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Combined Effects of Gepirone and (+)WAY 100135 on Territorial Aggression in Mice

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LOPEZ-MENDOZA, D., H. AGUILAR-BRAVO AND H. H. SWANSON. *Combined effects of Gepirone and (+)WAY 100135 on territorial aggression in mice.* PHARMACOL BIOCHEM BEHAV **61**(1) 1–8, 1998.—The purpose of this investigation was to elucidate the involvement of the serotonergic 5-HT_{1A} system in the control of aggression. The paradigm was the response of a resident mouse to an intruder into its territory. Three experiments were performed to assess the action of various doses of Gepirone (a partial agonist) and (+)WAY 100135 (a putative antagonist), separately and in combination, on aggression and on rectal body temperature. The most consistent action of Gepirone was an increase in the latency to attack. After initiation of fighting, rates of attack, chase, and tail rattling were reduced in a dose-dependent manner by IP administration of 2.5, 5, and 10 mg/kg of Gepirone. There was no evidence of sedation or motor impairment, but autogrooming was decreased. When doses of 2.5, 5, and 10 mg/kg of (+)WAY 100135 (WAY) were given, no effects whatsoever on aggressive or other behaviors were observed. In a third experiment, a two-factor design was followed in which injection of WAY (0, 2.5, and 5 mg/kg) was followed 15 min later by injection of Gepirone (0, 2.5, 5, and 10 mg/kg). WAY decreased attack latency, increased attack rate, and attenuated the marked dose-dependent aggression reducing properties of Gepirone. The test procedure resulted in "stress hyperthermia," which was reduced by Gepirone and increased by WAY. In both behavioral and temperature measures, the larger dose of WAY proved to be less effective than the smaller one. The results support the involvement of the 5-HT_{1A} system in the modulation of some forms of aggression. © 1998 Elsevier Science Inc.

Gepirone (+)WAY 100135 Aggression Resident/intruder Mice

GEPIRONE is a partial agonist with affinity for the serotonergic 5-HT_{1A} receptors that are believed to modulate fear, anxiety, and aggressiveness (10). The most widely accepted hypothesis to explain the functioning of 5-HT_{1A} partial agonists is that their effects are mediated (a) through an agonistic action on the presynaptic 5-HT_{1A} receptors (autoreceptors), which results in inhibition of serotonin (through an inhibition of the firing rate in raphe nuclei and a reduction of the serotonin released from the neurone); and (b) an antagonistic action on the postsynaptic receptors in certain limbic areas that enhance this inhibiting action (7,12,42). Classification as a partial agonist also implies incomplete agonistic action, possibly coupled with some antagonistic effects, resulting in an altered balance of serotonin production (42). There is, nevertheless, general agreement that acute treatment with Gepirone results in decreased 5-HT function.

Although its mechanism of action is still unclear, the effects of Gepirone in a battery of animal models have been classified as anxiolytic or antidepressive (9,10). Furthermore, Gepirone decreased various fear-mediated defensive responses to attack or threat by predators, humans, or conspecifics (5,18,34,35), presumably through a reduction in anxiety (9). However, it has been reported that Gepirone also decreases offense both in models of maternal attack (31) as well as in aggression of a resident towards an intruder (26,30,31,41,46). Although a common base for the three emotional disorders (anxiety, aggression, and depression) has been proposed (44), some authors consider aggression as belonging to a different category of disorders (lack of control or impulse disorders) (9). Furthermore, except for some theoretical speculation (1), the relationship between aggression and anxiety has not been extensively considered in aggression studies, thus remaining an issue to be enlightened.

In earlier studies, (+)WAY 100135 has been shown to have strong affinity and high selectivity for 5-HT_{1A} receptors and to act as antagonist at both pre- and postsynaptic levels (12,13,39). Although, at first, it did not have any intrinsic effects when applied alone, its action had to be revealed by counteracting ef-

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fects of the classical full agonist, 8-OH-DPAT. A list of responses to 8-OH-DPAT that were inhibited by (+)WAY 100135 included firing rate at the dorsal raphe nucleus, serotonin release, hyperphagia, hypothermia, hyperglycaemia, the serotonergic syndrome (12), and anxiogenic effects of bilateral administration of 8-OH-DPAT on dorsal hippocampus (11).

However, more recently biochemical and electrophysiological studies have shown that (+)WAY 100135 might have agonistic properties as it induced a dose-dependent decrease in the 5-HT level in the ventral hippocampus (2) and a decrease in the firing rate of single units in dorsal raphe nucleus (16). Such action was initially pointed out by behavioral studies in which (+)WAY 100135 reduced anxiety, increased exploratory behavior in the light compartment of the light–dark box (8), reduced risk assessment, and increased entrances in the open arm of the elevated plus-maze (38). On aggression, (+)WAY 100135 seemed to increase some of the aggressive elements at low doses, the same components were increased at higher doses (3). So far, no reports of (+)WAY 100135 and a 5-HT_{1A} partial agonist interaction in the modulation of animal aggression have been found.

The purpose of the present experiment was to elucidate the involvement of 5-HT_{1A} receptors in the control of aggression, in context with their known relationship to anxiety, by the use of Gepirone and (+)WAY 100135 (to be referred to as WAY), acting separately or in combination at various doses. Both drugs were administered to isolated resident male mice prior to the introduction of an intruder. This paradigm has been proven to be an ethologically valid model of offensive aggression (22,36).

The role of the serotonergic system in controlling body temperature was also considered by measuring temperature under the effects of both drugs. Gepirone has been shown to induce hypothermia (43), and WAY has been found to counteract both 8-OH-DPAT-induced (12) and Gepirone-induced hypothermia (43). In this experiment, we attempted to replicate these findings by taking rectal temperature before the injections and after the tests. The possible role of stress-induced hyperthermia as a correlate of anxiety was also considered.

METHODS

Subjects

All subjects were adult male mice of the BALB/C strain weighing 35 to 45 g. The heaviest animals were used as residents. These were housed in individual Plexiglas cages (size 16 × 10 × 6 cm) for 2–3 weeks before the beginning of each experiment. The remaining animals (intruders) weighed at least 10% less than residents and were placed in group cages of five animals per cage. All animals received food and water ad lib and were kept under 12-h reversed light conditions. Tests were carried out during the dark (active) period.

Drugs

Gepirone (Bristol-Myers Squibb Pharmaceuticals Ltd.) and (+)WAY 100135 (Wyeth Research Ltd.) were administered IP diluted in physiological saline solution (4 ml/kg). Controls received a similar volume of saline. All treatments were given only to the resident. When a single drug was used, testing began exactly 30 min after injection. When the interaction between two drugs was studied, the second drug was administered 15 min after the first, and testing began 30 min after the second injection.

Test Procedure

The test began when an intruder was placed in the resident's cage and was recorded on video for exactly 5 min.

Behavior

Only the resident's behavior was scored according to the criteria of Grant & Mackintosh (17). Although defensive behaviors such as upright and sideways defensive postures, escape attempts, and flight were occasionally exhibited by the resident, these were not scored as they depended on the aggressive attacks by the intruder. The frequencies of these behaviors were very low.

Aggressive behavior. The rates of attack, chase, and tail rattle expressed in counts per second were defined as the frequency of the behavior, after the first attack bite, divided by the total duration of the test (300 s) minus the attack latency in seconds.

Nonaggressive behaviors. Social sniff (any part of the body of the intruder), self-groom, exploratory sniff (subject sniffs cage or air) were scored as frequencies, whereas sitting attending (the subject is sitting still while scanning the surroundings or intruder) was scored as duration in seconds.

Scoring

The main investigator plus another trained observer marked the scoring sheet each time a specific behavior occurred. The concordance between observers was above 0.7. The scores of the main investigator were used for statistical analysis.

Temperature

Body rectal temperature was taken only in the third experimental group. It was taken twice per subject in a session: before the first injection and after the completion of each behavioral test. The mouse was restrained manually and a normal fever thermometer was inserted into the anus for 2 min.

Statistics

An SPSS computer program was used for statistical analysis. The attack latency, rate, frequency, or duration of the various behavioral elements were analyzed by repeated-measures ANOVA. The data obtained in Experiment C was analyzed by a repeated-measures ANOVA with one within-subject factor (Gepirone) and one between-subject factor (WAY).

Experimental Design

The study consisted of three separate experiments using different animals in each one. In Experiment A, effects of graded doses of Gepirone were assessed. In Experiment B, the action of (+)WAY 100135 was examined in a similar design. In Experiment C, WAY–Gepirone interaction was studied in a systematic manner.

Experiment A: Gepirone Only

A within-group experimental design was used. Subjects were 30 residents, each of which was tested four times (once with each dose). The sequence of treatments was assigned randomly. There were thus 30 measures of each dose (120 tests in total). The four doses were: saline, 2.5, 5, and 10 mg/kg Gepirone.

Experiment B: WAY Only

A within-group design, similar to Experiment A was used. The four treatments were 0, 2.5, 5, and 10 mg/kg WAY. An additional group of eight "special controls" was added to test for possible consequences of repeated fighting experience. These subjects were tested on four consecutive occasions, after saline injections, at the same time as the experimental subjects.

Experiment C: Interaction Between WAY and Gepirone

A two-factor (3 × 4) design was used: Gepirone had four dose levels (0, 2.5, 5, and 10 mg/kg) and the pretreatment with WAY had three (0, 2.5, and 5 mg/kg). There was a total of 12 combinations of treatments. Thirty-six residents were used (three residents per cell) and the factorial design was repeated four times. Therefore, the total number of tests was 144. In each test, each animal was injected twice: in the first place with WAY, and 15 min afterwards with Gepirone. The test started 30 min after the second injection. By means of the repetition, all residents received each of the four Gepirone treatments in a different order (within-subjects factor), but each subject only always received a the same dose of WAY (between-subjects factor). To control the possible effect of a repeated aggressive experience, six "special controls," injected

TABLE 1

EXPERIMENT A "GEPIRONE ONLY" AND EXPERIMENT B "WAY ONLY": MEAN (X) AND STANDARD ERRORS (SE)

	AGGRESSIVE BEHAVIOUR						NON-AG GRESSIVE BEHAVIOUR							
	Rate per second after first attack						Frequency of occurence during total test						Total duration (sec)	
Treatments mg/kg	Attack Rate		Chase Rate		Tail Rate		Explorat. Sniffing		Social Sniffing		Grooming		Attending	
	X	SE	X	SE	X	SE	X	SE	X	SE	X	SE	X	SE
EXPERIMENT A: "GEPIRONE ONLY"														
GEP = 0	0.10	0.01	0.01	0.002	0.04	0.007	13.1	1.4	13.3	1.4	2.3	0.4	9.8	3.5
2.5	0.07	0.01	0.01	0.003	0.03	0.006	11.9	0.8	11.9	1.2	2.03	0.3	18	5.5
5	0.02	0.01	0.003	0.002	0.01	0.005	13.8	0.7	11.8	1.5	0.66	0.1	30	6.0
10	0.002	0.002	0.000	0.000	0.003	0.003	13.8	0.8	7.3	0.8	0.7	0.2	41	5.5
ANOVA $F_{(3,87)}$	F	P	F	P	F	P	F	P	F	P	F	P	F	P
	11.3	***	4.1	**	9.7	***	0.9	ns	5.7	***	6.7	***	8.6	***
EXPERIMENT B: "WAY ONLY"														
	X	SE	X	SE	X	SE	X	SE	X	SE	X	SE	X	SE
WAY = 0	0.1	0.01	0.01	0.00	0.02	0.00	18.9	1.7	14.2	2.1	2.2	0.5	3.3	1.5
2.5	0.1	0.01	0.01	0.00	0.03	0.01	19.8	1.8	13.9	2.0	2.3	0.3	5.2	2.8
5	0.1	0.01	0.01	0.00	0.02	0.00	19.3	1.5	15.0	1.7	2.0	0.4	7.8	2.1
10	0.1	0.02	0.01	0.00	0.02	0.00	20.6	1.8	14.5	2.2	1.9	0.3	6.3	2.4
SPECIAL CONTROL GROUP														
Test: 1	0.08	0.04	0.01	0.00	0.08	0.07	27.0	2.3	22.0	3.3	0.4	0.26	5.7	5.7
2	0.09	0.02	0.01	0.00	0.02	0.01	27.3	2.4	20.8	1.9	1.0	0.42	3.3	1.7
3	0.08	0.03	0.00	0.00	0.02	0.01	32.6	3.8	17.6	4.7	1.1	0.74	3.7	2.6
4	0.10	0.01	0.01	0.00	0.01	0.01	33.0	2.8	31.1	4.4	1.6	0.65	0.0	0.0
ANOVA	F	P	F	P	F	P	F	P	F	P	F	P	F	P
WAY $F_{(3,87)}$	0.25	ns	1.19	ns	0.32	ns	0.22	ns	0.09	ns	0.20	ns	0.68	ns
Special Control Group $F_{(3,21)}$	0.17	ns	0.67	ns	0.72	ns	1.43	ns	2.30	ns	1.37	ns	0.51	ns

ANOVA: p: level of significance $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, ns: p is not significant.

twice with saline before each test, were tested on four consecutive occasions, together with the experimental subjects.

RESULTS

Experiment A: Gepirone Only (Table 1, Fig. 1)

Aggressive behavior. The most striking effect of Gepirone was the dose-dependent increase in attack latency, $F(3, 87) = 20$, $p < 0.001$. At the 10 mg/kg level, most subjects did not attack the intruder. The rates of the three principal measures of aggression (attack, chase, and tail rattle) were significantly decreased by Gepirone in a dose-dependent manner. The dose-dependent decrease in rates of aggressive acts suggests that even if the test were extended, there would be little likelihood of high levels of aggression being shown.

Nonaggressive behavior. Grooming was significantly decreased by 5 and 10 mg/kg Gepirone. A decrease in social sniffing was only seen with the largest dose. Exploratory sniffing, however, was not affected at any dose level. Attending was significantly increased in a dose-dependent manner, and there was no evidence of motor impairment.

Experiment B: WAY Only (Table 1, Fig. 1)

There was no significant effect of WAY at any dose level on any behavior, aggressive or otherwise. There was also no difference between consecutive tests in the "special controls," suggesting that in this paradigm, experience is not a factor in altering behavior.

Experiment C: Interaction Between WAY and Gepirone (Table 2, Fig. 2)

Aggressive behavior. As in Experiment A, Gepirone significantly increased attack latency, $F(3, 99) = 60$, $p < 0.001$, and decreased rates of aggressive behaviors after the initial attack in a dose-dependent manner. At the 10 mg/kg level, none of the subjects attacked the intruders during the test period. In contrast with the results of Experiment B, there was a main effect of WAY on attack latency, $F(2, 33) = 5.6$, $p < 0.01$, opposite to that of Gepirone: the lower dose of 2.5 mg/kg WAY decreased latency when acting alone and attenuated the effect of 2.5 and 5 and 10 mg/kg Gepirone. After the initiation of attack, there was a significant effect of WAY on attack rate, but not on chase or tail rattle. Any WAY effects on aggression were only apparent with the lower dose (2.5 mg/kg). The higher dose (5 mg/kg) had no effect by itself or in combination with Gepirone. A variation in procedure between Experiments B and C may account for the discrepancy in results regarding the efficacy of treatment with WAY. In Experiment B, different doses of WAY were given to the same subjects (within-subject design), whereas in Experiment C, the different doses of WAY were given to different subjects (between-subject design). The attack latency for the "special controls" on four consecutive tests was 34.63, 25.33, 28.00, and 11.17 s, showing that fighting experience had no significant effect on this parameter, $F(3, 15) = 0.68$, $p = 0.57$. Furthermore, there were no significant differences in the rates of attack, chase and tail rattle.

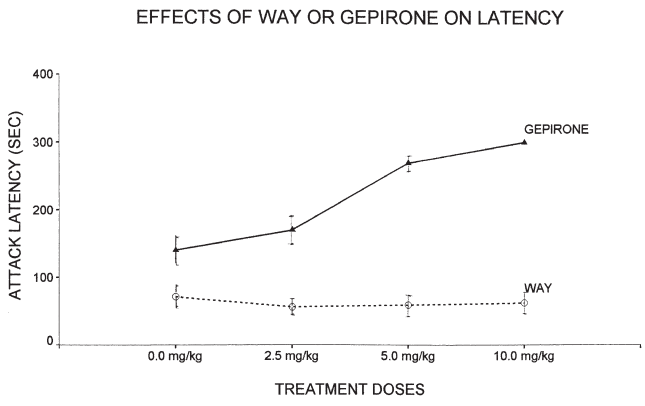

FIG. 1. Effects of Gepirone (Experiment A) and (+)WAY 100135 (Experiment B) on attack latency: mean of each treatment group. In each experiment, the line represents the effects of the various doses of each drug given to the same subjects in random order (within-subject design). The total duration of the test was 300 s.

Nonaggressive behavior. As in Experiment A, grooming was significantly decreased in a dose-dependent manner by Gepirone, but social sniffing was increased, whereas exploratory sniffing was unaltered. Again, in confirmation of Experiment A, attending was significantly increased by Gepirone in a dose-dependent manner. There was no evidence of sedation, nor were other abnormalities of motor function observed. Except for some changes in attending (which tended to occur when there was no other activity), the "special controls" showed no differences in nonaggressive behaviors with repeated tests.

Body temperature (Fig. 3). The graph depicts differences in rectal temperature before and after the test. It should be emphasized that the first reading was taken before injection of the drug and the second immediately after removal of the intruder. In the absence of drugs, body temperature was increased significantly by the test procedure alone [before vs. after, $t(11) = 2.52$, $p < 0.05$], a phenomenon known as "stress hyperthermia" (6,23,32,47). In comparison to saline controls, Gepirone decreased body temperature in a dose-dependent manner, $F(3, 63) = 15$, $p < 0.001$, counteracting the "stress" effect. WAY (2.5 mg/kg) had the opposite effect because this dose increased body temperature on its own and at all dosages of Gepirone above that produced in saline controls, $F(2, 21) = 6.3$, $p < 0.01$. In concordance with its lack of effect on behavioral measures, the larger dose of WAY (5 mg/kg) did not attenuate the Gepirone action, although on its own it increased body temperature above saline controls, $t(11) = 3.13$, $p < 0.01$. The "special controls" exhibited "stress hyperthermia" on all four tests (1.58, 0.95, 0.76, and 1.22°C), differences not being significant, $F(3, 6) = 2.39$, $p = 0.16$.

DISCUSSION

There is a paradox as to why substances such as Gepirone, which reduce 5-HT function (7,12,13,42,43) should reduce aggressiveness, whereas in the psychiatric literature low 5-HT levels are usually associated with explosive and uncontrolled violence (33). It has been reported that isolation in male rats and mice is associated with hyperirritability, hyperemotionality, and compulsive aggression (45), and more recently with decreased 5-HT turnover in the amygdala (21). Nevertheless, the resident/intruder model of aggression used in the present experiment is a natural adaptive response to invasion of personal space (36), and not a maladaptive or pathologic manifestation. We suggest that in the present investigation, Gepirone

TABLE 2

EXPERIMENT C: "INTERACTION BETWEEN WAY AND GEPIRONE"

	AGGRESSIVE BEHAVIOUR						NON-AGGRESSIVE BEHAVIOUR							
	Rate per second after first attack						Frequency of occurrence during total test						Total duration (sec)	
Treatments mg/kg	Attack Rate		Chase Rate		Tail Rate		Explor. Sniffing		Social Sniffing		Grooming		Attending	
	X	SE	X	SE	X	SE	X	SE	X	SE	X	SE	X	SE
WAY = 0														
GEP = 0	0.11	0.02	0.02	0.01	0.04	0.01	14	1.8	12	3.4	2.4	0.5	5	4.1
2.5	0.03	0.01	0.00	0.00	0.03	0.01	18	1.4	12	2.8	1.8	0.5	7	4.4
5	0.02	0.01	0.00	0.00	0.03	0.02	18	2.4	14	3.2	1.2	0.3	25	11
10	0.00	0.00	0.00	0.00	0.00	0.00	23	2.3	14	2.2	0.1	0.1	29	11
WAY = 2.5														
GEP = 0	0.13	0.02	0.02	0.01	0.04	0.01	18	1.7	10	1.7	1.5	0.2	3	1.9
2.5	0.08	0.01	0.02	0.01	0.02	0.01	19	2.0	10	2.0	1.8	0.4	1	0.8
5	0.05	0.01	0.01	0.00	0.02	0.01	19	1.3	15	2.8	1.7	0.6	14	11
10	0.01	0.00	0.00	0.00	0.01	0.00	23	1.8	16	2.1	1.4	0.5	17	7.6
WAY = 5														
GEP = 0	0.10	0.01	0.01	0.00	0.06	0.02	22	3.6	7	2.0	2.7	0.8	1	1.2
2.5	0.07	0.01	0.01	0.00	0.02	0.01	25	4.1	10	1.3	2.8	0.6	7	6.7
5	0.04	0.01	0.01	0.00	0.01	0.01	18	1.2	13	2.6	1.3	0.4	20	5.6
10	0.00	0.00	0.00	0.00	0.01	0.01	21	3.3	12	2.7	0.4	0.1	31	1.3
SPECIAL CONTROL GROUP														
Test: 1	0.08	0.02	0.02	0.00	0.03	0.01	20.3	4.39	10.8	3.17	1.1	0.31	1.33	1.33
2	0.09	0.01	0.01	0.01	0.03	0.02	21.5	4.04	4.3	0.88	2.1	0.61	10.1	5.90
3	0.1	0.03	0.02	0.01	0.02	0.01	22.0	1.61	8.6	2.73	2.3	1.14	1.67	1.67
4	0.1	0.02	0.01	0.00	0.02	0.00	23.5	3.52	9.8	3.56	3.5	0.43	0.00	0.00
ANOVA	F	P	F	P	F	P	F	P	F	P	F	P	F	P
GEP $F_{(3,99)}$	58.9	***	6	***	8.5	***	2.6	ns	2.7	*	7.4	***	6.4	***
WAY $F_{(2,33)}$	6.7	**	1.6	ns	0.11	ns	1.2	ns	0.92	ns	0.69	ns	1	ns
Interaction $F_{(6,99)}$	1.3	ns	0.62	ns	0.94	ns	1.6	ns	0.45	ns	0.93	ns	0.23	ns
ANOVA Special Control Group $F_{(3,15)}$	0.43	ns	1.01	ns	0.39	ns	1.25	ns	1.56	ns	1.82	ns	3.17	*

Mean (X) and standard errors (SE). ANOVA: p: level of significance $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, ns: p is not significant.

exerted its antiaggressive action through a reduction in anxiety associated with the test situation by reducing serotonin function. Other types of aggression may involve different neurochemical mechanisms.

A stranger in the home cage is likely to provoke anxiety in the resident (25,26,46). If the action of Gepirone is to decrease anxiety, then the resident may take more time to assess and investigate the intruder and become less motivated to attack. In the present experiment, treatment with Gepirone greatly increased the latency to attack and decreased the rate of aggressive acts while tending to increase attentiveness. At higher doses, the residents watched and monitored the activity of the intruder, but did not approach nor attack him. Reduction in anxiety was also suggested by the attenuation of

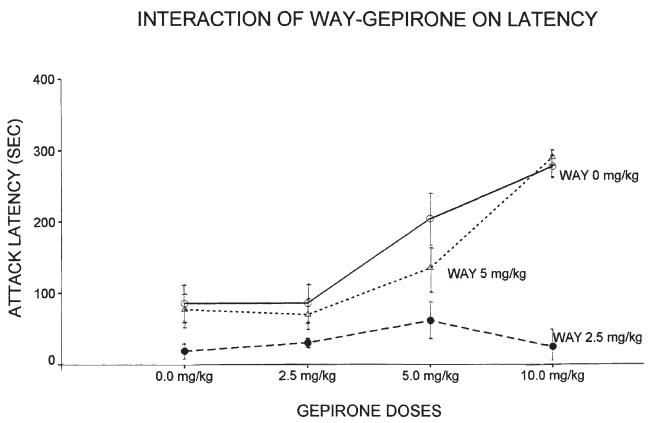

FIG. 2. Interaction of (+)WAY 100135 and Gepirone on attack latency (Experiment C). Mean latencies of each treatment group. Each line represents the effects of 0, 2.5, 5, and 10 mg/kg of Gepirone given to the same subjects (within-subject factor). The three different lines represent the additional effect of WAY pretreatment at the 0, 2.5, and 5.0 mg/kg level (between-subjects factor). Total duration of the test was 300 s.

autogrooming, a displacement activity generally associated with conflict and anxiety (24), and by the suppression of "stress hyperthermia" (19). It is important to mention that even the highest dose of Gepirone, which blocked all aggressive acts, did not decrease exploratory behavior and, therefore, was not sedative. Moreover, no abnormal motor reactions were observed. Our results support those of other investigators, who showed that, in isolated male mice trained and screened for aggressiveness towards intruders, attack latency was greatly increased by 5-HT_{1A} agonists including Gepirone (41). The authors concluded that although evidence pointed to decreased serotonin activity due to presynaptic stimulation, the involvement of postsynaptic receptors could not be discounted.

Different doses of (+)WAY 100135 given to the same subjects in random order 30 min before each test had no noticeable effects on the behavior of the resident. However, when WAY was given to different subjects prior to receiving saline

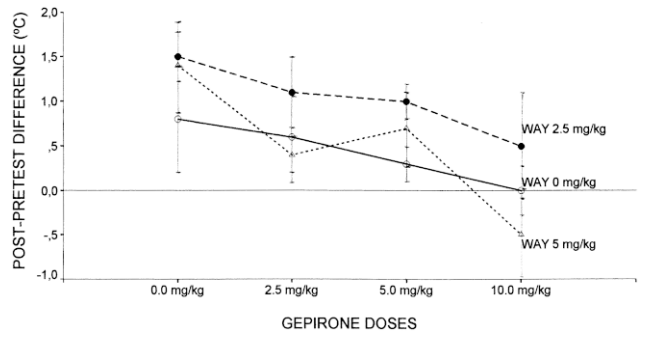

FIG. 3. Interaction of (+)WAY 100135 and Gepirone on rectal temperature (Experiment C). The graph represents the difference in temperature (°C) before injection and after the test. (Temperature after the test minus temperature before the injection.)

or Gepirone, some direct effects of WAY on aggression were observed. Latency to the first attack was diminished and the rate of attack was augmented. Differences in experimental procedure might account for some of the discrepancies in the efficacy of WAY. Thus, in the "WAY-only" experiment, the various doses of WAY were given to the same subjects in a within-group design, whereas in the "WAY–Gepirone interaction" experiment, the various doses of WAY were given to different individuals (between-group design). The attenuation by WAY of the aggression reducing properties of Gepirone is in accordance with the reputed ability of WAY to block the actions of 5-HT_{1A} agonists both at pre- and postsynaptic levels (12,28,39,40). The lower efficacy of the larger dose is problematical, but is partially supported by R. Bell et al. (3), who found that 10 mg/kg had less effect than 2.5 and 5 mg/kg on increasing offensive behavior. This differential effect may be due to a different balance in activity at pre- and postsynaptic levels, with some intrinsic anxiolytic properties (8,11,38) showing up with the higher dose. Moreover, concordance between behavioral and temperature effects, both mediated via the 5-HT_{1A} system, suggests that the dose-related observations are real and not spurious.

In the present experiment, fighting experience did not alter the behavior of residents because two sets of additional controls, injected only with saline and tested on four consecutive occasions, showed no differences between tests. As the treatments were equally distributed over test days, difference in response to the drugs could not be attributed to underlying differences in 5-HT metabolism due to experience.

Confrontation with an intruder was accompanied by a consistent rise in rectal temperature of about 1°C, which was not attenuated by repeated tests. A rise in body temperature in anticipation or in conjunction with an aversive event seems to be a common response in rodents and has been called "stress-induced hyperthermia" (SIH) (6,23,32,37,47). SIH has been correlated with increased plasma ACTH, corticosterone, and glucose levels that returned to the baseline in parallel to the temperature. The simultaneous increases in temperature and plasma stress hormones support the use of the SIH paradigm as an animal model to study putative anxiolytic properties of drugs (19). It was, therefore, interesting that only drugs classified as anxiolytics (as opposed to antidepressants, neuroleptics, and antipyretics) were able to counteract SIH (23). With particular reference to our work, Gepirone decreased SIH (32), and this was counteracted by (+)WAY 100135 (43). The involvement of the 5-HT_{1A} system was stressed. Similarly, in our study, Gepirone suppressed hyperthermia in a dose-dependent manner, whereas WAY accentuated the temperature rise, both in the absence and presence of Gepirone. The effects of Gepirone on stress hyperthermia, together with the decrease in grooming, reinforce the proposition that the decrease in aggression in territorial defense may be associated with a lessening of anxiety. Although WAY has been reported to reduce some anxiety-related behavior (4,8,38), this has not clearly happened in our experiment, as constated by its effects on temperature.

There are many reports of 5-HT_{1A} agonists (Gepirone, Buspirone) decreasing aggression in a resident/intruder model, but so far no 5-HT agonist or antagonist has been found to increase any kind of aggressive behavior in animals (27). Although not very robust, the finding that in our study, the 5-HT_{1A} antagonist (+)WAY 100135 increased aggression by itself as well as in combination with Gepirone, is clearly important. Recently, a more potent and selective 5-HT_{1A} antagonist, WAY 100635 that has antagonistic action at both pre- and

postsynaptic receptors without apparent agonistic activity, has become available (14,15,20,29). It will be interesting to compare the action of this new substance to that of (+)WAY 100135 on territorial aggression and stress-induced hyperthermia.

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