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Effects of Serotonergic Agents on Isolation-Induced Aggression

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WHITE, S. M., R. F. KUCHARIK AND J. A. MOYER. *Effects of serotonergic agents on isolation-induced aggression.* PHARMACOL BIOCHEM BEHAV **39**(3) 729–736, 1991.—A series of serotonergic agents were assessed for their ability to antagonize isolation-induced aggression and their activity to disrupt performance in the rotorod motor coordination test. All compounds with 5-HT_{1A} activity [buspirone, gepirone, ipsapirone, tandospirone (SM-3997), 8-OH-DPAT, Wy-48,723, BMY-7378, Wy-47,846] reduced aggression at doses below those which produced debilitation in the rotorod motor coordination test. In addition, the 5-HT_3 antagonist zacopride failed to attenuate aggression or produce debilitation at any of the doses tested; however, the 5-HT_2 antagonist ritanserin inhibited aggressive behavior at a high dose which was not debilitating. Benzodiazepines (chlordiazepoxide, diazepam and lorazepam), and antidepressant (desipramine) and an antipsychotic (haloperidol) reduced aggressive behavior only at debilitating doses. Activity at the 5-HT_{1A} receptor, and possibly nonsedative anxiolytic activity, appears to be related to antagonism of isolation-induced aggression.

Aggression (isolation-induced) 5-HT Buspirone Gepirone Ipsapirone Tandospirone (SM-3997) Wy-47,846 BMY-7378 8-OH-DPAT Wy-48,723 Zacopride Ritanserin

THE inhibition of isolation-induced aggressive behavior in male mice has been proposed as an animal model for assessing anxiolytic activity (8,26). The novel nonbenzodiazepine anxiolytics buspirone, gepirone, and ipsapirone have been shown to inhibit isolation-induced aggression at nonsedating doses (26,27), although their effects in classical anxiolytic screens are equivocal (5). It is thought that the anxiolytic and antiaggressive actions of these compounds are mediated through the serotonin$_{1A}$ (5-HT_{1A}) receptor (11, 27, 29). These compounds exhibit high affinity for the 5-HT_{1A} receptor and display partial agonist activity in the serotonin syndrome test (24, 36, 38), which is an in vivo test for postsynaptic 5-HT_{1A} receptor activity in rats (40). 8-OH-DPAT, a selective 5-HT_{1A} agonist in the serotonin syndrome test (38), has also been shown to inhibit isolation-induced aggression at nondebilitating doses (26). In addition to producing effects at the postsynaptic 5-HT_{1A} receptor, 8-OH-DPAT, buspirone, gepirone and ipsapirone are reported to be agonists at the presynaptic 5-HT_{1A} receptor, which when stimulated inhibits the firing of 5-HT neurons in the dorsal raphe (26, 39, 43). It has been postulated (31) that the antiaggressive effect of these compounds is produced by their agonist activity at the presynaptic 5-HT_{1A} receptor.

To further examine the antiaggressive effects of serotonergic agents, the ability of a number of compounds to antagonize isolation-induced aggression was determined. These compounds included those with varying activity at the 5-HT_{1A} postsynaptic receptor, the 5-HT_3 antagonist zacopride and the 5-HT_2 antagonist ritanserin. In addition, to assess the selectivity of the test, benzodiazepines, an antidepressant and an antipsychotic were examined.

METHOD

Animals

Male CF-1 mice (16–20 g) were obtained from Charles River Breeding Laboratories, Kingston, NY. Animals were allowed to acclimate for at least 3 days after their arrival. Food and water were available ad lib. The animal colony was maintained at 22°C with a 12-h light/dark cycle with lights on at 6 a.m.

Behavioral Testing

Antagonism of isolation-induced aggression tests were conducted according to a modification of the methods of (8) and (26). The mice were individually housed or group housed (6/cage) in self-cleaning cages (25 × 18 × 18 cm) for a period of 3 weeks. After the 3 week period of isolation, the individually housed (isolated) mice were trained to attack a group-housed (intruder) mouse. The cage containing the isolated mouse was removed from the cage rack and placed on a bench top covered with absorbent paper. After a 3 minute acclimation period, the isolated mouse was "bumped" into several times with the intruder mouse which was then released into the isolated mouse's home cage. After 3 minutes of exposure, the intruder mouse was removed and returned to its own cage. The isolated mice were trained on 5 successive days prior to their experimental use. The trained isolated mice were prescreened for aggressive behavior one day before the experiment. As in the training session, the intruder mouse was introduced into the isolated mouse's home cage for 3 minutes. The total fighting time (TFT) in seconds was

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recorded during the 3 minute test. Isolated mice fighting for more than 20 seconds were used for drug testing on the following day. On test day, test compound or vehicle was administered IP 60 minutes prior to aggression testing (N = 5–25/dose). As in prescreening, the cage containing the isolated mouse was removed from the cage rack and placed on a bench top covered with absorbent paper. After a 3 minute acclimation period, the isolated mouse was "bumped" into several times with the intruder mouse which was then immediately released into the isolated mouse's home cage. The TFT was recorded during the 3 minute test. Due to the lack of homogeneity of variance in the raw data, log-transformation was performed to normalize the variance prior to analysis of the data by one-way analysis of variance with subsequent Dunnett's comparison to control tests ($p \leq 0.05$). A minimally effective dose (MED) was determined to be the lowest dose which produced a mean TFT significantly less than that of the control group. For the purposes of graphical representation, the data were expressed as mean percent of control.

In order to differentiate between specific antiaggressive effects and possible animal debilitation, rotorod motor coordination tests were conducted according to a modification of the procedures of (10) and (29). Group-housed mice (20–25 g) were prescreened for their stability on a rotating rod (rotorod; 20 rpm) with 6 individual runs (Treadmill for mice, Ugo Basile, Varese, Italy). Only mice which could remain on the rotorod for 60 seconds in the last of 3 trials were used in subsequent testing. Test compound or vehicle was administered IP 60 minutes prior to testing (N = 5–20/dose). The mice were placed on the rotorod, and the amount of time spent on the rotorod (maximum of 60 seconds) was recorded. One-way ANOVA with subsequent Dunnett's comparison to control tests ($p \leq 0.05$) was performed on the data. A MED was determined to be the lowest dose which produced an average time spent on the rotorod that was significantly less than that of the control group.

Drugs

Wy-47,846 (3a,4,4a,6a,7,7a-hexahydro-2-[4-[4[(2-pyrimidinyl)-1-piperazinyl]butyl]-4,7-etheno-1*H*-cyclobut [*f*] isoindole-1,3 (2*H*)-dione, hydrochloride) was synthesized by Dr. Magid Abou-Gharbia (Wyeth-Ayerst Laboratories, Inc., Philadelphia, PA). Wy-48,723 (decahydro-3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl]-1,5 -methano-6,7,9-metheno-2*H*-pentaleno-[1,2-*d*]azepine-2,4(3*H*)-dione,dihydrochloride) was synthesized by Dr. Gary Stack (Wyeth-Ayerst Laboratories, Inc., Philadelphia, PA). (±)8-hydroxydipropylaminotetralin hydrogen bromide (8-OH-DPAT) was obtained from Research Biochemicals, Inc. (Natick, MA); buspirone HCl from Bristol-Myers Squibb Company (Wallingford, CT); haloperidol (free base) from McNeil Pharmaceuticals (Fort Washington, PA); chlordiazepoxide HCl from Sigma (St. Louis, MO); diazepam (free base) from Hoffmann-La Roche (Nutley, NJ); lorazepam (free base) from Wyeth-Ayerst Laboratories, Inc. (Philadelphia, PA); and desipramine HCl from Merrell Dow (Cincinnati, OH). Tandospirone (SM-3997) (hexahydro-2-[4-[4[(2-pyrimidinyl)-1-piperazinyl] butyl]-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione, citrate) was obtained from Sumitomo Chemical Co. (Osaka, Japan). Zacopride HCl was obtained from A.H. Robins (Richmond, VA), while ritanserin (free base) was obtained from Janssen Research Foundation (Beerse, Belgium). Gepirone HCl, ipsapirone HCl and BMY-7378 (8-[2-[4-[2-methoxyphenyl]-1-piperazinyl]ethyl]-8-azaspiro[4,5]decane-7,9-dione dihydrochloride) were synthesized at Wyeth-Ayerst Laboratories, Inc. (Philadelphia, PA). All drugs were suspended or solubilized in 0.25% Tween 80® except for zacopride HCl which was dissolved in distilled water for the rotorod motor coordination test. Drugs were administered in a volume of 10 ml/kg body weight for mice. Doses were calculated based on the weight of the free base.

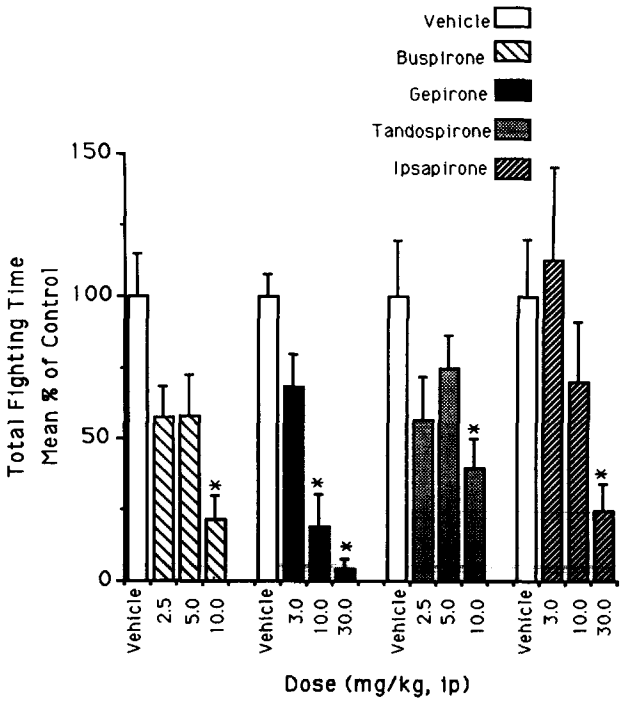

FIG. 1. Mice were treated with vehicle or test compound 60 minutes prior to aggression testing. Total Fighting Time (TFT) was measured for the 3 minute test period. Data are expressed as mean percent of control ± SE. N = 6–11/dose. *Significantly different from respective vehicle by one-way analysis of variance with subsequent Dunnett's comparison to control tests ($p \leq 0.05$) on the log-transformed TFT.

RESULTS

The nonbenzodiazepine anxiolytics buspirone, gepirone, ipsapirone, and tandospirone significantly reduced TFT at doses which did not decrease the mean time spent on the rotorod. Buspirone, gepirone, and tandospirone had MEDs for reducing aggression (TFT) of 10 mg/kg IP, $F(3,36) = 5.33$, $p < 0.01$; $F(3,20) = 22.03$, $p < 0.001$ and $F(3,38) = 7.36$, $p < 0.001$, respectively, while ipsapirone antagonized aggression at 30 mg/kg IP, $F(3,36) = 3.55$, $p < 0.05$ (Fig. 1). The MEDs for disruption of rotorod motor coordination following treatment with these postsynaptic 5-HT_{1A} partial agonists (buspirone, gepirone, ipsapirone and tandospirone) were equal to or greater than 60 mg/kg IP, $F(3,36) = 1.40$, $p = 0.26$; $F(3,36) = 11.08$, $p < 0.001$; $F(4,25) = 0.70$, $p = 0.60$; and $F(4,25) = 0.80$, $p = 0.54$, respectively (Table 1).

The postsynaptic 5-HT_{1A} agonists 8-OH-DPAT and Wy-48,723 potently reduced TFT at 0.6 mg/kg IP, $F(4,50) = 12.97$, $p < 0.001$, and 0.3 mg/kg IP, $F(6,82) = 6.62$, $p < 0.001$, respectively (Fig. 2). 8-OH-DPAT did not decrease the mean time spent on the rotorod, up to 30 mg/kg IP, $F(4,25) = 1.32$, $p = 0.27$. However, Wy-48,723 significantly reduced the mean time spent on the rotorod at 30 and 100 mg/kg IP, $F(4,25) = 8.90$, $p < 0.001$ (Table 2).

The postsynaptic 5-HT_{1A} antagonists BMY-7378 and Wy-47,846 both decreased TFT at 3.0 mg/kg IP, $F(3,40) = 9.71$,

TABLE 1

ACTIVITY OF 5-HT$_{1A}$ PARTIAL AGONISTS IN ROTOROD MOTOR COORDINATION TESTS

Compound	Dose (mg/kg IP)	Mean Time Spent on Rotorod ±SE (≤60 s)	MED
Buspirone	Vehicle	56.4 ± 3.2	
	10.0	52.6 ± 4.9	
	30.0	46.5 ± 5.3	
	60.0	43.0 ± 6.4	>60.0
Gepirone	Vehicle	49.6 ± 5.5	
	10.0	47.2 ± 5.8	
	30.0	42.3 ± 4.6	
	60.0	12.5 ± 4.7*	60.0
Ipsapirone	Vehicle	59.3 ± 0.7	
	3.0	60.0 ± 0	
	10.0	53.8 ± 6.2	
	30.0	60.0 ± 0	
	100.0	53.0 ± 7.0	>100.0
Tandospirone	Vehicle	60.0 ± 0	
	3.0	57.5 ± 2.5	
	10.0	50.5 ± 6.2	
	30.0	47.2 ± 7.8	
	60.0	51.8 ± 8.2	>60.0

*Significantly different from vehicle by one-way analysis of variance with subsequent Dunnett's comparison to control tests, $p \leq 0.05$.

SE = standard error of the mean, N = 6–10/dose, MED = minimally effective dose.

TABLE 2

ACTIVITY OF 5-HT$_{1A}$ AGONISTS IN ROTOROD MOTOR COORDINATION TESTS

Compound	Dose (mg/kg IP)	Mean Time Spent on Rotorod ± SE (≤60 s)	MED
8-OH-DPAT	Vehicle	60.0 ± 0	
	0.3	60.0 ± 0	
	3.0	55.5 ± 4.5	
	10.0	57.7 ± 2.3	
	30.0	51.5 ± 4.5	>30.0
Wy-48,723	Vehicle	60.0 ± 0	
	3.0	44.0 ± 10.1	
	10.0	41.8 ± 11.5	
	30.0	9.5 ± 1.8*	
	100.0	15.3 ± 3.6*	30.0

*Significantly different from vehicle by one-way analysis of variance with subsequent Dunnett's comparison to control tests, $p \leq 0.05$.

SE = standard error of the mean, N = 6/dose, MED = minimally effective dose.

$p<0.001$ and $F(3,46)=4.86$, $p<0.01$, respectively (Fig. 3), but didn't reduce the mean time spent on the rotorod until 60 mg/kg IP, $F(4,25)=28.26$, $p<0.001$, and 100 mg/kg IP, $F(4,25)=9.88$, $p<0.001$, respectively (Table 3).

The 5-HT$_3$ antagonist zacopride did not significantly reduce TFT over a wide dose range, 0.0001 to 10 mg/kg IP, $F(5,35)=1.19$, $p=0.33$ (Fig. 4). It also did not reduce the mean time spent on the rotorod up to 10 mg/kg IP, $F(6,41)=1.40$, $p=0.24$,

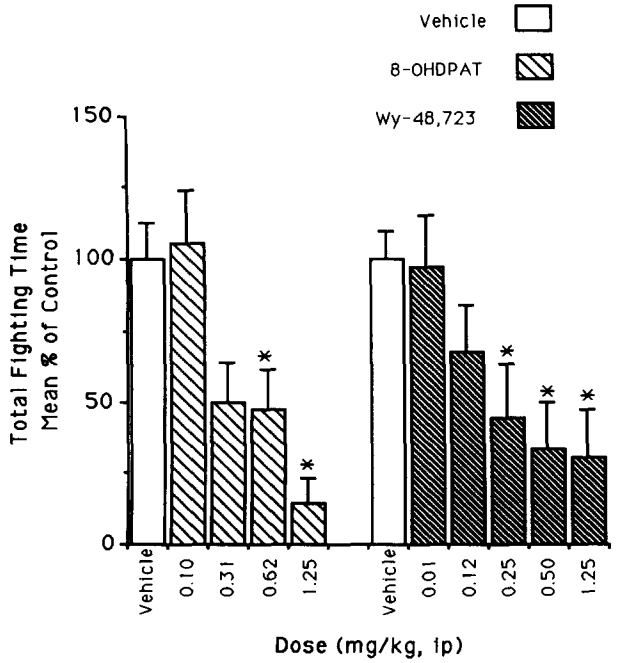

FIG. 2. Mice were treated with vehicle or test compound 60 minutes prior to aggression testing. Total Fighting Time (TFT) was measured for the 3 minute test period. Data are expressed as mean percent of control ± SE. N = 10–25/dose. *Significantly different from respective vehicle by one-way analysis of variance with subsequent Dunnett's comparison to control tests ($p \leq 0.05$) on the log-transformed TFT.

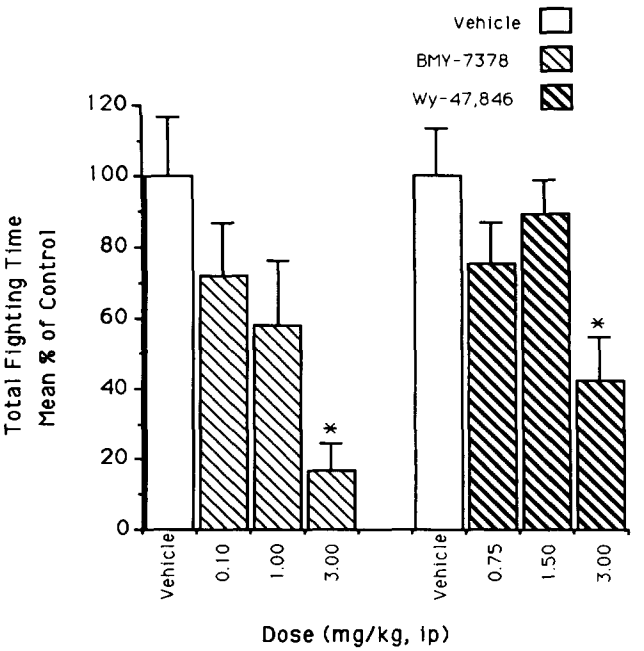

FIG. 3. Mice were treated with vehicle or test compound 60 minutes prior to aggression testing. Total Fighting Time (TFT) was measured for the 3 minute test period. Data are expressed as mean percent of control ± SE. N = 10–15/dose. *Significantly different from respective vehicle by one-way analysis of variance with subsequent Dunnett's comparison to control tests ($p \leq 0.05$) on the log-transformed TFT.

TABLE 3

ACTIVITY OF 5-HT_{1A} ANTAGONISTS IN ROTOROD MOTOR COORDINATION TESTS

Compound	Dose (mg/kg IP)	Mean Time Spent on Rotorod ± SE (≤60 s)	MED
BMY-7378	Vehicle	60.0 ± 0	
	3.0	60.0 ± 0	
	10.0	60.0 ± 0	
	30.0	60.0 ± 0	
	60.0	14.0 ± 8.7*	60.0
Wy-47,846	Vehicle	60.0 ± 0	
	3.0	55.2 ± 4.8	
	10.0	53.8 ± 6.2	
	30.0	41.2 ± 11.9	
	100.0	10.2 ± 2.1*	100.0

*Significantly different from vehicle by one-way analysis of variance with subsequent Dunnett's comparison to control tests, $p \leq 0.05$.

SE = standard error of the mean, N = 6/dose, MED = minimally effective dose.

TABLE 4

ACTIVITY OF 5-HT_2 AND 5-HT_3 ANTAGONISTS IN ROTOROD MOTOR COORDINATION TESTS

Compound	Dose (mg/kg IP)	Mean Time Spent on Rotorod ± SE (≤60 s)	MED
Zacopride	Vehicle*	56.1 ± 2.8	
	0.0001	60.0 ± 0	
	0.001	55.2 ± 4.3	
	0.01	60.0 ± 0	
	0.1	48.3 ± 7.8	
	1.0	60.0 ± 0	
	10.0	60.0 ± 0	>10.0
Ritanserin	Vehicle	60.0 ± 0	
	0.3	52.3 ± 7.7	
	1.0	57.0 ± 3.0	
	10.0	60.0 ± 0	
	30.0	52.3 ± 7.7	>30.0

*Distilled water.

SE = standard error of the mean, N = 5–6/dose, MED = minimally effective dose.

the highest dose tested (Table 4). In contrast, the 5-HT_2 antagonist ritanserin significantly decreased TFT at 10 mg/kg IP, $F(4,25) = 4.66$, $p < 0.01$ (Fig. 4), a dose that did not reduce the mean time spent on the rotorod, $F(4,24) = 0.54$, $p = 0.71$ (Table 4).

For comparison, benzodiazepines, an antidepressant, and an antipsychotic were also examined in these tests. These compounds did not significantly reduce TFT until doses at or greater than those which decreased the mean time spent on the rotorod were reached. Lorazepam produced an MED of 0.5 mg/kg IP for inhibition of isolation-induced aggression and for disruption of rotorod performance (debilitation), $F(4,57) = 5.22$, $p < 0.01$ and $F(3,36) = 10.14$, $p < 0.001$, respectively (Fig. 5, Table 5). Diazepam did not antagonize aggression until 10 mg/kg IP, $F(4,50) = 5.13$, $p < 0.01$, but produced debilitation at 2.5 mg/kg IP, $F(3,36) = 8.45$, $p < 0.001$ (Fig. 5, Table 5). Chlordiazepoxide produced MEDs of 20, $F(4,44) = 6.46$, $p < 0.01$, and 5.0 mg/kg IP, $F(4,55) = 14.48$, $p < 0.001$, for aggression and debilitation, respectively (Fig. 5, Table 5). Desipramine, a tricyclic antidepressant, antagonized aggression, $F(2,39) = 13.30$, $p < 0.001$, and produced debilitation at 40 mg/kg IP, $F(3,36) = 5.43$, $p < 0.01$ (Fig. 6, Table 6). The antipsychotic haloperidol inhibited aggression at 2 mg/kg IP, $F(3,36) = 5.97$, $p < 0.01$, but produced debilitation at 1 mg/kg IP, $F(3,20) = 5.50$, $p < 0.01$ (Fig. 6, Table 6).

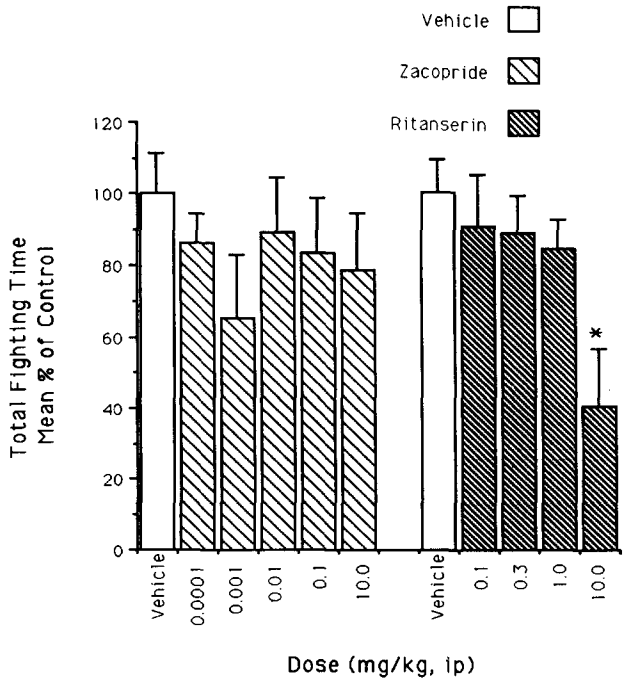

FIG. 4. Mice were treated with vehicle or test compound 60 minutes prior to aggression testing. Total Fighting Time (TFT) was measured for the 3 minute test period. Data are expressed as mean percent of control ± SE. N = 5–12/dose. *Significantly different from respective vehicle by one-way analysis of variance with subsequent Dunnett's comparison to control tests ($p \leq 0.05$) on the log-transformed TFT.

DISCUSSION

In this study, a number of serotonergic compounds were examined for their ability to antagonize isolation-induced aggression in male mice. It has long been recognized that serotonin plays an important role in isolation-induced aggression; however, previous studies attempting to characterize that role have produced conflicting results. There have been a number of reports of decreased 5-HT turnover in aggressive isolated male mice (22, 41, 42) which may be due to decreased 5-HT synthesis (44). In addition, compounds which increase 5-HT availability (5-hydroxytryptophan, zimelidine and parachloroamphetamine) antagonize isolation-induced aggression (21,34). These reports suggest that aggressive isolated male mice have decreased levels of 5-HT and treatments increasing 5-HT levels would decrease aggressiveness. In contrast, there are studies that suggest that manipulations which decrease 5-HT levels produce a decrease in aggression. Lesions of the raphe nuclei in isolation-induced aggressive mice and inhibition of 5-HT synthesis with parachlorophenylalanine have lead to a reduction in aggressive behavior (23,31). In addition, serotonin receptor antagonists (cinanserin, cyproheptadine, methiothepin, methysergide, mianserin, pizoty-

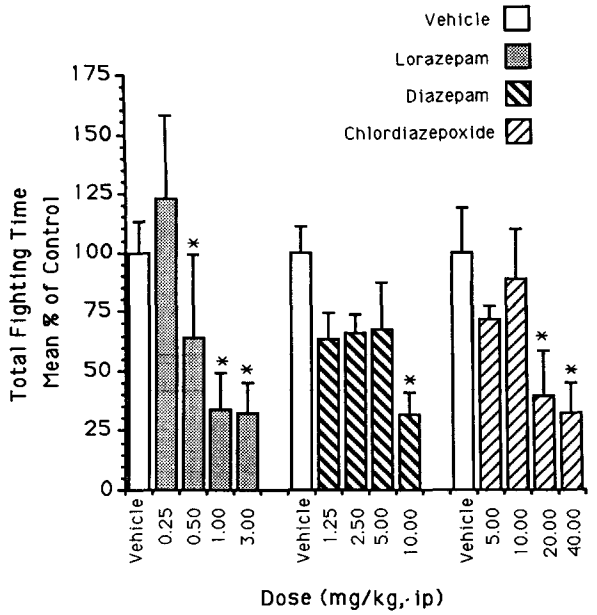

FIG. 5. Mice were treated with vehicle or test compound 60 minutes prior to aggression testing. Total Fighting Time (TFT) was measured for the 3 minute test period. Data are expressed as mean percent of control ± SE. N = 10–14/dose. *Significantly different from respective vehicle by one-way analysis of variance with subsequent Dunnett's comparison to control tests ($p \leq 0.05$) on the log-transformed TFT.

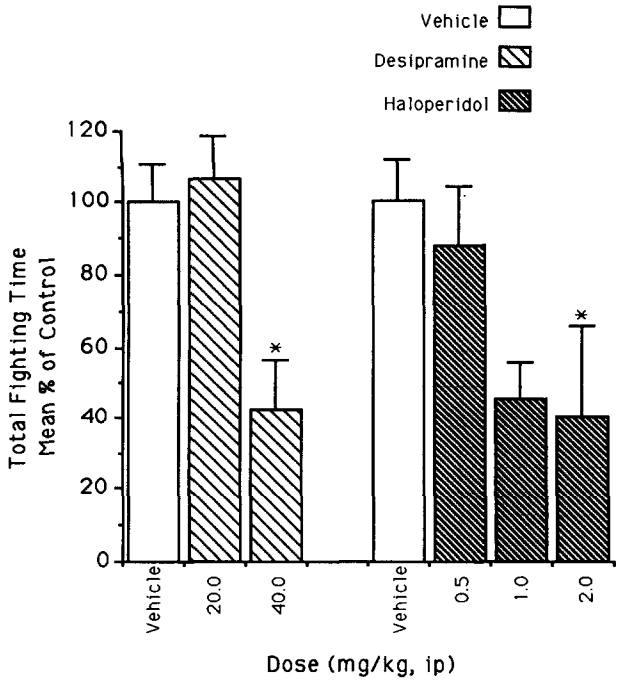

FIG. 6. Mice were treated with vehicle or test compound 60 minutes prior to aggression testing. Total Fighting Time (TFT) was measured for the 3 minute test period. Data are expressed as mean percent of control ± SE. N = 6–18/dose. *Significantly different from respective vehicle by one-way analysis of variance with subsequent Dunnett's comparison to control tests ($p \leq 0.05$) on the log-transformed TFT.

line and xylamidine) have been found to antagonize isolation-induced aggression (31).

With the identification of specific 5-HT receptor subtypes, there have been attempts to characterize the role of 5-HT in aggression through the use of ligands for specific receptor subtypes. In the current experiments, 5-HT_{1A} active compounds (buspirone, gepirone, ipsapirone, tandospirone, 8-OH-DPAT, Wy-48,723, BMY-7378, and Wy-47,846) antagonized isolation-induced aggression in mice at doses which did not produce debilitation in rotorod motor coordination tests (see Table 7). These compounds have been characterized as 5-HT_{1A} agonists, partial agonists and antagonists based on their activity in the serotonin syndrome test in rats; however, in mice their activity may be different. It is likely that only the presynaptic effects of 5-HT_{1A} active compounds are expressed in mice (16). The serotonin syndrome is not observed in mice (9), but 8-OH-DPAT has been shown to inhibit 5-HT synthesis (16) and to produce hypothermia, a presynaptic effect in mice (17). These results are consistent with suggestions that the antiaggressive effects of these compounds may be mediated by their action at presynaptic 5-HT_{1A} receptors (27).

In addition to the possibility that 5-HT_{1A} active compounds may have different effects in mice and rats, their activity in rats is dependent upon the procedure in which they are evaluated. In the rat serotonin syndrome test, an in vivo test for postsynaptic 5-HT_{1A} receptor activity (40), buspirone, gepirone, ipsapirone and tandospirone have been characterized as postsynaptic partial agonists (20, 24, 36, 38). 8-OH-DPAT and Wy-48,723 act as full postsynaptic agonists (24,38), while BMY-7378 and Wy-47,846 appear to be postsynaptic antagonists (24,25). In contrast to their differing activity at the postsynaptic 5-HT_{1A} receptor in serotonin syndrome tests, these compounds demonstrate some agonist activity at the presynaptic 5-HT_{1A} receptor because they (buspirone, gepirone, ipsapirone, tandospirone, 8-OH-DPAT, Wy-48,723, BMY-7378 and Wy-47,846) have all been reported to inhibit dorsal raphe 5-HT neuronal firing in the rat (1, 4, 15, 19, 26, 39, 43). Since these compounds behave differently at

TABLE 5

ACTIVITY OF BENZODIAZEPINES IN ROTOROD MOTOR COORDINATION TESTS

Compound	Dose (mg/kg IP)	Mean Time Spent on Rotorod ± SE (≤60 s)	MED
Lorazepam	Vehicle	54.7 ± 3.5	
	0.25	40.1 ± 6.3	
	0.5	28.8 ± 5.0*	
	1.0	17.7 ± 4.6*	0.5
Diazepam	Vehicle	55.0 ± 4.8	
	0.25	60.0 ± 0	
	2.5	33.2 ± 7.1*	
	5.0	25.1 ± 7.8*	2.5
Chlordiazepoxide	Vehicle	57.4 ± 1.8	
	1.25	53.0 ± 3.9	
	2.5	46.8 ± 5.9	
	5.0	33.1 ± 7.3*	
	10.0	15.4 ± 5.3*	5.0

*Significantly different from vehicle by one-way analysis of variance with subsequent Dunnett's comparison to control tests, $p \leq 0.05$.

SE = standard error of the mean, N = 10–20/dose, MED = minimally effective dose.

TABLE 6

ACTIVITY OF DESIPRAMINE AND HALOPERIDOL IN ROTOROD MOTOR COORDINATION TESTS

Compound	Dose (mg/kg IP)	Mean Time Spent on Rotorod ± SE (≤60 s)	MED
Desipramine	Vehicle	54.4 ± 3.8	
	10.0	48.0 ± 5.7	
	20.0	45.7 ± 4.6	
	40.0	25.7 ± 6.7*	40.0
Haloperidol	Vehicle	60.0 ± 0	
	0.5	36.0 ± 10.9	
	1.0	26.8 ± 5.9*	
	2.0	20.2 ± 8.2*	1.0

*Significantly different from vehicle by one-way analysis of variance with subsequent Dunnett's comparison to control tests, $p \leq 0.05$.

SE = standard error of the mean, N = 6–10/dose, MED = minimally effective dose.

TABLE 7

SUMMARY OF DOSES FOR INHIBITING AGGRESSION AND PRODUCING DEBILITATION

Compound	Aggression MED	Rotorod MED
Buspirone	10.0	>60.0
Gepirone	10.0	60.0
Ipsapirone	30.0	>100.0
Tandospirone	10.0	>60.0
8-OH-DPAT	0.6	>30.0
Wy-48,723	0.3	30.0
BMY-7378	3.0	60.0
Wy-47,846	3.0	30.0
Zacopride	NSE	>10.0
Ritanserin	10.0	>30.0
Lorazepam	0.5	0.5
Diazepam	10.0	2.5
Chlordiazepoxide	20.0	5.0
Desipramine	40.0	40.0
Haloperidol	2.0	1.0

MED = minimally effective dose, mg/kg IP, NSE = no significant effect.

5-HT_{1A} receptors located presynaptically and postsynaptically, they cannot unequivocally be categorized as agonists, partial agonists or antagonists by their activity in the serotonin syndrome test. Also, the current experiments did not allow us to determine whether the antiaggressive effects of these compounds in mice occur at presynaptic or postsynaptic 5-HT_{1A} receptors or are due to agonist or antagonist activity at these receptors.

As well as the 5-HT_{1A} agents, the 5-$HT_{1B/1C}$ agonists m-chlorophenyl-piperazine (mCPP) and 1-(a,a,a-trifluoro-m-tolyl)-piperazine (TFMPP) inhibited isolation-induced aggression, but only at doses which also produced debilitation (26). In the current experiments, the 5-HT_3 antagonist zacopride was unable to antagonize aggression at doses which are reported to be anxiolytic in mice (6). The 5-HT_2 antagonist ritanserin inhibited isolation-induced aggression without producing debilitation at 10 mg/kg IP, a dose reported to be anxiolytic in rats (33). However, at this dose (10 mg/kg IP), it is possible that ritanserin may be mediating its effects through receptors other that 5-HT_2 sites (i.e., 5-HT_{1C}). Further testing with more selective 5-HT receptor subtype agonists and antagonists should clarify the role of serotonin on isolation-induced aggression.

Other compounds which possess anxiolytic activity and inhibit isolation-induced aggression are the benzodiazepines chlordiazepoxide, diazepam and lorazepam. These compounds inhibited aggression only at doses which also produced debilitation (see Table 7). This finding is in agreement with previously published results (30). Benzodiazepines have sedative and muscle relaxant effects (2) which may interfere with their anxiolytic effects in this paradigm.

In this study, haloperidol antagonized aggression only at doses which also produced debilitation. These results are in agreement with previously reported studies (28). Furthermore, in the current experiment, desipramine only inhibited aggression at a dose which produced debilitation. However, both antipsychotics and antidepressants have been reported to reduce isolation-induced aggression without producing debilitation (30). Procedural differences for the measure of debilitation may explain these conflicting results. In addition, it has been proposed that anticholinergics (and antihistamines with significant anticholinergic activity) also antagonize isolation-induced aggression without producing debilitation (30); however, these compounds have not yet been tested in our laboratory.

From the results presented in this paper and previous studies (26,27), it is clear that compounds with activity at the 5-HT_{1A} receptor and the 5-HT_2 antagonist ritanserin selectively antagonize isolation-induced aggression (i.e., they reduce TFT at doses which do not produce debilitation in rotorod motor coordination tests). It is interesting to note that 5-HT_{1A} and 5-HT_2 serotonergic compounds which were active in reducing isolation-induced aggression were also active in the pigeon conflict, a paradigm indicative of anxiolytic activity (14). What is still unclear is whether the selective inhibition of isolation-induced aggression is related to nonsedative anxiolytic activity. The benzodiazepines, which are effective anxiolytics and sedatives (2), decreased aggression only at doses which also caused debilitation in rotorod motor coordination tests. While 5-HT_3 antagonists have shown anxiolytic activity in some preclinical tests (6), but not others (14), zacopride did not inhibit isolation-induced aggression at any of the doses tested. However, buspirone, gepirone, ipsapirone and ritanserin selectively antagonized isolation-induced aggression, and have been reported to have anxiolytic activity in clinical trials (3, 7, 13, 19, 36, 38). Tandospirone and Wy-47,846, currently under development as anxiolytics, also inhibited isolation-induced aggression selectively. Therefore, the results of further clinical trials for anxiolytic activity of serotonergic compounds are needed to determine whether antagonism of isolation-induced aggression without disruption of rotorod motor coordination is predictive of nonsedative anxiolytic activity.

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