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# 'Taming' of Wild Rats (*Rattus rattus*) By $5HT_{1A}$ Agonists Buspirone and Gepirone[1]

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BLANCHARD, D. C., R. J. RODGERS, C. A. HENDRIE AND K. HORI. *'Taming' of wild rats* (Rattus rattus) *by $5HT_{1A}$ agonists buspirone and gepirone*. PHARMACOL BIOCHEM BEHAV 31(2) 269–278, 1988.—A battery of tests designed to elicit reactions to a variety of nonpainful threat stimuli was used to study the effects of the $5HT_{1A}$ agonists buspirone (5–20 mg/kg), and gepirone (5–20 mg/kg) on the defensive repertoire of wild *Rattus rattus*. These two compounds produced very similar patterns of results on the test battery, with gepirone generally more effective: Both compounds failed to interfere with either spontaneous motor activity or avoidance/flight to an approaching experimenter. However, both reduced defensive reactivity to proximal threat stimuli, increasing passive contacts with the experimenter in an inescapable situation and reducing "proximal" defensive reactions: jump/flinch reactions to dorsal contact, and, boxing, and biting to a number of threat stimuli. Defensive threat vocalizations and jump attacks were also reduced, but less consistently, as was the experimenter's rating of subject's defensiveness to being picked up. This pattern of results suggested specific "taming" effects of buspirone and, especially, gepirone on defensive reactions. In combination with findings indicating somewhat different (benzodiazepines) to very different (ethanol) profiles for other anxiolytics in the same test battery, these results suggest that the Defense Test Battery may be capable of providing behavioural differentiation among various classes of anxiolytics.

5HT $5HT_{1A}$ Serotonin Buspirone Gepirone Ethoexperimental analysis Defensive behaviour
Fear Anxiety Wild rat

SEROTONERGIC (5HT) mechanisms have long been implicated in the brain 'punishment' system (63), the initial hypothesis being that aversive stimuli activate 5HT cells in the raphe system leading to behavioural suppression. Some support for this hypothesis comes from the following observations: Electrical activity in the dorsal raphe nucleus increases specifically during defensive behaviour (75); electrical stimulation of the raphe system elicits fear-like responses (30,58); and raphe lesions produce anxiolytic effects (68,72). Furthermore, anticonflict effects have also been found with intraraphe injection of chlordiazepoxide, suggesting the possible involvement of 5HT substrates in the anxiolytic activity of benzodiazepines (59). Against this profile, however, is a substantive body of data indicating that raphe lesions (dorsal and/or median nuclei) actually *enhance* defensive reactions to a variety of stimuli (1, 17, 20, 23, 26, 33, 35, 52, 74, 77).

Inconsistencies concerning 5HT involvement in defense/fear/anxiety are also prevalent in the pharmacological literature. Thus, evidence (albeit controversial) exists for anxiolytic activity of antiserotonergic compounds including synthesis inhibitors, such as PCPA, and receptor antagonists, such as methysergide [for review, see (32, 34, 57, 67)]. In contrast, in aggression studies, PCPA has been found to *enhance* reactivity and defensiveness (13, 18, 21, 45, 47, 53, 56), whereas 5HT receptor agonists *and* antagonists have both been reported to inhibit defensiveness (11, 36, 55, 56).

A potential resolution to this conflicting evidence may rest with recent developments in serotonin receptor pharmacology. Radioligand binding techniques have identified three major subtypes of 5HT receptors, $5HT_1$, $5HT_2$ and $5HT_3$ (12, 27, 51) with further subdivision of type 1 into $5HT_{1A}$ and $5HT_{1B}$ sites (14,48). Considerable interest is currently focused upon $5HT_{1A}$ sites in view of the finding that a

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range of selective ligands (agonists/partial agonists) at this site exert anxiolytic effects in a number of species (16, 50, 70). Examples include 8OH-DPAT (22), and the related compounds ipsapirone (15, 60, 71), buspirone and gepirone (2, 19, 28, 29, 31, 41, 54, 65, 66, 76). Consistent with these findings are the reports that buspirone and gepirone and ipsapirone also decrease attack and defense in mice, rats and monkeys (42, 44, 46, 64, 69, 70). Further indirect support for the involvement of $5HT_1$ sites in the inhibitory modulation of defense derives from the observations that quipazine reduces footshock-induced defensive fighting in rats and mice (55,56) while quipazine and 5-methoxytryptamine potently inhibit agonistic behaviour in mice (40).

To further examine the involvement of $5HT_{1A}$ sites in defense, and to provide comparative data for ethanol (7) and benzodiazepines (9), we have assessed the effects of the pyrimidinylpiperazine derivatives, buspirone and gepirone, on the defensive repertoire of wild *Rattus rattus*. In contrast to laboratory rats, wild rats display a full range of defensive reactions (flight, freezing, boxing, biting, vocalization and jump attacks) to *nonpainful* threat stimuli and a test battery has been developed whereby the effects of drugs on these reactions may be studied in depth (8).

## METHOD

### *Subjects*

The subjects were 20 male and 20 female *Rattus rattus*, trapped on the island of Oahu. All animals were singly housed in 19×27×15 cm suspended metal cages, for 30–60 days prior to testing. The room in which the subjects were housed was kept on a constant 12:12 light-dark cycle and food and water were available ad lib. The animals' weights ranged from 100 to 250 grams at the time of testing.

### *Drugs*

Buspirone hydrochloride and gepirone hydrochloride (Bristol-Myers, Evansville, IN) were dissolved in physiological (0.9%) saline, which, alone, served for control injections. All injections were performed intraperitoneally (IP) in a volume of 3 cc per kg, thirty minutes prior to testing. Doses cited (5–20 mg/kg for both compounds) refer to the salts.

### *Procedure*

A separate experiment, with equal numbers of males (n=10) and females (n=10), was conducted with each compound. Order of testing under control and drug-treatment conditions was counterbalanced within each experiment, with behavioural tests spaced at least 4 days apart. In all tests, the experimenters who ran and rated the subjects were blind with respect to the drug being tested.

Each subject was run in a set of procedures specifically designed to provide a relatively complete array of species-typical defensive behaviours to nonpainful threat stimuli in wild rats (4, 5, 8).

### *Oval Runway*

*Apparatus.* The oval runway was formed by enclosing a 6×2 meter area with plywood. The runway consisted of a 4×2 meter straight section divided down the center by a partition, making each side 4 m long ×1 m wide. Both ends of the runway were rounded by a curved radius of 1 meter to keep the width constant throughout. The floor of the runway was marked at 1 meter intervals.

*Five-minute pretest.* The experimenter gently slid each subject out of its cage into the runway, then left the runway area to observe and record the subject's line crossings during a 5-min pretest period.

*Discriminated avoidance.* After the pretest, the experimenter entered the runway at the end opposite the subject and made 5 approaches (approach speed was approximately half a meter per second) toward the subject, until contact (a light touch with the experimenter's shoe) was recorded, or, the subject ran away. If the subject avoided by running away, the distance between the experimenter and the subject (avoidance distance) and the distance the subject fled (escape distance) were recorded. An interval of 30 seconds separated each approach toward the subject.

*Flight speed.* Flight testing was conducted immediately following the avoidance test. The experimenter rapidly approached the subject from the opposite end of the runway at a speed of roughly 1.5 to 2 meters per second, and, using a stopwatch, recorded the time it took to chase the subject a distance of 36 meters. If the subject did not flee, the experimenter remained in contact with the subject for 60 seconds. If no flight was elicited a chase time of 300 seconds was assigned to the subject and the trial was terminated. Chase time was converted to flight speed for statistical analysis.

### *Inescapable Runway*

*Apparatus.* The oval runway was converted into an inescapable runway by the closing of a partition at both ends of the straight segment. This produced a 4×1 meter straight runway with no escape possible from either end.

*Responses to an approaching experimenter.* The experimenter made 5 approaches toward the subject from the far end of the runway, making a mild noise by clapping his hands before each approach to ensure that the subject was aware of his presence. The experimenter approached the subject at a speed of a half meter per second, pausing for 30 seconds at distances of 4, 3, 2, 1 and 0.5 meters from the subject. Subject freezing and flight, as well as defensive threat and attack behaviours—box, vocalize, jump attacks, and bites—were recorded at each distance. If flight or other types of active defense were seen, the experimenter moved in to lightly contact the subject, and recorded defensive threat or flight if these occurred to the contact.

### *Proximal Testing*

*Apparatus.* At the conclusion of runway testing, subjects were placed into an aluminum barrel, 50 cm in diameter and 120 cm in height. The following defensive tests were conducted while the subject was in the barrel.

*Dorsal contact.* Jump/flinch reactions to dorsal contact were measured by lightly tapping the subject on the dorsal flank with a 1 meter wooden dowel. Four trials were given with 30 seconds between each trial. Jump/flinch scores were scored as: 1) Startle 1—a local flinch reaction; 2) Startle 2—a flinch reaction of the animal's entire body; 3) Jump 1—a rapid movement in which two of the animal's paws left the floor; 4) Jump 2—rapid movement in which all four of the animal's paws left the floor; 5) Jump 3—rapid movement in which the animal jumped 10 cm or higher. Each of these scores was assigned a value, with 1 for "Startle 1" through 5 for "Jump 3," and a total startle score calculated by adding together these values for all four trials.

*Vibrissal stimulation.* Two circular brushes, 2.5 cm in diameter, fixed perpendicularly to a 1 meter long wooden dowel,

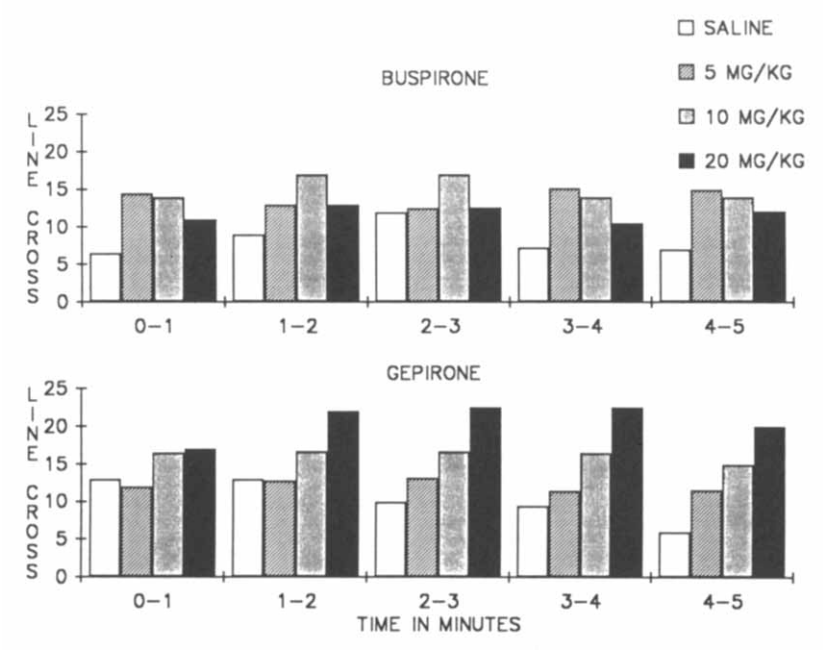


FIG. 1. Mean line crossings during each minute of a 5-minute period in the oval runway prior to the appearance of the experimenter, for subjects under varying doses (0, 5, 10 or 20 milligrams per kilogram) of buspirone and gepirone.

were used to stimulate the subject's vibrissae, in a series of four trials. The experimenter made short upward strokes with the hairs of the brush, making extensive contact with the vibrissae, and being very careful not to touch the subject's snout. Four defensive threat and attack reactions to vibrissal stimulation were recorded: boxing, biting vocalizing, and jump attacks.

*Anesthetized conspecific.* A terminally anesthetized conspecific, held and presented at ground level with its snout facing the subject, was moved toward the subject at a rate of 5 cm per second, until contact occurred. Four trials were given. The frequency of defensive threat and attack reactions—boxing, biting, vocalizing, and jump attacks toward the head and snout of the anesthetized conspecific—were recorded.

*Reaction to handling.* The last procedure measured the subject's defensiveness in response to an attempt by the experimenter to pick it up. Only one pickup attempt was made. Defensive threat and attack behaviours—boxing, biting, vocalizing, and jump attacks—toward the experimenter's gloved hand, were recorded. The experimenter also rated the success of the attempt in terms of actually picking the animal up and out of the barrel. The experimenter also rated subject defensiveness during pickup, on a rating scale from 0 to 5, with a score of 0 given to a totally docile animal that was easily picked up and showed no defensive reaction and 5 to subjects that could not be picked up and showed a full range of defensive threat and attack behaviours.

### *Statistical Analyses*

Data were initially analyzed by 2- or 3-factor Analysis of Variance (ANOVA), except as noted below. Follow-up tests were performed using Dunnett's procedure for comparing all treatment means with a control. Since no main effects of sex were found on any measure, and a significant sex interaction was found only for freezing to the approach of the experimenter, data were collapsed across sex except with reference to this measure.

Behavioural elements which were recorded as present/absent, or by subjective intensity (i.e., boxing, defensive threat vocalization, biting, and jump attacks) were analyzed using the Wilcoxon test for matched pairs. McNemar tests were used to analyze single trial scores in which a procedure was run on only one occasion for each animal within each drug condition

Although each experiment was analyzed separately, results are presented in terms of procedure.

## RESULTS

### *Five Minute Pretest*

Figure 1 presents the results of line crossings in the initial five-minute pretest period in the circular runway, for both buspirone and gepirone. Line crossings during 1-minute blocks of the initial 5-minute period before the experimenter entered the apparatus appeared to show a curvilinear relationship as a function of increasing doses of buspirone, first increasing and then decreasing with higher doses. However, analysis of variance failed to show a statistically significant effect, $F(3,54)=2.14$, $p>0.05$, of buspirone dose, while the effects of time, $F(4,72)=0.98$, $p>0.05$, and the dose-time interaction were similarly nonsignificant, $F(12,216)=0.85$, $p>0.05$. For gepirone, increasing doses were associated with a greater number of line crossings, $F(3,54)=3.86$, $p>0.05$. Subsequent analyses indicated that 20 mg/kg produced reliable changes in line crossings, $t(54)=3.65$, $p<0.01$. Changes across the five, one-minute periods were significant, $F(4,72)=3.44$, $p<0.05$, with fewer lines crossed in the last

TABLE 1

DEFENSIVE BEHAVIORS IN WILD RATS UNDER SALINE, OR, 3 DOSE LEVELS OF BUSPIRONE OR GEPIRONE

| | Buspirone | | | | Gepirone | | | |
|---|---|---|---|---|---|---|---|---|
| Defensive Behavior | 0.0 | 5.0 | 10.0 | 20.0 | 0.0 | 5.0 | 10.0 | 20.0 |
| Oval Runway | | | | | | | | |
| Avoidance distance | 2.63 | 2.30 | 1.77 | 1.95 | 3.00 | 2.93 | 2.85 | 2.62 |
| Flight Distance | .81 | 1.60 | 1.11 | 1.79 | 1.10 | 1.15 | 1.39 | 1.62 |
| Flight Speed | 1.22 | .81 | 1.63 | .85 | .82 | 1.19 | .82 | .43 |
| Avoidance (%) | 85.00 | 98.00 | 76.00 | 86.00 | 98.00 | 96.00 | 100.00 | 97.00 |
| Dorsal Contact | | | | | | | | |
| Flinch/jump | 13.9 | 11.8 | 11.25 | 10.45 | 13.6 | 10.8 | 10.1 | 9.55 |
| Def. threat vocal. | 2.15 | 2.25 | 1.80 | 1.30 | 1.67 | 1.35 | 1.05 | .95 |
| Experimenter Pick Up | | | | | | | | |
| Rated defense | 3.26 | 2.74 | 2.62 | 2.58 | 3.14 | 2.53 | 2.34 | 2.23 |

TABLE 2

FREEZING (SEC) AS A FUNCTION OF EXPERIMENTER-SUBJECT DISTANCE FOR MALE AND FEMALE WILD RATS UNDER SALINE, OR, 3 DOSE LEVELS OF BUSPIRONE OR GEPIRONE

| | Experimenter-Subject Distance (meters) | | | | |
|---|---|---|---|---|---|
| | Buspirone | | | | |
| Males | 4 | 3 | 2 | 1 | 0.5 |
| Saline | 26.2 | 29.4 | 29.0 | 29.5 | 24.0 |
| 5 mg/kg | 24.5 | 26.1 | 27.1 | 24.5 | 22.8 |
| 10 mg/kg | 20.8 | 28.7 | 26.7 | 25.8 | 20.6 |
| 20 mg/kg | 22.8 | 22.6 | 27.5 | 26.3 | 21.1 |
| Females | | | | | |
| Saline | 23.5 | 25.0 | 26.8 | 26.1 | 18.0 |
| 5 mg/kg | 18.0 | 22.7 | 26.9 | 24.0 | 21.0 |
| 10 mg/kg | 24.8 | 27.4 | 26.9 | 28.3 | 27.9 |
| 20 mg/kg | 29.3 | 30.0 | 28.8 | 29.8 | 29.9 |
| | Gepirone | | | | |
| Males | | | | | |
| Saline | 15.1 | 20.6 | 24.4 | 19.9 | 22.1 |
| 5 mg/kg | 16.2 | 25.1 | 26.8 | 24.0 | 24.0 |
| 10 mg/kg | 18.7 | 21.4 | 27.0 | 25.2 | 20.5 |
| 20 mg/kg | 24.5 | 28.2 | 25.3 | 22.9 | 18.8 |
| Females | | | | | |
| Saline | 23.5 | 26.7 | 27.9 | 30.0 | 30.0 |
| 5 mg/kg | 20.6 | 26.3 | 26.9 | 29.0 | 28.7 |
| 10 mg/kg | 19.8 | 26.5 | 28.8 | 20.2 | 18.4 |
| 20 mg/kg | 26.9 | 28.2 | 24.2 | 24.8 | 18.4 |

minutes. The gepirone dose by time interaction was not significant, $F(12,216)=1.26$, $p>0.05$.

*Flight and Avoidance to the Experimenter*

Table 1 provides avoidance results for the saline and drug conditions. The distance between experimenter and subject which elicited avoidance was not significantly altered following either buspirone, $F(3,54)=2.37$, $p>0.05$, or gepirone, $F(3,54)=0.62$, $p>0.05$. The distance that subjects fled following the initial avoidance was greater after buspirone, $F(3,54)=5.08$, $p<0.01$, but failed to show a statistically significant difference following gepirone administration, $F(3,54)=2.21$, $p>0.05$. Subsequent analyses indicated that for buspirone both 5 and 20 mg/kg doses, but not 10 mg/kg, reliably influenced flight distance [$t(54)=3.56$ and 3.66, respectively, $p<0.01$ in either case]. The percentage of subjects avoiding is also given in Table 1. A Friedman ANOVA indicated that buspirone produced a significant effect, $\chi^2=3.30$, $p<0.02$, but gepirone did not, $\chi^2=0.24$, $p>0.05$. Subsequent comparisons of the saline control with each buspirone level, however, were not significant. It might be noted that for the buspirone experiment the highest, and lowest, % avoidances, respectively, were for 5 and 10 mg/kg buspirone.

*Flight Speed*

Table 1 also presents the results of flight speed (meters per second) in traversing 36 meters, when pursued by the experimenter. Flight speed remained unchanged under the various doses of both buspirone, $F(3,54)=0.74$, $p>0.05$ and gepirone, $F(3,54)=0.89$, $p>0.05$.

*Inescapable Runway Test*

Table 2 provides freezing results during approaches by the experimenter in the inescapable runway. There was a significant effect of experimenter distance for both studies: buspirone, $F(4,72)=5.25$, $p<0.001$; and gepirone, $F(4,72)=6.83$, $p<0.001$, with duration of freezing initially increasing as the distance between experimenter and subject decreased, and then declining as contact between the two became imminent. No statistically significant effects on freezing were obtained for either buspirone, $F(3,54)=1.25$, $p>0.05$, or gepirone, $F(3,54)=0.66$, $p>0.05$. However, closer examination of the data revealed complexities for both compounds: For buspirone, although the overall effect of subject sex was not statistically significant, $F(1,18)=0.05$, $p>0.05$, there was a significant interaction between subject sex and dose level, $F(3,54)=3.56$, $p<0.05$, reflecting a tendency for females to show increases from an initially lower freezing level with higher buspirone doses, while males showed decreases in freezing from an initially higher level.

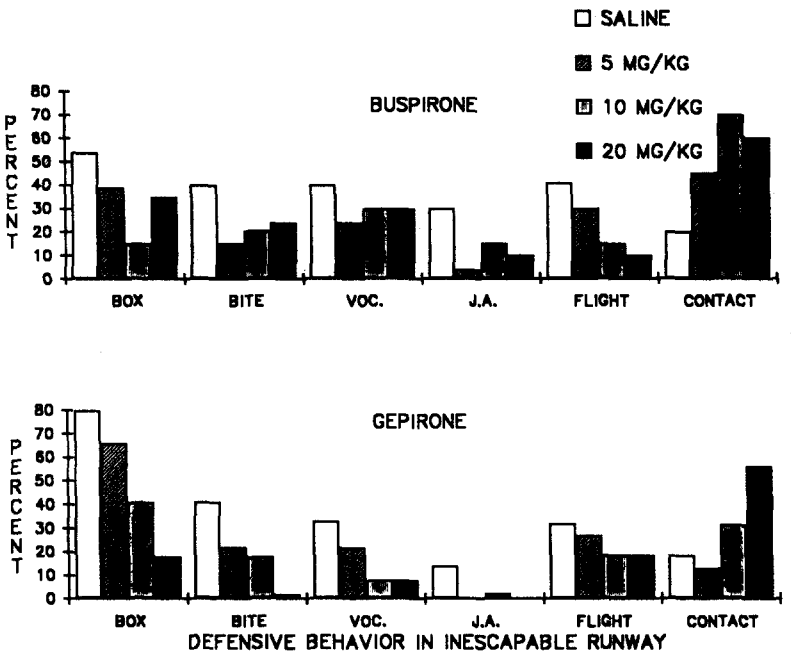


FIG. 2. Percentage of subjects showing boxing, biting, defensive threat vocalization, jump attacks and flight and passive contact to an approaching experimenter in the straight alley for rats under varying doses (0, 5, 10, or 20 milligrams per kilogram) of buspirone and gepirone.

For gepirone, the dose/distance interaction was reliable, $F(12,216)=2.94$, $p<0.01$, which appeared to reflect a relatively specific reduction in freezing for subjects under the higher (10 and 20 mg/kg) doses of gepirone at short experimenter-subject distances. At the 0.5 m experimenter-subject distance, 10 mg/kg gepirone reliably reduced freezing, $t(54)=2.77$, $p<0.05$.

The typical reactions seen when an experimenter closely approaches a wild rat subject in the alley include flight, various aspects of defensive threat and attack, and, more rarely, passive contact. The defensive reactions of the wild rat subjects under different doses of buspirone and gepirone are presented in Fig. 2. Buspirone reduced boxing at 10 mg/kg, $\chi^2(1)=6.13$, $p<0.01$, and 20 mg/kg, $\chi^2(1)=4.9$, $p<0.025$; biting at 5 mg/kg, $\chi^2(1)=3.2$, $p<0.05$; jump attack at 5 mg/kg, $\chi^2(1)=3.2$, $p<0.05$; and flight at 20 mg/kg, $\chi^2(1)=4.17$, $p<0.025$ levels; and increased the number of passive contacts at 10 mg/kg, $\chi^2(1)=8.1$, $p<0.01$, and 20 mg/kg, $\chi^2(1)=7.11$, $p<0.01$, levels. Buspirone did not affect defensive threat vocalization.

Gepirone reliably reduced boxing at both the 10 and 20 mg/kg dose levels, $\chi^2(1)=6.13$ and 4.0, $p<0.02$ and $p<0.05$, respectively. Gepirone also reduced biting at the 20 mg/kg dose level, $\chi^2(1)=8.53$, $p<0.01$. Reductions in jump attacks with gepirone approached, but failed to reach, an acceptable level of statistical significance at the 5 and 20 mg/kg levels [$\chi^2(1)=3.24$ in either case, $0.05<p<0.10$]. The number of passive contacts was increased at the highest gepirone level, 20 mg/kg, $\chi^2(1)=5.23$, $p<0.05$. Defensive threat vocalizations were not changed.

*Dorsal Contact*

Table 1 also presents the results of the flinch/jump ratings to dorsal contact. For buspirone there was a significant dose effect on dorsal contact flinch/jump scores, $F(3,54)=3.46$, $p<0.05$. Subsequent comparisons indicated that flinch/jump reactions to dorsal contact were reliably decreased at both the 10 and the 20 mg/kg dose levels, $t(54)=2.19$ and 2.80, $p<0.05$ and $p<0.01$, respectively. The gepirone effect on flinch/jump ratings to dorsal contact was also reliable, $F(3,54)=2.95$, $p<0.05$. Subsequent analyses indicated that these ratings were again reliably decreased at both the 10 and the 20 mg/kg dose levels, $t(54)=2.37$, $p<0.05$ and 3.16, $p<0.01$, respectively.

Defensive threat vocalization to dorsal contact (also given in Table 1) was significantly reduced under the highest (20 mg/kg) buspirone level, Wilcoxon $T(N=11)=-9$, $p<0.05$: No significant defensive threat differences were found for the other buspirone doses, nor at any gepirone level.

*Vibrissae Stimulation*

Figure 3 gives the mean frequency of defensive reactions to vibrissae stimulation for the two compounds over the 4 vibrissae-stimulation trials. Wilcoxon matched-pairs tests comparing saline controls and each buspirone dose failed to show statistically significant differences for bites, defensive threat vocalization, and jump attacks. However, boxing was reliably reduced under 20 mg/kg Wilcoxon $T(8)=-1$, $p>0.02$ buspirone. Similar comparisons for gepirone showed significant reductions in vocalization: 5 mg/kg, Wilcoxon $T(9)=6$, $p<0.05$; 10 mg/kg, Wilcoxon $T(7)=0$, $p<0.02$; and 20 mg/kg, Wilcoxon $T(11)=0$, $p<0.01$. Boxing was also reduced at 5 mg/kg, Wilcoxon $T(8)=-1$, $p<0.02$; and 10 mg/kg, Wilcoxon $T(10)=8$, $p<0.01$; but not at 20 mg/kg Wilcoxon $T(7)=4$, $p>0.05$ gepirone. Biting and jump attacks showed

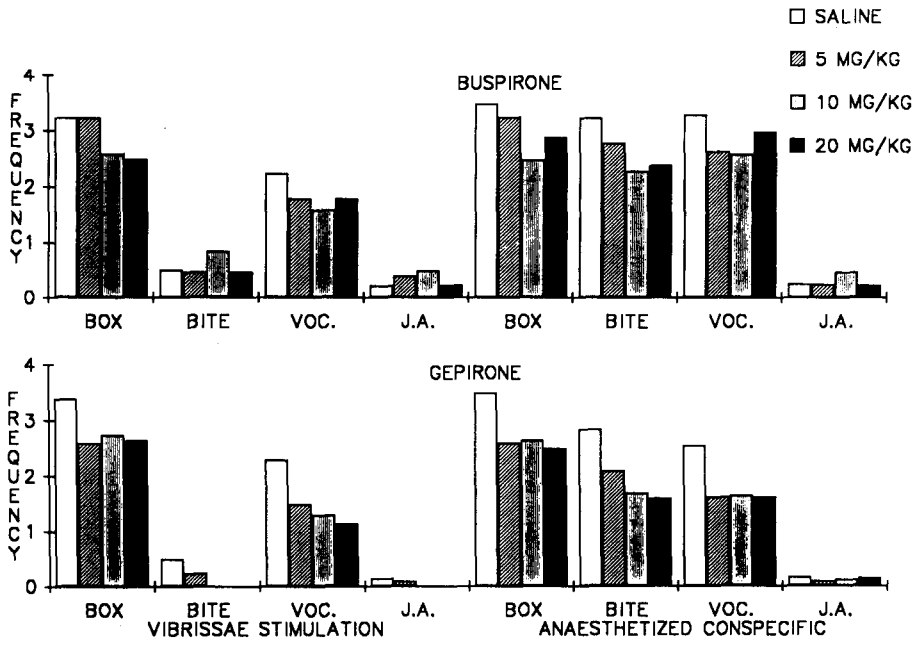


FIG. 3. Mean frequency of boxing, biting, defensive threat vocalization and jump attacks to brush stimulation of the vibrissae, and, to a deeply anesthetized conspecific for subjects under varying doses (0, 5, 10, or 20 milligrams per kilogram) of buspirone and gepirone.

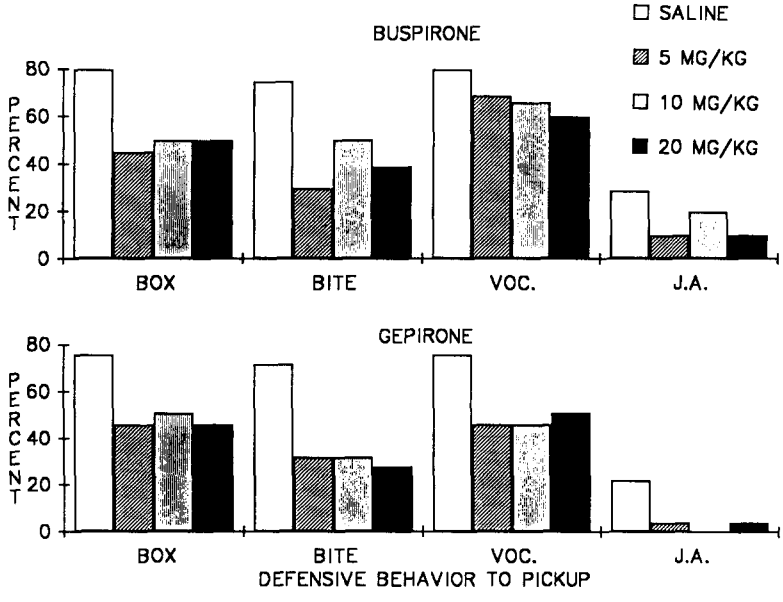


FIG. 4. Percentage of subjects showing boxing, biting, defensive threat vocalization and jump attacks to an attempted pickup by the experimenter, for subjects under varying doses (0, 5, 10, or 20 milligrams per kilogram) of buspirone and gepirone.

no statistically significant differences with gepirone, though they both tended to decline under all doses.

*Anesthetized Conspecific*

Figure 3 also provides defensive reactions to the anesthetized conspecific. Increasing doses of buspirone tended to decrease defensive threat and attack, with a reliable reduction in boxing at 10 mg/kg, Wilcoxon $T(9)=-1$, $p<0.01$, and reliable reductions in biting at 10 and 20 mg/kg levels, Wilcoxon $T(9)=-1$, $p<0.01$ and $T(7)=-1$, $p<0.05$,

respectively. Although defensive threat vocalization showed the same apparent trend toward reduction with buspirone this effect did not reach significance. Jump attacks appeared to be stable over the various levels of buspirone.

Gepirone produced dramatic reductions in boxing, biting, and defensive threat vocalization to the anesthetized conspecific, especially at higher doses. Boxing was reliably reduced with 10 mg/kg Wilcoxon $T(8)=-1$, $p<0.02$ and 20 mg/kg Wilcoxon $T(8)=0$, $p<0.01$ gepirone; biting was reliably reduced with 10 mg/kg Wilcoxon $T(8)=-1$, $p<0.02$ and 20 mg/kg Wilcoxon $T(10)=0$, $p<0.01$ gepirone; and defensive threat vocalization was reliably reduced with 5 mg/kg Wilcoxon $T(11)=-8$, $p<0.05$, 10 mg/kg Wilcoxon $T(12)=12$, $p<0.05$ and 20 mg/kg Wilcoxon $T(9)=-4$, $p<0.05$ gepirone. Like buspirone, gepirone at the levels given had no effect on jump attacks.

*Reaction to Attempted Pickup*

Figure 4 presents defensive reactions for both drugs. McNemar tests indicated that buspirone reduced boxing to an attempted pickup of the subject, at all levels given: 5 mg/kg, $\chi^2(1)=4.0$, $p<0.025$; 10 mg/kg, $\chi^2(1)=4.16$, $p<0.05$; 20 mg/kg, $\chi^2(1)=3.12$, $p<0.05$. Buspirone also reduced biting to attempted pickup at the 5 mg/kg, $\chi^2(1)=4.00$, $p<0.02$, 10 mg/kg $\chi^2(1)=4.16$, $p<0.025$, and 20 mg/kg, $\chi^2(1)=5,14$, $p<0.025$, levels. Buspirone did not affect defensive threat vocalizations or jump attacks.

Gepirone also reduced boxing to an attempted pickup of the subject, but at the highest dose level only; 20 mg/kg, $\chi^2(1)=3.12$, $p<0.05$. Gepirone reduced biting to attempted pickup at all levels: 5 mg/kg, $\chi^2(1)=5.14$, $p<0.05$; 10 mg/kg, $\chi^2(1)=6.12$, $p<0.01$; and 20 mg/kg, $\chi^2(1)=7.11$, $p<0.005$, dose levels. Defensive threat vocalizations declined under 10 mg/kg gepirone, $\chi^2(1)=3.12$, $p<0.05$.

The experimenter's ratings of defensiveness to attempted pickup are presented in Table 1. ANOVA indicated that gepirone reduced rated defensiveness to attempted pickup, $F(3,54)=7.10$, $p<0.01$, with the buspirone effect just failing to reach an acceptable level of significance, $F(3,54)=2.66$, $0.10<p>0.05$. Subsequent pair-wise comparisons between saline and each gepirone dose level indicated significant differences at 5 mg/kg, $t(54)=2.37$, $p<0.05$; 10 mg/kg, $t(54)=3.42$, $p<0.01$; and 20 mg/kg, $t(54)=4.11$, $p<0.001$, levels.

## DISCUSSION

Recent advances in 5HT receptor pharmacology have led to renewed interest in the hypothesis, initially forwarded by Stein *et al.* (62), that serotonin may play a key role in mechanisms of anxiety. Of particular significance is the apparent anxiolytic efficacy of several compounds which have agonist/partial agonist activity at the $5HT_{1A}$ site (16, 50, 70). These compounds include the pyrimidinyl piperazine derivatives, buspirone, gepirone and ipsapirone, which share in common a high affinity for $5HT_{1A}$sites [e.g., (19, 29, 71)]. Since all of these drugs potently inhibit the firing of dorsal raphe neurons (10, 61, 73), it has been proposed that their anxiolytic efficacy results from reduced serotonergic impulse flow and that benzodiazepines may also share this final common pathway (70).

Despite the attractiveness of the above hypothesis, $5HT_{1A}$ receptor agonists do not exert anxiolytic effects in all animal models of anxiety [e.g., (49)]. This finding suggests either that the role of these sites in anxiety is more complex than previously thought or that there may be a mechanism of anxiety reduction to which certain animal tests are insensitive (25). In this context, it has been argued that defensive behaviour is of vital importance to our understanding of the mechanisms of fear and anxiety (3, 6, 8, 24, 39). It is therefore relevant to note that $5HT_{1A}$ agonists have been reported to inhibit aspects of attack and defense in a range of species (42, 44, 46, 64, 69, 70). The results of the present study substantially extend these observations in that they provide a comprehensive analysis of $5HT_{1A}$ anxiolytic effects on the well-defined, precisely elicited and complete defensive repertoire of wild rats.

In particular, these results show that buspirone and gepirone produce complex, but relative similar, patterns of behavioural change in wild rat subjects and, as will be discussed below, that these changes differ from those seen with other anxiolytics such as ethanol (7) and the benzodiazepines (9). Differences observed between the $5HT_{1A}$ compounds may most parsimoniously be attributed to their differential selectivity for 5HT mechanisms since buspirone, unlike gepirone, is known to have dopamine antagonist properties (44).

Neither buspirone nor gepirone interfered with spontaneous locomotor activity during the 5-minute pretest in the oval runway; indeed, gepirone significantly increased the number of line crossings in this period. For buspirone, these findings are consistent with the reports that this compound has no significant muscle relaxant/sedative effects up to 400 mg/kg (65) and is without effect (at 4 mg/kg) on open-field behaviour in rats (38). However, in accordance with its greater selectivity for $5HT_{1A}$ receptors (44), gepirone is known to induce the '5HT-syndrome' (hindlimb abduction, flattened body, Straub tail, forepaw treading, head-weaving, tremor) in male laboratory rats with an ED50 of 17.1 mg/kg (19). We observed no evidence of such effects even at the highest dose tested (20 mg/kg), suggesting either reduced sensitivity of wild rats to this syndrome or, more probably, their faster metabolic rate. A similar explanation has recently been forwarded concerning the apparent absence of the 5HT syndrome in mice treated with gepirone (44). This absence of a performance impairment in the pretest argues strongly against a sedative/muscle relaxant interpretation of effects observed with these compounds on specific tests of defensive responding.

In the circular runway test, neither buspirone nor gepirone impaired performance (avoidance distance, flight speed) although it is interesting to note that buspirone (5 and 20 mg/kg) increased the distance that subjects fled (flight distance) in response to an approaching experimenter. These data indicate that flight-related behaviours remain largely intact under $5HT_{1A}$ anxiolytics and confirm the pretest finding of no impairment in motor behavior per se. Against this background, the generally marked inhibitory effects of buspirone and gepirone on other aspects of the defensive repertoire assume particular significance.

In the inescapable runway procedure, both compounds significantly increased the number of subjects that could be approached by the experimenter to the point of actual physical contact, while gepirone additionally reduced freezing at short (0.5 m) experimenter-subject distances. These findings would appear to imply a 'taming' action of $5HT_{1A}$ agonists, a conclusion supported by the reduced ratings of defensiveness in the attempted pickup procedure. However, it should perhaps be stressed that this taming effect is by no means as pronounced as that produced in wild rats by le-

sions of the basal ganglia (4), mesencephalic central gray (5), or amygdaloid complex (37).

The most consistent effect observed with both compounds in the present test battery was a reduction in defensive threat and attack behaviours towards proximal stimuli. These reactions were assessed in four situations; approach by experimenter in the inescapable runway, stimulation of the vibrissae, an anesthetized conspecific and attempted pickup. Although there was some variability in the specific elements reduced on particular tasks, the overall pattern in these 'terminal' defense elements was remarkably constant. Furthermore, the effects observed with gepirone were clearly more dose-dependent than those seen with buspirone, perhaps reflecting the previously noted difference in the pharmacological specificity of the two compounds. Nevertheless, over the four test situations, both buspirone and gepirone reliably reduced boxing in all four tasks and biting in three of four tasks. Vocalizations were reduced in only one task by buspirone but in two tasks by gepirone. Although both drugs reduced jump attacks in one task only, gepirone tended to produce a pattern of nonsignificant reductions in one other task. It might be noted that the level of jump attacks obtained to some of the stimuli used here, notably vibrissae stimulation and the anesthetized conspecific, was so low that reliable reductions may be very difficult to obtain on these tests. The tests are included because they provide a range of initial defensive threat/attack behaviours such that bidirectional changes are possible: Ethanol, at intermediate doses, increases jump attack on some of these tests (7).

This pattern of reduced defensive threat and attack agrees with the report that buspirone decreases defensive responding in timid mice (64), and in the absence of detailed ethopharmacological data, may also be consistent with the finding that buspirone and gepirone inhibit isolation-induced fighting in this species (42,44). Although not currently tested, it is pertinent to note that the related compound ipsapirone reduced footshock-induced defensive fighting in mice and fear-related behaviours in defeated male rats (70).

Flinch/jump reactions to dorsal contact (a light tap) were reliably inhibited by both compounds and, since the magnitude of such reactions has been interpreted as indicative of readiness to make the high energy 'terminal' defensive reactions (7), this finding is in accord with the described reductions in defensive threat and attack behaviours. Interestingly, however, buspirone and gepirone have previously been found to enhance acoustic startle reactions in laboratory rats over the same dose range as currently used (19), suggesting differences in the ecological significance (proximity of threat?) of sudden, novel acoustic versus tactile stimulation. In this context, it may be pertinent to note that buspirone has been reported to decrease 'aggressive' reactivity of rhesus monkeys in the pole-prodding test (69).

In overview, buspirone and gepirone reduced many aspects of defensive responding in wild rat subjects without producing any signs of motor impairment. While flight remained largely intact under both drugs, freezing and particularly defensive threat and attacks were inhibited. This pattern, together with the increased number of passive contacts and reduced reactivity to handling, indicates that $5HT_{1A}$ anxiolytics exert a significant taming effect in feral rats. Importantly, this profile differs from the changes in defensiveness produced by benzodiazepine anxiolytics in the same test procedure (9). Although benzodiazepines (chlordiazepoxide, diazepam, midazolam) also reduced defensive threat and attack behaviours, the pattern of reductions was quite different to that seen with $5HT_{1A}$ anxiolytics. Indeed, the only behaviour on which the two groups of compounds had a similar effect was jump attack, where neither class of anxiolytic produced a consistent change. Instead, benzodiazepines consistently inhibited defensive threat vocalizations, whereas only very limited effects were observed with buspirone and gepirone. On the other hand, the latter compounds fairly consistently reduced boxing and biting, whereas the benzodiazepines only had marginal effects on these measures. Furthermore, unlike the benzodiazepines, buspirone and gepirone decreased freezing in the inescapable runway and increased the percentage of subjects that could actually be approached to the point of physical contact. Finally, even at low doses, benzodiazepines reduced locomotor activity during the pretest while the $5HT_{1A}$ compounds generally exerted the opposite effect.

Ethanol, also widely regarded as an anxiolytic, is another compound which has been assessed on wild rats in the present test battery (7). However, while also providing evidence for anxiety or fear reduction, the ethanol pattern is even more different from the $5HT_{1A}$ profile than that of the benzodiazepines. Thus, while not affecting line crossings in the pretest, ethanol significantly reduced several aspects of flight but, at low doses, actually potentiated jump attack and vocalization. This latter finding, which is particularly interesting in terms of a hypothesis that ethanol promotes 'aggressiveness' also suggests that decreases in some aspects of fear or anxiety may 'release' defensive threat and attack behaviours.

In conclusion, it would seem that the defensive test battery, unlike the more traditional 'single-point determination' animal tests of fear and anxiety provides behavioural measures capable of differentiating between various classes of anxiolytics. As such, these results from wild rats indicate that fear/anxiety comprises an extremely complex behavioural and functional system, and that analysis of this system is necessary in order to conceptualize different profiles of anxiolytic action. This approach may help to rectify some of the shortcomings of current animal models of anxiety as recently expressed by File (25).

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