OH-DPAT were somewhat different from those obtained with buspirone, particularly with regard to their effects on response rate when they were administered alone. At the doses tested, NAN-190 dose dependently decreased the overall response rate in both components, whereas only the highest dose of buspirone decreased overall response rate, and then only in the acquisition component. Moreover, the disruptive effects produced by the combination of NAN-190 and 8-OH-DPAT were most evident on overall rate of responding, whereas the disruptive effects produced by the combination of buspirone and 8-OH-DPAT were most evident on percentage of errors.

The results obtained with NAN-190 and buspirone support and extend the existing literature concerning the partial agonist properties of NAN-190 and its dissimilarity from azaspirones such as buspirone (e.g., Rydelek-Fitzgerald et al., 1990; Millan et al., 1994). Certainly, additional studies will be required to determine which pharmacological properties of NAN-190 and buspirone were responsible for the observed differences in effect. As was true for buspirone, there are many possible explanations for the pattern of disruptive effects of NAN-190 in vivo such as the involvement of another receptor (e.g., alpha adrenoreceptors) or its differential efficacy at pre- and postsynaptic 5-HT$_{1A}$ receptors. Interestingly, buspirone has been shown to be considerably more efficacious at presynaptic 5-HT$_{1A}$ autoreceptors than postsynaptic receptors (Traber and Glaser, 1987), and NAN-190 has been shown to be more efficacious at postsynaptic 5-HT$_{1A}$ receptors than presynaptic autoreceptors (Rydelek-Fitzgerald et al., 1990; Detke et al., 1995). In any case, the present study suggests that the pharmacological differences between buspirone and NAN-190 have important behavioral ramifications, and potential ramifications for the use of these drugs as atypical anxiolytics.

Of the three drugs tested in combination with 8-OH-DPAT in the present study, only *p*-MPPI significantly antagonized the 8-OH-DPAT-induced disruptions in responding under the multiple schedule across a broad range of doses. The two doses of *p*-MPPI, which had little or no effect when administered alone, shifted the 8-OH-DPAT dose-effect curves for overall response rate and percentage of errors in both components approximately ½ log unit to the right. However, the antagonism of the disruptive effects of 8-OH-DPAT was not as robust on both behavioral measures when examined from the perspective of the individual subject data. More specifically, the antagonism of 8-OH-DPAT's rate-decreasing effects was more complete than the antagonism of its error-increasing effects in a

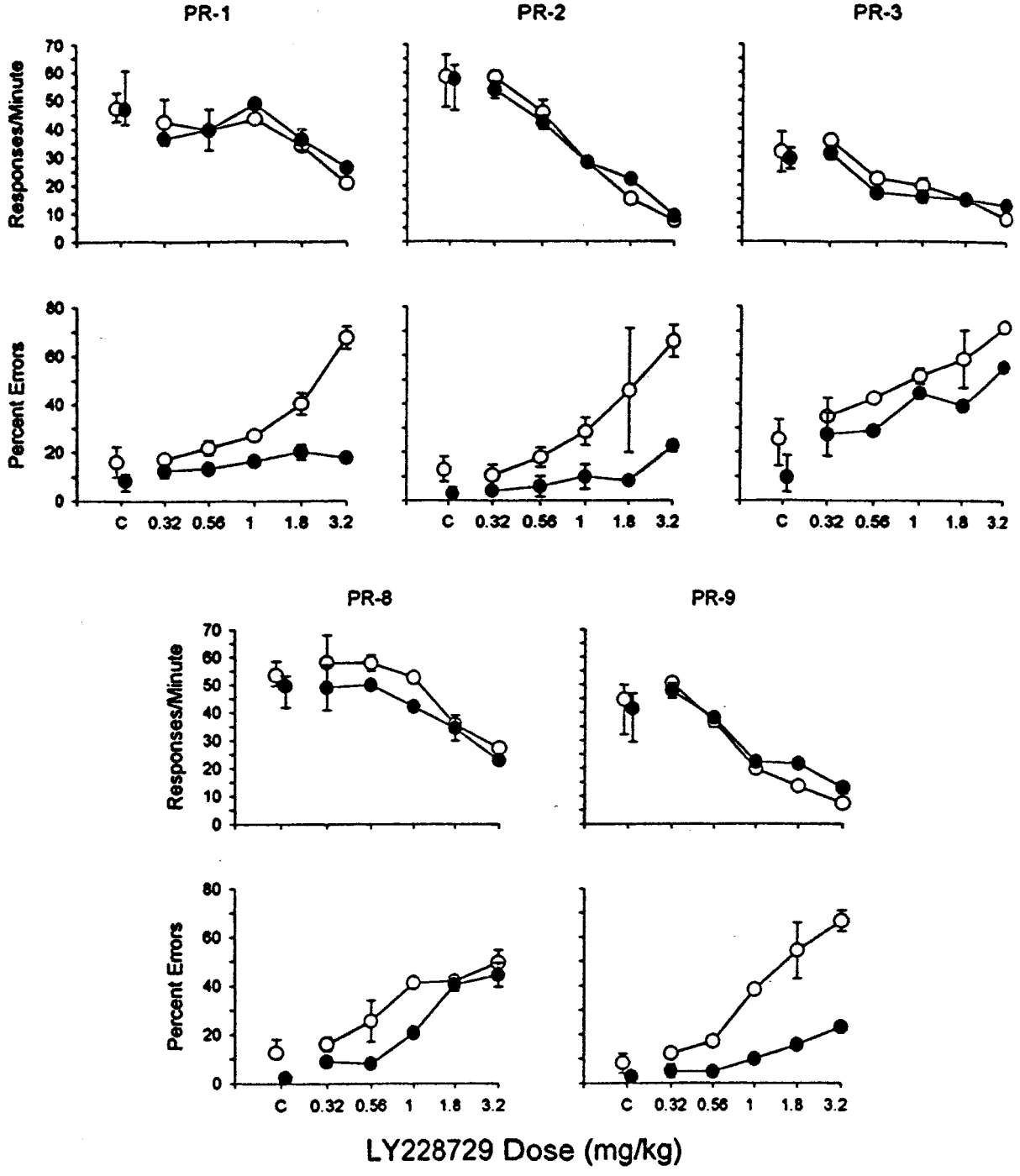

Fig. 10. Effects of LY228729 on overall response rate and percentage of errors in the acquisition and performance components of the multiple schedule for five subjects. The unconnected points with vertical lines at C indicate the mean and range of 9 to 11 control sessions obtained with each subject. The points with vertical lines in the dose-effect curves indicate the mean and range for one or two determinations of that dose; points without vertical lines indicate either a single determination (i.e., the 1-mg/kg dose for PR-1, PR-8, and PR-9) or an instance in which the range is encompassed by the point.

large number of subjects tested (see Fig. 7). Despite the fact that *p*-MPPI has been shown to be effective at blocking behavioral responses mediated by both pre- and postsynaptic 5-HT receptors, other studies have reported a similar inability of *p*-MPPI to completely antagonize certain effects of 8-OH-DPAT, particularly the hypothermic effects produced by 8-OH-DPAT (Thielen and Frazer, 1995; Allen et al., 1997). For example, Thielen and Frazer (1995) reported that a 10-mg/kg dose of *p*-MPPI could antagonize the hypothermia induced by a 0.5-mg/kg dose of 8-OH-DPAT administered s.c., but the combined effect of the two doses was still significantly different from saline control levels. In that same report, however, a 10-mg/kg dose of *p*-MPPI completely reversed the forepaw treading induced by a 2-mg/kg dose of 8-OH-DPAT. These data, along with the data presented in this study, indicate that there are

some limits in the ability of *p*-MPPI to antagonize the behavioral effects of 8-OH-DPAT in vivo even though the interaction between the two drugs in vitro appears to be largely competitive in nature (e.g., Kung et al., 1994; Kung et al., 1995). Whether or not this aspect of *p*-MPPI's antagonist properties relates to its affinity at pre- versus postsynaptic receptors would be an interesting question for future studies.

The data obtained in this study clearly indicated that the species differences observed in a previous study (i.e., Winsauer et al., 1996) were not an artifact of the different baselines used to assay the effects of buspirone and 8-OH-DPAT. More specifically, the addition of a performance component in the present study did not change the finding from the previous study with rats that indicated that the partial agonist buspirone was as disruptive or more disruptive to learning than a full agonist such as 8-OH-DPAT at comparable doses. In addition, the present study extended this finding by demonstrating that buspirone was also as disruptive as LY228729 (another full agonist at 5-HT$_{1A}$ receptors), and demonstrating that it was unusually disruptive to responding in the performance components. The large error-increasing effects produced by buspirone in the performance components where responding is considered to be under relatively strong stimulus control were not only surprising, but they were another indicator of the extent to which the effects of buspirone differed between rhesus monkeys and rats (i.e., the effects of buspirone on errors in performance were negligible in monkeys). In fact, neither 8-OH-DPAT nor LY228729 were as selectively disruptive to learning in rats as was demonstrated for 8-OH-DPAT in monkeys. For these reasons in particular, there is a need to continue to explore the pharmacological and behavioral variables mediating the effects of the 5-HT$_{1A}$ receptor agonists in these species.

In summary, the present experiments involving rats responding under a multiple schedule of repeated acquisition and performance demonstrated that 5-HT$_{1A}$ receptor agonists such as 8-OH-DPAT and LY228729 generally disrupt learning at doses that also disrupt other behavioral processes. The studies with buspirone and NAN-190 demonstrated that both drugs can disrupt learning and performance, although each drug differentially affected the two dependent measures of responding under the multiple schedule. The manner in which buspirone and NAN-190 interacted with 8-OH-DPAT also differed in this complex operant procedure even though they are both classified as partial agonists at 5-HT$_{1A}$ receptors. Finally, the interaction experiment with *p*-MPPI indicated that it is a relatively effective antagonist of the disruptive effects of 8-OH-DPAT on learning and performance.

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