The GABAergic Effect of Low Doses of Lorazepam on Social Behavior

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The aim of this work was to test the antiaggressive effects of lorazepam and to determine whether these effects were mediated by benzodiazepine receptors. In a first experiment, male mice were injected with lorazepam in a range of low doses (0.05, 0.1, 0.2, and 0.6 mg/kg) or saline solution. In a second experiment, 1 mg/kg of Ro 15-1788, a benzodiazepine receptor antagonist, and a saline solution were injected before the behavioral test. Results showed that 0.6 mg/kg of lorazepam was the only dose that decreased the total duration of threat ($P < .01$) and social investigation ($P < .05$) and that 1 mg/kg of Ro 15-1788 had no effects. In the third experiment, animals received two injections: 0.6 mg/kg of lorazepam plus 1 mg/kg of Ro 15-1788, 0.6 mg/kg of lorazepam plus saline solution, or saline solution plus saline solution. Those treated with lorazepam and saline solution spent less time digging ($P < .001$), threatening ($P < .001$), and attacking ($P < .05$) and more time avoiding the opponent ($P < .01$) or being immobile ($P < .001$) than the controls. Ro 15-1788 was successful in completely antagonizing the behavior modulated by lorazepam. Aggr. Behav. 28:248– 256, 2002. © 2002 Wiley-Liss, Inc.

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INTRODUCTION

In the past few decades, the effects of benzodiazepines on aggression have been investigated in numerous pharmacological studies [Christmas and Maxwell, 1970; Cilia and Piper, 1997; Da Vanzo et al., 1966; Krsiak, 1979; Krsiak et al., 1981; Mos and Olivier, 1989; Pabis and Stanislav, 1996; Parmigiani et al., 1998; Poshivalov et al., 1987; Vale and Montgomery, 1997], but, on the whole, it could be said that there is no complete agreement as to their action on this behavior. Classically, decreases in aggression have been reported as a consequence of treatment with these drugs, although several researchers have reported increases, naming them "benzodiazepines' paradoxical effect" [Cutler et al., 1997; Feldman, 1986; Weerts and Miczek, 1996; Weisman et al., 1998].

With respect to the relationship between benzodiazepines and isolation-induced aggression, the most investigated drugs have been chlordiazepoxide and diazepam. The results, however, have proved to be contradictory because doses between 5 and 50 mg/kg of chlordiazepoxide in

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most cases have reduced aggression [Da Vanzo et al., 1966; Ferrari et al., 1997; Krsiak, 1975; Krsiak, 1979; Miczek and O'Donnell, 1980; Poole, 1973; Scriabine and Blake, 1962; Sofia, 1969; Sulcova and Krsiak, 1989; Vale and Montgomery, 1997; Valzelli and Bernasconi, 1976; Valzelli et al., 1967], although on some occasions no effects [Krsiak, 1979; Miczek and O'Donnell, 1980] or even increases with the same dose and type of administration have been observed [Borgesova et al., 1971]. Other benzodiazepine substances, such as alprazolam and oxacepam, have acted to reduce defense behavior and attack and increase social investigation and nonsocial exploration [Delini-Stula and Vassout, 1979; Krsiak and Sulcova, 1990; Sulcova and Krsiak, 1989], although low doses have had no effect on attack [Krsiak and Sulcova, 1990]. Several factors, such as individual differences and/or the use of different substances, have explained the contradictory results.

Lorazepam (commercial name, Orfidal), a benzodiazepine that is frequently being used at the present in clinical practice, is one of the less-studied benzodiazepines in relation to aggressive behavior. Comparisons with other benzodiazepines (alprazolam, diazepam, nitrazepam, and oxacepam) have shown that lorazepam has a higher sedative potency [Krsiak and Sulcova, 1990; Sulcova and Krsiak, 1989]. Independently of this effect, lorazepam, as other benzodiazepines, has proved to be more effective than neuroleptics in the management of aggression and agitation [Buckley, 1999; Dorevitch, et al., 1999; Lenox et al, 1992; Salzman et al., 1991], although the most effective choice is the combination with a neuroleptic [Bieniek et al., 1998]. Using the isolation-induced aggression model, Sulcova and Krsiak [1989] and Krsiak and Sulcova [1990] found that lorazepam diminished the occurrence of defenses and escapes at doses that decreased motor activity, reduced aggressive behavior (attacks) at doses that suppressed rearing, and had no effects on attack at low doses (0.2 and 0.6 mg/kg).

The "taming" or antiaggressive effects of benzodiazepines are due to their action as benzodiazepine receptor agonists at the GABA receptor complex. GABAergic and opioidergic neurotransmissions are more closely related to modifications in aggressive, defensive, and submissive behaviors compared with serotoninergic and dopaminergic action [Miczek et al., 1994]. The inhibiting effect of the GABAergic system on aggression has been suggested by several studies using neuropharmacological manipulations. This is the case of Mandel et al. [1981] who, after injection of GABA into the olfactory bulb, found temporary inhibition of the muricide behavior in rats. At the same time, they found lower GABA levels in this area in muricide rats compared with the nonmuricide.

Ro 15-1788 (flumazenil) is a benzodiazepine receptor antagonist that antagonizes the central effects of benzodiazepines [Bonetti et al., 1982; Skolnick et al., 1985] and that also has several behavioral effects at moderate-high doses. Ro 15-1788 blocks the benzodiazepine receptors, increasing motor activity and social investigation at doses between 1.25 and 20 mg/kg [Rodgers and Waters, 1984; Rodgers et al., 1983] and reverting the low levels of aggression induced by diazepam and beta-carboline [Skolnik et al., 1985]. This substance at doses between 20 and 40 mg/kg blocks the analgesic effect of defeat [Rodgers and Randall, 1987, 1988] and at doses higher than 40 mg/kg induces seizures [Corda et al., 1982]. The proconvulsive action could be related to the hypothesis that considers that flumazenil could act as a partial agonist of benzodiazepine receptors at very high doses [File, 1982; Nutt et al., 1982; Rodgers and Randall, 1988; Rodgers et al., 1983]. Miachon and Cespuglio [1997] found that as a benzodiazepine receptor antagonist, pretreatment with flumazenil (Ro 15-1788) prevented the adrenalectomy-induced muricidal behavior in male wistar rats. The corticotropin-induced muricidal behavior was prevented by flumazenil, although the posttreatment had no effects. The benzodiazepine receptors have been involved in this inhibiting effect.

The main aims of the present study were to determine the effect on social behavior of lorazepam (a benzodiazepine receptor agonist) and Ro 15-1788 (a benzodiazepine receptor antagonist) and their action on individually housed male mice during an agonistic encounter in a neutral area. In the first experiment, we studied the effects of a single administration in a range of low doses (0.05, 0.1, 0.2, and 0.6 mg/kg) of lorazepam to select the dose that had the greatest effect on agonistic behavior. In Experiment 2, to verify the lack of behavioral effects of Ro 15-1788 at low doses, a single administration of 1 mg/kg of this drug and a saline solution were injected before the behavioral test. Finally, as in the first experiment, the most efficient dose at reducing aggression turned out to be 0.6 mg/kg; this was the dose selected to be used in Experiment 3, and to confirm its specificity of action at the benzodiazepine receptor, a second injection with Ro 15-1788 (1 mg/kg) was given before the behavior was tested.

MATERIALS AND METHODS

Subjects

Five hundred sixty-four OF1 male mice from Iffa Credo (France), aged 42 days, were employed in the three experiments. Half of them were individually housed for 6 weeks in plastic cages ($24 \times 13 \times 14$ cm) and used as experimental and control subjects. The other animals were housed in groups of 10 in larger cages ($28 \times 28 \times 14$ cm) and used as "standard opponents" after being rendered temporally anosmic by intranasal lavage with a 4% zinc sulphate solution a day before testing. Mice were fed food (Panlab) and water ad libitum and subjected to a 12-hour light-dark cycle (lights on 10:00-22:00 hours local time). Laboratory temperature was kept at $20 \pm 2°C$. Subjects were weighed once a week.

Procedure

Drug administration. The lorazepam employed was by courtesy of Septa Farma Laboratory (Barcelona, Spain) and the Ro 15-1788 was by courtesy of Roche Laboratory (commercial name Anexate; Barcelona, Spain).

Experiment 1. Four groups of animals were injected intraperitoneally with 0.05 (n = 13), 0.1 (n = 12), 0.2 (n = 14), or 0.6 (n = 14) mg/kg of lorazepam and one group (n = 13) with 5 ml/kg of physiological saline solution (control group) 30 min before the behavioral test.

Experiment 2. The experimental group (n = 14) received an intraperitoneal injection of 5 ml/kg of physiological saline solution 30 min before the behavioral test and an injection of 1 mg/kg of Ro 15-1788 twenty minutes after the first injection. The control group (n = 14) was injected with 5 ml/kg of physiological saline solution 30 and 10 min before the behavioral test.

Experiment 3. Two groups of animals were injected intraperitoneally with 0.6 mg/kg of lorazepam 30 min before the behavioral test. Twenty minutes after the first injection, one of them received an intraperitoneal injection with physiological saline (n = 14) and the other with 1 mg/kg of Ro 15-1788 (n = 13). Finally, a third group, the control (n = 14), was injected with 5 ml/kg of physiological saline solution 30 and 10 min before the behavioral test.

Social encounter test. Encounters lasting 10 min between an isolated mouse and an anosmic opponent in a neutral area ($60 \times 40 \times 20$ transparent glass cage) illuminated by a white light (60 W) were carried out. This was preceded by a minute of adaptation in which the animals were separated by a plastic partition. Encounters (in which each animal participated only once) took place starting in the second hour of the subjects' dark period and were recorded with a video camera positioned in front of the test cage. Anosmic grouped mice were employed as "standard"

opponents because they elicit attack but never initiate such behavior [Parmigiani and Brain, 1983]. On some rare occasions, anosmic animals show aggressive behaviors, presumably due to a failure in the anosmic procedure; in these cases, the tests are interrupted and suppressed in posterior analyses.

Behavioral analysis. The behavior of experimental animals was assessed using an ethological technique based on a computerized observational procedure [Brain et al., 1989]. The behaviors are classified into the following 11 broad categories, which include a variety of different behavioral postures and elements: (1) body care (abbreviated groom, self-groom, wash, shake, scratch); (2) digging (dig, kick dig, push dig); (3) nonsocial exploration (explore, rear, supported rear, scan); (4) exploration from a distance (approach, attend, circle, head orient, stretched attention); (5) social investigation (crawl over, crawl under, follow, groom, head groom, investigate, nose sniff, sniff, push past, walk around); (6) threat (aggressive groom, sideways offensive, upright offensive, tail rattle); (7) attack (charge, lunge, attack, chase); (8) avoidance/flee (evade, flinch, retreat, ricochet, wheel, startle, jump, leave, wall clutch); (9) defensive/submissive (upright defensive, upright submissive, sideways defensive); (10) sexual behavior (attempted mount, mount); and (11) immobility (squat, cringe). A detailed description of all elements can be found in Brain et al. [1989] and Martínez et al. [1986]. The analysis of the videotapes only included the behavior of the experimental and control animals. This analysis was performed by a trained observer who was masked to the experimental group to which each animal belonged. The computer program gives information about total duration (accumulated time spent in each category). No sexual behavior was recorded, so this category does not appear in the results.

Statistical Analysis

Kruskal-Wallis tests were carried out to assess the variance in total duration in the behavioral categories. The comparisons between groups were performed using the Mann-Whitney U-test. The analyses were performed using nonparametric statistics because the criteria for parametric statistics (ANOVA) were not met by the data.

RESULTS
Experiment 1

Animals treated with the highest dose of lorazepam (0.6 mg/kg) were the only ones that showed a diminution in the total duration of threat ($P < .01$) and social investigation ($P < .05$). Only animals injected with the lowest doses of lorazepam (0.05 and 0.1 mg/kg) spent significantly more time exhibiting body care than their controls ($P < .01$ and .05, respectively). Apart from the lowest dose (0.05 mg/kg), treated animals spent less time exploring the environment (nonsocial exploration category) compared with the control group (0.1, 0.2, and 0.6 mg/kg; $P < .01$). The time in which they were immobilized or exploring the opponent from a distance was significantly high in all treated animals, and their statistical probability in both categories is as follows: 0.05 mg/kg of lorazepam ($P < .02$); 0.1 mg/kg ($P < .02$); 0.2 mg/kg ($P < .01$ in immobility and $P < .02$ in exploration from a distance); and 0.6 mg/kg ($P < .01$) (see Table I).

Experiment 2

Nonstatistically significant differences were found between the experimental group (treated with Ro 15-1788 and saline solution) and their controls in all of the behavioral categories exhibited (see Table II). None of the animals of either group displayed the defense category.

TABLE I. Median (Range) of Total Duration (in Seconds) of Behavioral Categories Displayed by Lorazepam-Treated Animals and Controls

| | Vehicle | Lorazepam, mg/kg | | | |
		0.05	0.1	0.2	0.6
Body care	7.71	24.74***	24.64*	15.39	3.8
	(1.05–48.37)	(8.47–50.8)	(7.86–72.1)	(0–54.8)	(0–63)
Digging	10.62	17.53	35.18	14.76	0.65
	(0–20.2)	(0–3.65)	(0–27.88)	(0–11.94)	(0–50.2)
Nonsocial	356.01	336.76	293.33***	291.81***	217***
exploration	(285.02–408.66)	(259.63–376.07)	(224.7–375.82)	(200.88–390.72)	(30.9–351.3)
Exploration	1.74	5.1**	4.74**	4.38**	7.3***
from a distance	(0–5.6)	(0–19.04)	(0–14.89)	(0–23.66)	(0–16.6)
Social investigation	40.19	51.03	33.86	51.55	16.1*
	(3.01–207.51)	(10.45–141.15)	(0–188.36)	(2.23–116)	(0–107.2)
Threat	55.19	42.05	61.18	72.26	14.1***
	(28.65–198.98)	(20.23–117.34)	(5.32–242.85)	(0–163.19)	(0–93.2)
Attack	67.84	80.41	97.14	124.74	53.25
	(3.39–149.27)	(49.59–143.98)	(0–266.92)	(0–267.87)	(0–224.2)
Avoidance/flee	0	0	0	0	0
	(0–13.49)		(0–1.65)	(0–5.2)	(0–16.2)
Defensive/submissive	0	0	0	0	0
				(0–2.94)	(0–16.7)
Immobility	0.58	1.5**	1.3**	4.31***	250.35***
	(0.03–2.45)	(0.38–2.94)	(0.27–11.46)	(0.47–313.69)	(0.9–569.1)

*$P < .05$.
**$P < .02$.
***$P < .01$.

Experiment 3

Those treated with lorazepam (0.6 mg/kg) and saline solution spent less time digging ($P < .001$), threatening ($P < .001$), and attacking ($P < .05$) and more time avoiding the opponent ($P < .01$) or being immobile ($P < .001$) than the controls.

Those that received lorazepam (0.6 mg/kg) and Ro 15-1788 showed higher total duration in the immobility category than the controls ($P < .05$).

Comparisons between the group injected with lorazepam (0.6 mg/kg) plus saline solution and that injected with lorazepam (0.6 mg/kg) plus Ro 15-1788 showed statistical differences in the following categories: threat, attack, avoidance, and immobility. Animals treated with lorazepam

TABLE II. Median (Range) of Total Duration (in Seconds) of Behavioral Categories Displayed by Animals That Received Saline Solution + Saline Solution or Saline Solution + Ro 15-1788 (1mg/kg)

	Saline solution + saline solution	Saline solution + Ro-15-1788
Body care	18.2 (10.8–67.6)	30.65 (0–68.5)
Digging	19.45 (0–79.6)	19.95 (0–79.2)
Nonsocial exploration	334.15 (245.9–428.9)	348.7 (154.6–439.9)
Exploration from a distance	0.9 (0–1.3)	4.1 (0–11)
Social investigation	48.1 (5.8–128.8)	52.45 (13.9–279.4)
Threat	60.55 (0–194.9)	42.65 (0–120.8)
Attack	85.85 (0–194.5)	50.7 (0–73.2)
Avoidance/flee	0 (0–0.9)	0 (0–6.8)
Defensive/submissive	0	0
Immobility	0.6 (0.2–4.9)	0.65 (0.3–168.8)

and saline solution showed less total duration in threat and attack ($P < .05$) and more in avoidance ($P < .01$), and immobility ($P < .05$) than those that received lorazepam and Ro 15-1788 (see Table III).

DISCUSSION

In the first experiment, the inhibition of threat could be explained in terms of general inhibition of locomotor activity as it is caused only by the highest dose of lorazepam. In addition, decreases in nonsocial exploration with all doses except the smallest one and decreases in social investigation, which were only found in those animals treated with 0.6 mg/kg of lorazepam, could also be related to benzodiazepines' sedative effects. However, the effect of lorazepam on social isolation could also be affected by the social isolation. In fact, Wongwidtdecha and Marsden [1996] found that 2.5 mg/kg of diazepam increased passive interactions in socially reared rats and decreased active interaction in isolation-reared rats, and Kumar et al. [1999] found increases in social investigation in rhesus monkeys living in social colonies, administrating 0.5 to 1 mg/kg of lorazepam together with decreases in aggression. The long duration of exploration from a distance shows, first, that this behavior is not affected by benzodiazepine sedation and, second,

TABLE III. Median (Range) of Total Duration (in Seconds) of Behavioural Categories Displayed by Animals That Received Saline Solution + Saline Solution, Lorazepam (0.6 mg/kg) + Saline Solution, or Lorazepam (0.6 mg/kg) + Ro 15-1788 (1 mg/kg)[a]

	Saline solution + saline solution	Lorazepam + saline solution	Lorazepam + Ro 15-1788
Body care	28.65	19.25	17.5
	(3.3–58.7)	(0–57.9)	(0–46.7)
Digging	23.7	***3	8.2
	(0–71.5)	(0–21.4)	(0–239.9)
Nonsocial exploration	297.6	224.85	252.7
	(232.1–415)	(42–385)	(6.8–358.1)
Exploration from a distance	3.15	2.25	7.5
	(0–21.3)	(0–78)	(0–27.9)
Social investigation	22.6	15.5	40.9
	(1.7–106.3)	(0–53.5)	(0–201)
Threat	65.65	***31.35+	60.4
	(29.7–151)	(0–87.7)	(0–194.8)
Attack	130.6	*67.65+	115.8
	(56.8–240.7)	(0–195.3)	(0–387.8)
Avoidance/flee	0	**3.3++	0
	—	(0–33.3)	—
Defensive/submissive	0	0	0
	—	(0–90)	(0–0.4)
Immobility	0.4	***161.3+	*21
	(0.3–6.7)	(0–433.9)	(0–202)

[a]Differences between groups that received lorazepam (lorazepam + saline solution or lorazepam + Ro 15-1788) and control group:
*$P < .05$.
**$P < .01$.
***$P < .001$.
Differences between lorazepam + saline solution and lorazepam + Ro 15-1788 groups:
+$P < .05$.
++$P < .01$.

that it could be increased to compensate for the decreases found in nonsocial exploration and social investigation. The increment of total duration in body care with low doses of lorazepam (0.05 and 0.1 mg/kg) could be related to the rare disinhibitory action of benzodiazepines and, in some aspects, to the interaction between GABAergic and dopaminergic neurotransmission.

Interestingly, behavioral effects of 0.6 mg/kg of lorazepam were slightly different in the third experiment. Exploratory behaviors were unaffected by lorazepam, whereas there was an increment of defensive behaviors and an inhibition of threat and attack due to lorazepam treatment. The action on offensive behaviors, such as occurred in the first experiment, could be explained by lorazepam-induced sedation, as was shown by the dramatic increase in immobility, which is not completely antagonized by flumazenil. This fact could support the idea that the sedative effects of benzodiazepines could be modulated not only by benzodiazepine receptor ligands. As observed, controls of both experiments showed differences in exploratory and offensive behaviors, probably due to the stressing effect of handling and injections because there were two injections within a short interval. This stressing effect could also explain the increases in avoidance and nonsocial exploration. These previously mentioned differences could be responsible for the varying action of lorazepam administered at the same dose and with the same method. Weerts et al. [1992] found that mice selectively bred depending on aggression levels criteria had a different response to benzodiazepine treatment, which means a different response to the GABA-dependent chloride uptake. High doses of chlordiazepoxide (17 and 30 mg/kg) in aggressive mice decreased motor behavior and in low-aggressive mice increased social behavior and reduced aggression. Furthermore, the GABA-dependent chloride uptake was affected differently, augmented in low-aggressive mice and decreased in high-aggressive mice. Other studies have showed that the proaggressive effects of benzodiazepines have been observed in animals with previous fighting experiences [Ferrari et al., 1997; Palanza et al., 1996; Parmigiani et al., 1998]. In the present study, controls in the third experiment spent more time in social investigation and less in attack categories than controls of the first experiment.

Our most remarkable findings are that flumazenil was successful in completely antagonizing the behavior modulated by lorazepam (immobility, attack, threat, and digging) at 0.6 mg/kg dose and that some (potentially emotion-related) behaviors (social investigation, threat, and attack) may be disinhibited at low doses of lorazepam.

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