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Effects of Buspirone Differ From Those of Gepirone and 8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) on Unpunished Responding of Pigeons

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BARRETT, J. E., C. FLECK-KANDATH AND R. S. MANSBACH. *Effects of buspirone differ from those of gepirone and 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) on unpunished responding of pigeons.* PHARMACOL BIOCHEM BEHAV **30**(3) 723–727, 1988.—Under several behavioral procedures, such as punished responding and drug discrimination, the effects of the atypical anxiolytic buspirone are similar to those of its analogue gepirone, and to those of the 5-HT_{1A} receptor agonist 8-OH-DPAT. Similarities in the effects of these compounds occur despite the fact that buspirone produces strong dopaminergic actions, whereas both gepirone and 8-OH-DPAT effects mainly appear to be serotonergically mediated. When keypeck responding of pigeons was maintained under a multiple 3-min fixed-interval, 30-response fixed ratio schedule of food presentation, responding under both the fixed-interval and fixed-ratio schedules was decreased over a range of buspirone doses (0.3–5.6 mg/kg). As has been reported with many antipsychotic compounds, performance under the fixed-interval schedule was more sensitive to the rate-decreasing effects of buspirone. In contrast, both gepirone (0.03–3.0 mg/kg) and 8-OH-DPAT (0.03–1.0 mg/kg) increased responding under the two schedules. Differences in the effects of buspirone from the other compounds in this study, compared to the similar effects of these drugs obtained using other procedures, emphasize the importance of the specific behavior as a determinant of drug action. The multiple fixed-interval, fixed-ratio schedule may be useful for delineating the relative balance of dopaminergic and serotonergic effects produced by drugs that are less apparent using other behavioral procedures. Additionally, since the effects of these substances under the multiple fixed-interval, fixed-ratio schedule closely parallel the different neurochemical changes produced by these drugs, further analyses of other novel anxiolytic drugs under this procedure will complement the study of these compounds using other methods and should aid in the eventual clarification of the behavioral and neurochemical actions of this class of drugs.

Buspirone Gepirone 8-OH-DPAT MJ 13805 Novel anxiolytics Pigeons

THE novel anxiolytic, buspirone, has attracted considerable attention because of its several unique behavioral and neurochemical actions. Buspirone typically produces little or no effects in mammals under traditional punishment or "conflict" procedures that have usually been very sensitive to and selective for anxiolytic drug actions [4, 11, 19, 21, 22, 27]. In contrast to the generally weak actions of buspirone on punished performances of mammals, however, this this compound produces large increases in punished responding of pigeons that are comparable in magnitude to those found with typical anxiolytic agents such as chlordiazepoxide [3,29]. Increases in punished responding of pigeons also occur with a buspirone analogue, gepirone (formerly MJ-13805), as well as with the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) [3,18]. In drug discrimination procedures with pigeons trained to discriminate buspirone from saline, buspirone has been shown to produce discriminative stimulus effects similar to gepirone and 8-OH-DPAT [17]. Similar results have been found in rats trained to discriminate 8-OH-DPAT from saline, with generalization occurring to buspirone as well as to a structurally similar compound, ipsapirone [6,24]. When ipsapirone has

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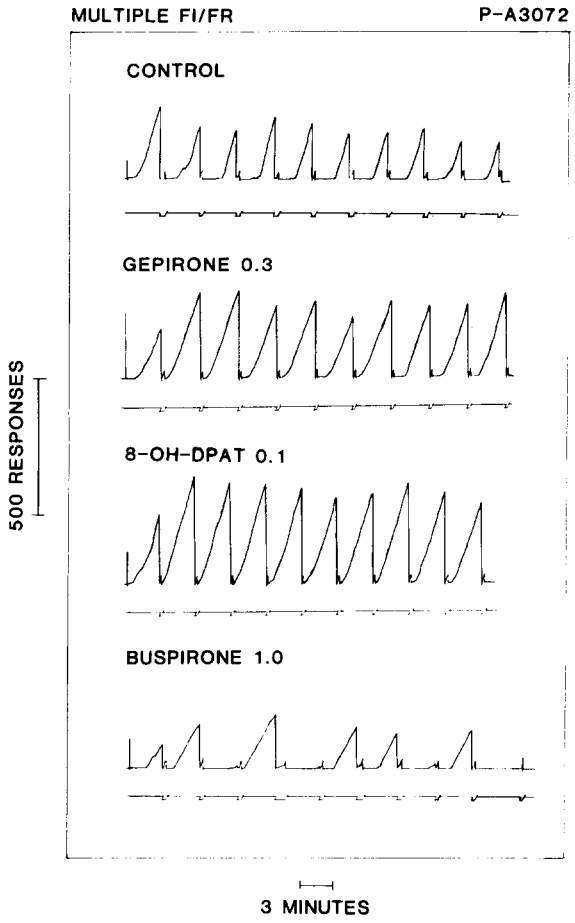

FIG. 1. Cumulative response records depicting control performances and representative effects of gepirone, 8-OH-DPAT and buspirone. Ordinate: cumulative responses; Abscissa: time. The lower pen in each record was deflected during the fixed-ratio component. The pens stepped with each response and were reset with the delivery of reinforcement.

been used as a training drug, rats also respond on the drug-appropriate lever when tested with buspirone and 8-OH-DPAT [23]. At present, it appears that the discriminative stimulus effects, as well as the effects of buspirone on punished responding, are mediated through a 5-HT_{1A} receptor mechanism [9, 18, 23, 24].

It was clear from the outset of research with buspirone that this compound possessed a strong dopaminergic component [5, 13–15, 20, 25, 26]. In both pigeons and rats for example, buspirone increases the dopamine metabolites homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) [13, 15, 18]; the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), is decreased after buspirone administration [18]. Gepirone and 8-OH-DPAT, like buspirone, decrease metabolites of serotonin while leaving dopamine metabolites unaffected [18]. In keeping with dopamine antagonist effects, buspirone blocks the behavioral effects of apomorphine [29]. Thus, although many of the behavioral effects of the three compounds—buspirone, gepirone and 8-OH-DPAT—are very similar, these neurochemical differences would suggest that differences should appear in the activity of these compounds under some behavioral procedures. The present experiment examined the effects of buspirone, gepirone and 8-OH-DPAT under a multiple fixed-interval, fixed-ratio schedule of food presentation in an attempt to further explore the similarities and differences in the behavioral actions of these compounds. Unlike previous studies in which the effects of these substances on schedule-controlled behavior and drug discrimination were similar, however, in the present study the effects of buspirone differed considerably from the actions of gepirone and 8-OH-DPAT.

METHOD

Subjects

Six adult male White Carneaux pigeons, obtained from the Palmetto Pigeon Plant, Sumter, SC were used. All subjects were maintained at 85% of their free-feeding body weights. The pigeons were experimentally naive and were housed in individual cages with water and crushed oyster shells continuously available. The vivarium was maintained at a constant temperature and humidity, with a 12 hr light-dark cycle.

Apparatus

Experiments were conducted in a standard operant conditioning chamber (22×27×31 cm) that was located in a sound- and light-attenuating enclosure. The enclosure was furnished with a ventillating fan and white noise to mask extraneous noise. The front panel of the chamber contained a Plexiglas response key (R. Gerbrands Co., Arlington, MA) located in the center of the panel, 23 cm above a wire-mesh floor. The key could be transilluminated with differently colored 7 W lamps. A minimum force of 0.15 N (15 g) applied to the key produced the click of a feedback relay mounted behind the front wall and was recorded as a response. A rectangular opening located below the key provided access to mixed grain delivered by the activation of a solenoid-operated feeder. Food presentation, which lasted 4 sec, was accompanied by the illumination of the grain magazine and by extinguishing the key lights.

Procedure

After the pigeons were reduced to 85% of their free-feeding body weights they were trained to key peck by the method of successive approximations [8]. Initially, each key peck in the presence of a white key light produced food; over the course of two to three sessions conducted once per day, the number of responses required to produce food was gradually increased to 30 (fixed-ratio 30 response schedule). After approximately 5 sessions exposure to the fixed-ratio schedule alone, the fixed-interval component was introduced in the presence of red key lights. Initially, the fixed-interval value was 1 min, i.e., the first response occurrence after 1 min elapsed in the presence of the red lights produced food. Over a 3-day period the interval value was increased to 3 min where it remained for the duration of the experiment. When responding was stabilizing under the multiple fixed-interval, fixed-ratio schedule a 30-sec timeout period was inserted between the two alternating schedule conditions. During timeout the chamber was dark and responding had no scheduled consequences. When responding stabilized (i.e., no consistent trends in response rates over a 5-day period), a limited hold was added to the schedules that specified time

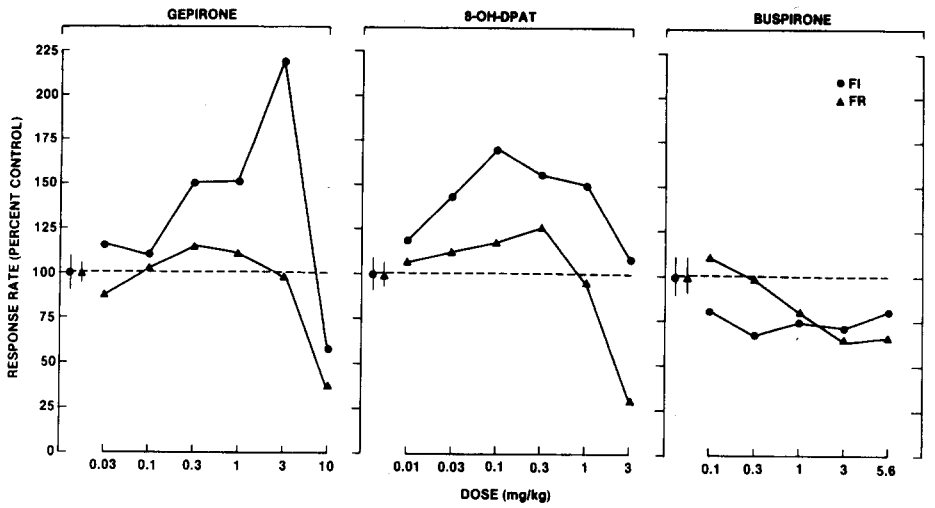

FIG. 2. Dose response curves showing the effects of gepirone, 8-OH-DPAT and buspirone on responding under the multiple fixed-ratio, fixed-interval schedule. Points on the left of each curve denote control performances (±2 S.D.) for an average of 6 pigeons. Points are shown as percent of control performance.

limitations for the completion of the two schedule requirements. Under the ratio schedule, the 30-response requirement had to be completed within 1 min otherwise the key light was extinguished, timeout occurred, and the schedule alternated into the fixed-interval component. Under the interval schedule, if a response did not occur within 1 min of the end of the fixed interval, timeout occurred automatically and the schedule alternated to the next component. Daily experimental sessions (M–F) consisted of exposure to 20 components of the schedule (10 each of the fixed-interval and fixed-ratio schedule components).

Drug Procedure

Drugs were administered after responding of individual pigeons under the two schedules showed no systematic trends for a two-week period. After first receiving injections of sterile 0.9% saline, dose-effect curves were determined for buspirone HCl, gepirone HCl (generously furnished by Bristol Myers) and 8-OH-DPAT HBr (Research Biochemicals Inc.). All drugs were dissolved in sterile saline solutions and were given intramuscularly in a volume of 1.0 ml/kg body weight immediately before the session. Buspirone was generally studied first, followed by gepirone and then 8-OH-DPAT; however, to ensure that there was no sequence effect, some pigeons received either 8-OH-DPAT or gepirone as the initial compound. Doses were administered in a mixed sequence and were given at least twice in each pigeon. Drugs were administered on Tuesdays and Fridays, given that performances on the preceding day were stable compared to performance prior to the initiation of drug series. All doses are expressed in terms of the salt.

Data Analysis

Response rates (responses per sec) were computed separately for each component of the multiple schedule by dividing the total number of responses made during each component within a session by the total elapsed time in each of the components. Response rates during drug sessions were compared with response rates on control days (i.e., Thursdays or days when saline was administered rather than a drug) for each pigeon. At least 7 controls for each pigeon were used in determining dose-response curves with each drug. Drug effects for individual pigeons, expressed as percentages of control performances, were averaged together to produce composite dose-response curves for each compound. Drug effects were considered significant in individual pigeons if response rates under drug deviated more than two standard deviations from control levels.

RESULTS

Representative control performances under the multiple fixed-interval, fixed-ratio schedule are shown in Fig. 1. Performance in each component was under good discriminative control: in the presence of the key light stimulus correlated with the fixed-interval schedule, responding did not occur or occurred at very low rates during the initial portion of the interval; responding increased towards the end of the interval and was occurring at a high rate when food became available at the end of the three-minute period. Under the fixed-ratio portion of the schedule, there was only a brief initial pause followed by the occurrence of a high, steady rate of responding until food delivery upon completion of the 30-response requirement. Average rates of responding under the fixed-interval schedule were 0.78 (±0.08) responses per sec, whereas under the fixed-ratio schedule these rates were 2.79 (±0.13) responses per sec (N=6).

The buspirone analogue, gepirone, produced large increases in responding under the fixed-interval schedule across a wide range of doses (0.3–3.0 mg/kg); increases in responding at these doses exceeded ±2. S.D. of control values in all pigeons (Fig. 2). Doses below 0.3 mg/kg increased responding beyond the measure of control values in only 2 of the 6 pigeons. Gepirone also significantly increased responding under the fixed-ratio schedule, although to a much

smaller extent and only at the 0.3 and 1.0 mg/kg doses (6/6 pigeons). Responding under the fixed-interval schedule was increased to over 200 percent of control levels at the 3.0 mg/kg dose that did not affect responding under the fixed-ratio schedule. Responding was decreased significantly with all pigeons at the 10 mg/kg dose of gepirone. Cumulative response records depicting changes in the rate and pattern of responding after the administration of gepirone are shown in Fig. 1. With gepirone the initial pause under the fixed-interval schedule was decreased but still present and the time taken to complete the fixed-ratio requirement was also decreased or eliminated.

Results similar to those found with gepirone were also obtained with 8-OH-DPAT. However, increases under the fixed-interval schedule were slightly less at peak doses of each drug and increases under the fixed-ratio schedule were somewhat greater with 8-OH-DPAT compared to gepirone. 8-OH-DPAT was also more potent than gepirone, with peak increases in responding occurring at the 0.1 mg/kg dose, compared to that of 3.0 mg/kg with gepirone. All pigeons showed significant increases in responding at doses of 0.03–1.0 mg/kg 8-OH-DPAT under the fixed-interval schedule; significant increases under the fixed-ratio schedule occurred with all pigeons at the 0.1 and 0.3 mg/kg doses. At 1.0 mg/kg of 8-OH-DPAT, fixed-interval rates of responding remained elevated, whereas responding under the fixed-ratio schedule was on the descending limb of the dose-response curve and was at control performance levels. The 3.0 mg/kg dose of 8-OH-DPAT produced large decreases in responding of all pigeons under the fixed-ratio schedule; responding under the fixed-interval schedule, though on the descending portion of the dose-response curve, remained slightly above control levels. Records taken from a session in which 0.1 mg/kg 8-OH-DPAT was administered are shown in Fig. 1. At this dose, the initial pause in the fixed-interval was reduced and responding occurred at a high steady rate throughout the entire interval. Additionally, the time to complete the fixed-ratio schedule was also markedly decreased after the administration of 8-OH-DPAT.

In contrast to the effects obtained with gepirone and 8-OH-DPAT, buspirone did not increase responding under either schedule at any dose (Fig. 2). Low buspirone doses (0.1–0.3 mg/kg) significantly decreased responding under the fixed-interval schedule but did not affect responding under the fixed-ratio schedule. Doses below 0.1 mg/kg (i.e., 0.01 and 0.03 mg/kg) did not affect performance in any of the pigeons (data not shown). Doses of buspirone above 1.0 mg/kg decreased responding significantly under both schedules to approximately 75% of control levels. Decreases beyond the 2 S.D. range of control values occurred in 5 of 6 pigeons at the 1.0 and 3.0 mg/kg doses. At 3.0 and 5.6 mg/kg, responding was decreased significantly in all pigeons. Cumulative response records shown in Fig. 1 reveal the marked reduction in response rates that occurred under both schedule components at the low buspirone doses. Performances under the fixed-interval schedule tended to oscillate during the session at this dose (1.0 mg/kg), with some intervals showing response rates and patterns near control levels whereas in other intervals responding was markedly reduced.

DISCUSSION

In previous studies using punished responding and drug discrimination procedures with pigeons as subjects, gepirone, 8-OH-DPAT and buspirone have shown similar effects [3, 17, 18, 28]. In the present experiment, however, the effects of buspirone differed considerably from those of the other two compounds. Both gepirone and 8-OH-DPAT produced large increases in responding under the fixed-interval schedule at doses that did not affect or also increased responding under the fixed-ratio schedule. In contrast, buspirone only decreased responding under both schedules at behaviorally active doses.

In previous experiments with pigeons these three compounds have been shown to share discriminative stimulus effects [6,17] and to increase punished responding [3, 18, 28, 29]. These results taken together with other studies using rats [6, 23, 24] lend support to the view that, although buspirone alone possesses prominent dopaminergic properties, it behavioral and, primarily, anxiolytic actions derive mainly from its interaction with the serotonergic system. Gepirone has been shown to be essentially devoid of direct actions on the dopamine system and to interact mainly with serotonin [7,18]. Similarly, 8-OH-DPAT is commonly regarded as a serotonin agonist with specificity for the 5-HT_{1A} receptor [9]. Buspirone, as well as a structurally similar compound ipsapirone (TVX Q 7821), have also been shown to interact with this recognition site in neurochemical studies and to share discriminative stimulus properties with 8-OH-DPAT [23]. Thus, although buspirone does produce substantial effects on dopamine systems, its antipunishment and anxiolytic actions appear to be mediated through interactions with the serotonin system.

The findings in the present manuscript indicate that buspirone's effects can be differentiated from those of gepirone and 8-OH-DPAT under the multiple fixed-interval, fixed-ratio schedule even though these compounds produce similar effects under punishment procedures and share discriminative stimulus properties. Effects of buspirone on pigeons in the present study are similar to those found with many antipsychotic dopamine antagonist compounds such as chlorpromazine and haloperidol under identical procedures [1]. In contrast, many serotonin antagonists produce increases in responding under the fixed-interval and fixed-ratio schedules [16]. Thus, performance under the multiple fixed-interval, fixed-ratio schedule may uniquely reflect relative differences in the dopaminergic/serotonergic balances that are obscured using other behavioral procedures.

The importance of the type of behavior under study as a significant factor in analyzing the effects of drugs has been a recurring theme in behavioral pharmacological research [2, 10, 12]. In the present study, the effects of buspirone differed from those of gepirone and 8-OH-DPAT, whereas previously, these compounds have been reported to affect behavior in a similar manner. The multiple fixed-interval, fixed-ratio schedule seems able to detect differences in the actions of these drugs that are not noticeable using other behavioral procedures. Neurochemical assays of cerebrospinal fluid from pigeons after administration of these compounds show clear differences between the effects produced by buspirone compared to those produced by gepirone and 8-OH-DPAT [18]. Therefore, the similar behavioral effects reported in previous studies appeared difficult to reconcile. Based on previous studies and the present data, however, it seem most reasonable to suggest that different behavioral procedures either recruit different neurochemical mechanisms or are differently controlled by these systems and will show different sensitivity and selectivity to various compounds depending on the specific procedure being employed.

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