Psychopharmacology (2001) 157:131–141
DOI 10.1007/s002130100778

ORIGINAL INVESTIGATION

Rosa M. M. de Almeida · Ella M. Nikulina
Sara Faccidomo · Eric W. Fish · Klaus A. Miczek

Zolmitriptan – a 5-$HT_{1B/D}$ agonist, alcohol, and aggression in mice

Received: 23 August 2000 / Accepted: 14 March 2001 / Published online: 21 June 2001

Abstract *Rationale*: Zolmitriptan is an anti-migraine agent with action at 5-$HT_{1B/D}$ receptors. It penetrates into the central nervous system and, like other 5-$HT_{1B/D}$ agonists, its pharmacotherapeutic profile may include significant anti-aggressive effects. *Objectives*: To examine whether zolmitriptan has potential anti-aggressive effects by studying two kinds of aggressive behavior in mice – species-typical and aggression under the influence of alcohol. A second objective was to study whether pre- or post-synaptic receptors mediate these anti-aggressive effects. *Methods*: Initially, the anti-aggressive effects of zolmitriptan were studied in male CFW mice during 5-min resident–intruder confrontations. To confirm the 5-HT_{1B} receptor as a critical site of action for the anti-aggressive effects, the zolmitriptan dose–effect determinations were repeated after pretreatment with GR 127935 (10 mg/kg, i.p.). In further experiments, mice were treated concurrently with alcohol (1.0 g/kg, p.o.) and zolmitriptan (1–30 mg/kg, i.p.) in order to compare the effects of this agonist on species-typical and alcohol-heightened aggression. Finally, mice were infused with the neurotoxin 5,7-DHT (10 µg) into the raphé area to eliminate somatodendritic and presynaptic autoreceptors. The anti-aggressive effects of zolmitriptan (17 mg/kg, i.p.) or CP-94,253 (10 mg/kg, i.p.) were assessed 10 days after the lesion, and levels of 5-HT and 5-HIAA were measured in the hippocampus and prefrontal cortex. *Results*: Zolmitriptan exerted behaviorally specific anti-aggressive effects. The reduction in aggression was antagonized by GR 127935, indicated by a rightward shift in the dose–effect curves of zolmitriptan, showing the specificity for the 5-HT_{1B} receptors. Zolmitriptan also decreased alcohol-heightened aggression with equal efficacy. The anti-aggressive effects of CP-94,253 and zolmitriptan remained unaltered by 5,7-DHT lesions that depleted cortical and hippocampal 5-HT by 60–80%. *Conclusions*: Zolmitriptan proved to be an effective and behaviorally specific anti-aggressive agent in situations that engender moderate and alcohol-heightened levels of aggression. These effects are potentially due to activation of post-synaptic 5-$HT_{1B/D}$ receptors.

Keywords Alcohol · 5-HT receptor · Aggression · Zolmitriptan · CP-94,253 · 5,7 DHT · Social behavior · Serotonin · Raphé nuclei · Hippocampus · Frontal cortex

R.M.M. de Almeida · E.M. Nikulina · S. Faccidomo · E.W. Fish
K.A. Miczek (✉)
Department of Psychology, Bacon Hall,
Tufts University, 530 Boston Ave., Medford,
MA 02155, USA
e-mail: kmiczek@emerald.tufts.edu
Tel.: +1-617-6273414, Fax: +1-617-6273939

E.M. Nikulina · K.A. Miczek
Department of Psychiatry, New England Medical Center,
Boston, Massachusetts, USA

Introduction

Clinical and pre-clinical evidence has consistently pointed to brain serotonin (5-hydroxytryptamine, 5-HT) as a critical component in the neurobiological mechanisms for aggressive behavior. Across multiple species, levels of tryptophan in blood and 5-hydroxyindolacetic acid (5-HIAA) in cerebrospinal fluid (CSF) are often inversely correlated with the propensity to be violent and to engage in impulsive behavior (Valzelli and Garattini 1968; Virkkunen 1979; Linnoila et al. 1983, 1989; Virkkunen et al. 1994; Cleare and Bond 1995; Higley et al. 1996; Higley and Bennett 1999). Selective 5-HT agonists reduce aggression in animals, suggesting that these agents may have therapeutic potential for managing violent offenders (Olivier et al. 1989; Mos et al. 1993; Sanchez et al. 1993; Miczek et al. 1998a; Fish et al. 1999; for review see Schreiber and DeVry 1993; Miczek et al. 1995).

Among the 5-HT receptor subtypes that have been identified through molecular cloning techniques, the 5-HT_{1B} receptors appear to be particularly relevant to aggressive behavior, as agonists at this site reduce aggression without impairing locomotor behavior in mice and rats (Olivier et al. 1989; Sijbesma et al. 1991; Sanchez et

al. 1996; Fish et al. 1999; Sekinda et al. 1999). The selective 5-HT_{1B} receptor agonist, CP-94,253, has also been shown to be capable of reducing very high levels of aggressive behavior, levels in excess of species-typical norms (Fish et al. 1999). Furthermore, anpirtoline, another piperidine derivative with 5-HT_{1B} agonist effects, decreases intense aggression without compromising motor functions (Miczek and de Almeida 2001).

The triptans are a family of 5-HT_{1B} receptor agonists that have been used clinically for the treatment of migraine (Goadsby 1998). While many of these agonists exert primary actions on vascular receptors, zolmitriptan penetrates into the central nervous system more easily than other triptans due to its lipophilic properties (Proietti-Cecchini et al. 1997; Hargreaves and Shepheard 1999). Centrally mediated effects of zolmitriptan on growth hormone levels have been seen in patients with obsessive compulsive disorder (Whale et al. 1999), but the behavioral effects of zolmitriptan in laboratory animals have not been systematically studied. Given the current clinical use of zolmitriptan, it is important to determine other potential applications. One objective of the present study was to examine the effects of zolmitriptan on aggressive behavior in male mice. To more thoroughly characterize the efficacy of zolmiptriptan, two kinds of aggressive behavior were studied – species-typical aggression and heightened aggression under the influence of alcohol.

The effects of alcohol on aggression are largely dependent on the amount of alcohol and the individual's behavioral history and vulnerability. Large amounts of alcohol are sedative and decrease aggression (Krsiak and Borgesova 1973; Lagerspetz and Ekqvist 1978; Smoothy et al. 1982). However, low to moderate amounts of alcohol can engender very large increases in aggressive behavior, but only in certain vulnerable individuals (van Erp and Miczek 1997; Miczek et al. 1998b). In outbred rats and mice, a subgroup of about 25% consistently becomes very aggressive while under the influence of alcohol; these animals are referred to as AHA (alcohol-heightened aggressors) (Miczek et al. 1992, 1998b; van Erp and Miczek 1997). Most mice and rats, however, do not consistently become more aggressive after alcohol; these individuals are referred to as ANA (alcohol-non-heightened aggressors). Alcohol-heightened aggression has been shown to be more sensitive to the anti-aggressive effects of the 5-HT_{1B} agonist CP-94,253 than alcohol-non-heightened aggression (Fish et al. 1999). The demonstration that zolmitriptan reduces aggression after alcohol would strengthen the clinical potential of this compound because most acts of aggression and violence in humans are related to alcohol use (Miczek et al. 1994; Roizen 1996). If zolmitriptan is effective in those mice that are highly aggressive after alcohol, it would support the hypothesis that 5-HT_{1B} receptors are of significance, presumably indirectly, in the aggression-heightening effects of alcohol (Fish et al. 1999).

The mouse and rat 5-HT_{1B} receptors are functionally homologous to the human 5- HT_{1B} receptor, differing by a single amino acid (Adham et al. 1992; Oksenberg et al. 1992; Price et al. 1996; Schlicker et al. 1997). The receptors are coupled to $G_{i/o}$ proteins and are located both pre- and post-synaptically in the basal ganglia, striatum, and frontal cortex, as well as in the raphé nuclei (Boschert et al. 1994; Davidson and Stamford 1995). Activation of pre-synaptic 5-HT_{1B} receptors decreases extracellular concentrations of 5-HT in the cortex, ventral hippocampus, striatum, and hypothalamus (Roberts et al. 1997; Knobelman et al. 2000).

Evidence from studies with the 5-$HT_{1B/D}$ receptor antagonist GR 127935 points to the 5-HT_{1B} receptor as the relevant site of action for reversing anti-aggressive, antidepressant, locomotor stimulating and anxiolytic-like effects, as well as the effects on dopamine and serotonin neurotransmission by agonists acting at the 5-HT_{1B} receptor in rodents (Miczek and Barry 1977; Bell et al. 1995; O'Neill et al. 1996, 1997; Parsons et al. 1998; Fish et al. 1999, 2000; Fletcher and Korth 1999; Sarhan et al. 1999; Knobelman et al. 2000). However, the precise pool of 5-HT_{1B} receptors that is critical for the specific behavioral and physiological effects of these agonist drugs remains unknown. Some evidence with mixed 5-HT_{1B} agonists points to post-synaptic receptors as mediating the anorectic, anti-aggressive, and locomotor-stimulating effects (Kennett et al. 1987; Oberlander et al. 1987; Fernandez-Guasti and Escalante 1991; Sijbesma et al. 1991). To address whether the effects of zolmitriptan and CP-94,253 are preferentially mediated by pre- or post-synaptic receptors, the median effective doses of these drugs were studied in mice after degeneration of 5-HT-containing neurons via injection of 5,7-DHT into the raphé nuclei. If the efficacy of zolmitriptan or CP-94,253 were diminished after the neurochemical lesion, it would indicate that pre-synaptic receptors are involved in the anti-aggressive effects of these drugs.

Methods

Subjects

Adult male CFW mice (Charles River Laboratories, Wilmington, Mass.), weighing approximately 25 g on arrival, were housed in clear polycarbonate cages (28×17×14 cm) with wood-chip bedding and wire lids through which Purina rodent chow and water were freely available. Mice (n=50) were housed as "residents" with females of the same strain. Each cage contained a male and female pair. Additional male CFW mice (n=100) were housed in groups of ten and served as "intruder" mice. The mice acclimated to the laboratory for 3–5 weeks before behavioral testing. All mice were housed in a controlled vivarium maintained at 22±1°C with 30–40% humidity on a 12-h:12-h photocycle. All procedures followed the Guide for the Care and Use of Laboratory Animals (National Research Council 1996) and were approved by the Animal Care and Use Committee at Tufts University.

Apparatus and measurements

The behavior of the mice was recorded via a low-lux video camera and a standard video cassette recorder. Salient aggressive and non-aggressive behaviors were scored by a trained observer using the

custom-designed data acquisition system similar to that in previously described methods (Miczek 1982). The behavioral acts comprised the following aggressive elements: anogenital contact with the intruder, pursuit, sideways threat, bite, and tail rattle, as well as the following non-aggressive elements: grooming, walking, and rearing. Intra-observer reliability for encoding these behaviors was calculated using the Spearman correlation coefficient and ranged from 0.85 for the duration of walking to 0.98 for the frequency of attack bites.

Drugs

Zolmitriptan [(*S*)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]-methyl]-2-oxazolidinone); AstraZeneca Pharmaceuticals Limited, London, England] and GR 127935 [*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2-methyl-4'-(methyl-1,2,4-oxadiozol-3-yl)-[1,1-biphenyl]-4-carboxamide; Glaxo Research and Development Ltd., London, England] were suspended with the aid of sonication in 20% and 10% BCD (hydroxypropyl-betacyclodextrin), respectively. CP-94,253 [(3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypirolo[3,2-b]pyridine); Charles Pfizer, Groton, CT] was dissolved with the aid of sonication in a vehicle of 5% Tween 80, 5% DMSO (dimethyl sulfoxide), and 90% distilled water. Zolmitriptan, CP-94,253, and GR 127935 were administered i.p. in a volume of 1 ml/100 g body weight. 5,7-Dihydroxytryptamine creatinine sulfate [3-(2-aminoethyl)-1H-indole-5,7-diol creatinine sulfate; Research Biochemicals International, Natick, Mass.] was dissolved in 0.9% physiological saline with 0.1% ascorbic acid and injected locally into the raphé area (for injection parameters see below). The alcohol solution was prepared by diluting 100% alcohol (AAPER Alcohol CO., Shelbyvile, Ky.) to 10.0% (w/v) with distilled water and was administered orally in a volume of 1 ml/100 g body weight. For anesthesia, Avertin (2–2-2 tribromoethanol; Sigma-Aldrich, St. Louis, Mo.) was dissolved in tert-amyl alcohol and diluted with saline to 40 mg/ml and administered i.p. in a volume of 1 ml/100 g body weight.

Experimental procedures

Resident–intruder confrontations

The first phase ensured that all mice achieved stable levels of aggression toward an intruder (Miczek and O'Donnell 1978). After the females and pups were removed from the home cage, an intruder mouse was introduced. Tests lasted for 5 min after the first attack bite or for 5 min if the mouse did not bite. By the tenth confrontation, the frequency of attack bites stabilized around a baseline level of aggression of about 25 attack bites. For the next 2–4 tests, the residents were habituated to either an i.p. or a p.o. injection, depending on the specific experiment. During all aggression experiments, the mice were tested twice a week, with a minimum of 72 h between each test session. All encounters were conducted between 0900 hours and 1300 hours, and the behaviors were analyzed at a later date. New intruders were introduced after approximately ten confrontations. Vehicle trials were repeated if the frequency of attack bites was lower than ten or less than 20% of baseline.

Zolmitriptan dose–effect and antagonism by GR 127935

Eighteen mice were used to determine the effects of zolmitriptan (3–30 mg/kg) on aggressive behavior. Different doses of zolmitriptan were administered in a counterbalanced sequence 15 min before the confrontation with the intruder. Each drug test alternated with a vehicle test. Fifteen mice were used to determine the effect of pre-treatment with GR 127935 (10.0 mg/kg) on the dose–effect curve for zolmitriptan (10–56.0 mg/kg). GR 127935 was administered 30 min prior to zolmitriptan, and all tests occurred 15 min after the administration of zolmitriptan.

Effects of zolmitriptan and alcohol on aggression

A separate group of mice (n=32) was used to determine whether zolmitriptan could also reduce the high levels of aggression that can occur after the administration of a moderate dose of alcohol (i.e., 1.0 g/kg). This dose of alcohol was selected because previous experiments showed that it was the most effective in increasing aggression toward an intruder in the largest number of mice (Miczek et al. 1993, 1998b). To distinguish mice that consistently showed large increases in aggressive behavior from those that did not, the effects of 1.0 g/kg alcohol were determined four times and compared with the interspersed four vehicle control tests. If the average number of attack bites after alcohol exceeded the vehicle baseline by at least 2 SD, based on a statistical outlier criterion (Barnett and Lewis 1984), then the mouse was considered an AHA. All other mice were considered ANA. Following categorization of AHA and ANA mice, zolmitriptan (3–17 mg/kg) was administered to these mice immediately following an injection with alcohol (1.0 g/kg). The doses of 1.0 mg/kg and 30.0 mg/kg zolmitriptan were administered to subgroups of mice (n=14 and n=18, respectively). The remaining doses of zolmitriptan were administered in a counterbalanced sequence and each drug test was altered with a vehicle test. Aggression tests occurred 15 min after administration of both drugs.

Lesion with 5,7 DHT

Surgery. Mice from the previous studies were randomly assigned to the 5,7-DHT lesion subgroup (n=13) and to the vehicle-treated subgroup (n=12). Desimipramine (20 mg/kg, i.p.) was administered 20 min before the neurotoxin injection to protect catecholaminergic neurons. After anesthesia, the mice were placed in a stereotaxic apparatus with a mouse frame adapter (David Kopf; Tujunga, Calif.). Freshly dissolved 5,7-DHT (10 µg in 2 µl sterile saline, containing 0.1% ascorbic acid) was infused into the dorsal raphé at the following coordinates: 4.48 mm posterior to bregma; 2.75 mm below the dura mater (Franklin and Paxinos 1997). The solution was delivered at a rate of 0.5 µl/min for 4 min, through a 30-G stainless-steel cannula connected to a microinfusion pump. Sham-operated, vehicle-injected mice were used for comparison in all experimental conditions. Four weeks later, parts of the frontal cortex and hippocampus were removed for later analysis of 5-HT and 5-hydroxyindolacetic acid (5-HIAA) as described below.

Aggression tests. Ten days after surgery, the anti-aggressive effects of zolmitriptan (17 mg/kg) and CP-94,253 (10 mg/kg) were tested. Zolmitriptan, CP-94,253, and their respective vehicles were administered in a counterbalanced sequence 15 min before an aggressive confrontation. Aggressive and non-aggressive behaviors were analyzed as described above.

Measurement of 5-HT and 5-HIAA. The mice were decapitated and their brains were removed from the skull on an ice-cooled block. Frontal cortex and hippocampus were dissected, and the samples were frozen in dry ice and stored at –70°C. For the assay, the tissue samples were weighed, 200 ml of homogenization solution [0.1 M phosphate buffer and 0.0001% ethylene diamine tetraacetic acid (EDTA)] was added, and then they were homogenized by sonication and centrifuged at 14,000 r.p.m. for 12 min. Supernatants were collected and the concentrations of 5-HT and 5-HIAA were measured using high-performance liquid chromatography (HPLC) with electrochemical detection. The HPLC mobile phase (0.1 M phosphate buffer, 5% acetonitrile, 0.0001% EDTA, pH 3.4) was pumped through a reverse-phase 4.6× 50.00-mm column (Rainin, Woburn, Mass.) at a flow rate of 0.8 ml/min. The amount of 5-HT and 5-HIAA was quantified from their respective peak heights on the chromatogram obtained from an internal standard of *N*-acetyl-5-hydroxytryptamine.

Data analysis

All data for the dose–effect and antagonism experiments were analyzed using a one-way repeated-measure analysis of variance (ANOVA) and, when appropriate, Dunnett's post-hoc tests were used with vehicle values as the common control. The effect of GR 127935 alone compared with vehicle was analyzed using a paired *t*-test. The ED_{50} value was defined as the dose of zolmitriptan that produced a 50% reduction in behavior relative to the baseline and was calculated using linear regression. Non-overlapping 95% confidence intervals were considered as statistically different. The data for the alcohol and zolmitriptan interaction study were also analyzed using a one-way repeated-measures ANOVA. However, when appropriate, Dunnett's post-hoc tests were run with average alcohol values as the common control. The magnitude of the effect of alcohol on aggressive behavior within and between AHA and ANA mice was analyzed using *t*-tests. The effects of 1 mg/kg and 30 mg/kg zolmitriptan with 1.0 g/kg ethanol were analyzed using a paired *t*-test, since these treatments were added in a subgroup of animals only. The behavioral data from the 5,7-DHT experiment were analyzed using a two-way repeated-measures ANOVA and, when appropriate, Student Newman-Keuls as a post-hoc test. The alpha level was set at 0.05. *T*-tests were used to compare sham and lesion levels of 5-HT and 5-HIAA in the frontal cortex and hippocampus. A Bonferroni adjustment corrected for multiple comparisons. The level for these comparisons was set at 0.0125.

Results

All "residents" engaged in stable levels of species-typical aggression throughout all phases of this study. On average, these mice attacked the intruders with short latencies (i.e., 1–10 s), high frequencies (approximately 25), and low inter-trial variability (<20%).

Zolmitriptan dose–effect and antagonism by GR 127935

Aggression

Zolmitriptan significantly decreased the frequency of attack bites ($F_{4,17}$=38.95, P<0.001) and sideways threats ($F_{4,17}$=14.17, P<0.001) at the 3.0–30.0 mg/kg doses, and tail rattles ($F_{4,17}$=5.96, P<0.001) at the doses of 5.6–17 mg/kg (Fig. 1 and Table 1). When administered alone, GR 127935 significantly decreased the frequency of pursuit (t_{14}=2.16, P<0.048) but did not affect other aggressive behaviors. When administered prior to zolmitriptan, GR 127935 produced a significant rightward shift in the bite frequency dose–effect curve of zolmitriptan (Fig. 1). The ED_{50} values and 95% confidence intervals (CI_{95}) for the effects of zolmitriptan on bite and threat frequency were 5.64 mg/kg (2.52, 9.05) and 11.2 mg/kg (4.56, 25.56). In the presence of GR 127935, the ED_{50} and CI_{95} values were 20.47 mg/kg (14.6, 26.97) and 22.02 mg/kg (15.26, 28.50) for GR 127935, respectively. In the presence of GR 127935 (10 mg/kg), 10.0–56.0 mg/kg zolmitriptan was necessary to decrease the frequency of attack bite ($F_{3,14}$=68.21, P<0.0001) and sideways threats ($F_{3,14}$=56.91, P<0.0001; Fig. 1; Table 1). The frequency of tail rattles ($F_{3,14}$=18.80, P<0.001) was significantly decreased at the doses of 30 mg/kg and 56 mg/kg, and the frequency of pursuit ($F_{3,14}$=3.66, P<0.02) was decreased at the dose of 56 mg/kg (Table 1).

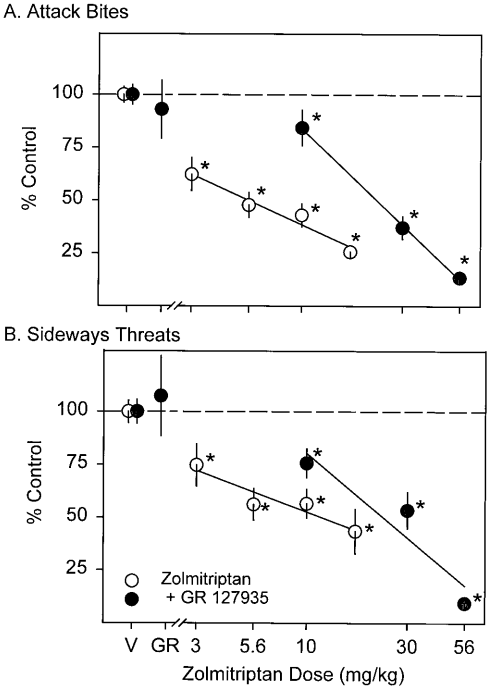

Fig. 1 **A** The effects of zolmitriptan on the frequency of attack bites. *Open symbols* represent data after administration of the agonist doses alone. *Filled symbols* represent the effects of agonist administration after pretreatment with 10 mg/kg GR 127935. Data are presented as percentage change from baseline levels (mean±SEM; *vertical lines*). A regression line is fitted to these data. *Asterisks* denote statistical significance compared with vehicle (P<0.05). **B** The effects of zolmitriptan on the frequency of sideways threats. *Open symbols* represent data after administration of the agonist doses alone. *Filled symbols* represent the effects of agonist administration after pretreatment with 10 mg/kg GR 127935. Data are presented as percentage change from baseline levels (mean±SEM; *vertical lines*). A regression line is fitted to these data points. *Asterisks* denote statistical significance compared with vehicle (P<0.05)

Locomotor behavior

The effects of zolmitriptan were specific to aggression as the durations of walking, rearing, and grooming were not significantly altered by these doses of zolmitriptan (Table 1). However, when administered after pre-treatment with GR 127935, the highest dose of zolmitriptan (56.0 mg/kg) decreased the duration of walking ($F_{3,14}$= 3.76, P=0.018; Table 1). GR 127935 alone did not affect any of the locomotor behaviors (Table 1).

Behavioral effects of alcohol

Twelve of thirty-two mice were determined to be AHAs, because the frequency of attack bites after alcohol exceeded the individual's vehicle baseline by 2 SD (Fig. 2).

Table 1 Effects of zolmitriptan and GR 127935 on aggressive and non-aggressive behaviors

Zolmitriptan dose (mg/kg)	Baseline	0	3.0	5.6	10.0	17.0	30.0	56.0
Aggressive behaviors								
Pursuit frequency								
Zolmitriptan	0.50±0.1		0.33±0.2	0.67±0.3	0.06±0.1	0.11±0.1		
+ GR 127935	0.76±.31	0.07±0.1			0.20±0.2		1.0±0.5	**0.0**
Threat frequency								
Zolmitriptan	29.4±1.5		**21.5±2.9**	**16.4±2.2**	**16.3±2.2**	**11.8±1.9**		
+ GR 127935	23.9±1.2	24.1±3.6			**17.6±1.7**		**11.6±1.4**	**2.6±0.7**
Bite frequency								
Zolmitriptan	25.9±1.0		**16.1±2.0**	**12.7±1.7**	**11.4±1.7**	**6.7±0.8**		
+ GR 127935	24.0±1.0	20.9±2.7			**19.5±1.8**		**8.6±1.3**	**3.1±0.7**
Tail rattle frequency								
Zolmitriptan	30.8±2.4		27.9±3.6	**20.4±2.7**	**18.7±2.9**	**19.2±3.1**		
+ GR 127935	28.8±1.9	29.9±4.5			27.5±4.1		**19.1±2.8**	**6.0±2.7**
Non-aggressive behaviors								
Groom duration								
Zolmitriptan	14.9±1.9		18.5±3.8	24.6±4.1	26.1±6.1	13.5±3.8		
+ GR 127935	10.9±1.8	12.2±4.0			9.1±1.6		12.9±3.4	5.3±2.1
Rear duration								
Zolmitriptan	46.0±4.9		44.1±6.0	49.7±6.9	43.6±6.9	30.9±4.9		
+ GR 127935	26.8±3.1	30.2±5.6			20.5±4.1		24.8±5.1	16.1±6.1
Walk duration								
Zolmitriptan	94.8±3.8		85.4±4.6	78.0±4.6	87.0±5.9	82.2±6.1		
+ GR 127935	84.5±4.3	74.9±5.1			77.9±5.8		79.9±5.9	**63.9±5.5**
Contact duration								
Zolmitriptan	3.53±1.8		3.0±2.0	1.9±0.9	4.9±1.7	3.7±2.1		
+ GR 127935	4.39±1.2	2.5±0.9			4.9±2.5		8.0±3.0	4.8±2.1

Data for each behavior are mean (±SEM). Values that are significantly different from baseline (avg. vehicle) are expressed in **boldface** (P<0.05)

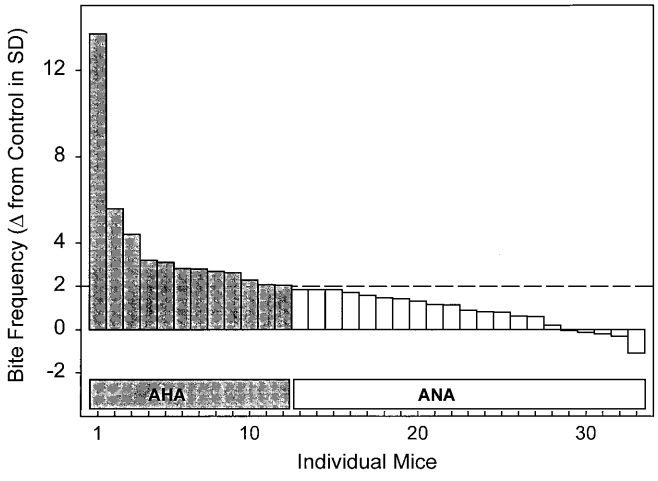

Fig. 2 Differences in the response to orally administered alcohol (1.0 g/kg) are indicated by the change in attack frequency of each individual mouse when compared with its vehicle control level. The *vertical bars* represent the change in attack frequency expressed as standard deviations from the average vehicle control level for each individual. If the number of attacks exceeded the individual's vehicle control by two standard deviations or more, then the mouse was considered to exhibit alcohol-heightened aggression (*AHA*); mice whose aggressive behavior did not meet this criterion were considered to be non-heightened (*ANA*)

The mice (n=20) that did not demonstrate this degree of enhanced aggression were termed ANA. While under the influence of alcohol, both the AHA and ANA mice demonstrated a significantly heightened level of attack bites (AHA t_{11}=9.39, P<0.001; ANA t_{19}=4.83, P<0.0001) and sideways threats (AHA t_{11}=7.72, P<0.001; ANA t_{19}=4.20, P<0.001; Fig. 3 and Table 2), although the increase was significantly larger in AHA than ANA mice (t_{30}=4.49, P<0.001; Fig. 3). In the AHA mice, alcohol increased the frequency of pursuit (t_{11}=2.42, P<0.034; Table 2) and the duration of walking (t_{11}=2.96, P<0.013; Table 2).

Effects of zolmitriptan and alcohol on aggression

The effects of zolmitriptan on measures of aggression after alcohol were similar between AHA and ANA mice. Administration of zolmitriptan dose dependently decreased alcohol-heightened aggression as indicated by the frequency of attack bites (AHA $F_{4,11}$=21.60, P<0.001; ANA $F_{4,19}$=26.80, P<0.001; Fig. 3) and sideways threats (AHA $F_{4,11}$=9.47, P<0.001; ANA $F_{4,19}$= 13.92, P<0.001) at the doses of 3–17 mg/kg. The fre-

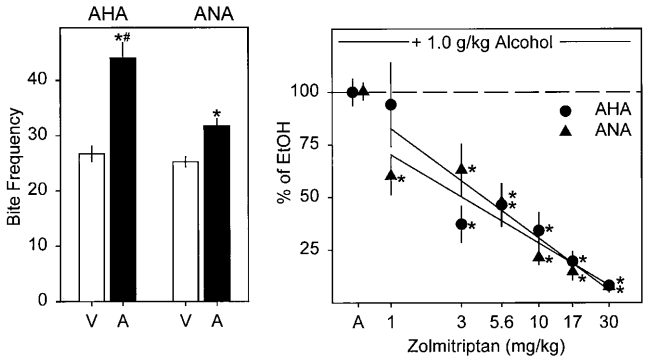

Fig. 3 *Left*: the aggressive behavior portrayed is the frequency of attack bites after administration of vehicle and alcohol in alcohol-heightened aggressor (*AHA*) and alcohol-non-heightened aggressor (*ANA*) mice. *V* average vehicle and *A* average alcohol. *Asterisks* indicate statistical significance compared with vehicle levels ($P<0.05$). #Statistical significance between AHA and ANA mice ($P<0.05$). *Right*; the effects of zolmitriptan on alcohol-heightened (*circles*) and alcohol non-heightened (*triangles*) aggression. Data are presented as percentage change from alcohol±SEM (*vertical lines*). Regression lines are shown, fitting to these data points. *Asterisks* indicate statistical significance compared with alcohol ($P<0.05$)

quency of tail rattles was decreased at 17 mg/kg zolmitriptan and the 10-mg/kg dose for the ANA mice (AHA $F_{4,11}=2.65$, $P<0.046$; ANA $F_{4,19}=8.10$, $P<0.001$). The frequency of attack bites (AHA $t_8=12.10$, $P<0.001$; ANA $t_8=18.12$, $P<0.001$), sideways threats (AHA $t_8=5.48$, $P<0.001$; ANA $t_8=7.01$, $P<.001$), and tail rattles (AHA $t_8=3.14$, $P<0.014$; ANA $t_8=4.64$, $P<0.002$) were significantly reduced after administration of 30.0 mg/kg zolmitriptan and alcohol. For the ANA mice, the 1.0-mg/kg dose of zolmitriptan reduced the frequency of attack bites ($t_{11}=3.68$, $P<0.004$) and sideways threats ($t_{11}=3.05$, $P<0.012$).

For the AHA mice, zolmitriptan significantly reduced the duration of walking ($F_{4,11}=3.52$, $P<0.014$; Table 2) at the 3-mg/kg and 17-mg/kg doses. In the ANA mice, zolmitriptan decreased the duration of rearing ($F_{4,19}=3.142$, $P<0.019$; Table 2) at the doses of 5.6–17 mg/kg. None of the other elements of motor behavior was affected by this treatment (Table 2).

5,7 DHT lesion

Lesioned mice had significantly less 5-HT and 5-HIAA in the frontal cortex ($t_{23}=5.83$, $P<0.001$ for 5-HT;

Table 2 Interaction between ethanol and zolmitriptan on aggressive (AHA) and non-aggressive (ANA) behaviors

Zolmitriptan dose(mg/kg) Alcohol dose(g/kg)	0.0 1.0	0.0 0.0	1.0 1.0	3.0 1.0	5.6 1.0	10.0 1.0	17.0 1.0	30.0 1.0
Aggressive behaviors								
Pursuit frequency								
AHA	2.88±.58	**2.02±.54**	0	0.17±.11	1.25±.76	3.83±2.0	0.83±.66	**0.67±.67**
ANA	1.11±.20	0.86±.14	0.36±0.2	0.65±0.2	1.00±.34	0.35±.22	0.30±.18	0
Threat frequency								
AHA	38.8±3.2	**24.6±2.0**	31.3±14.3	**12.8±3.6**	**22.0±4.8**	**16.8±5.1**	**9.33±2.8**	**14.2±3.3**
ANA	26.3±1.8	**20.6±1.3**	**15.5±3.0**	**16.3±3.7**	**17.6±2.9**	**8.55±1.9**	**5.25±1.9**	**8.00±2.7**
Bite frequency								
AHA	44.0±2.8	**26.7±1.4**	36.7±10.2	**16.6±3.7**	**20.7±4.7**	**14.5±3.5**	**8.33±2.1**	**3.67±1.1**
ANA	31.7±1.3	**25.3±0.9**	**18.8±3.0**	**19.3±3.7**	**14.7±2.3**	**6.95±1.2**	**4.60±1.3**	**2.56±0.9**
Tail rattle frequency								
AHA	37.3±6.0	32.8±4.8	96.7±40.6	29.6±9.6	32.9±12.1	22.6±4.5	**14.7±5.1**	**16.3±4.7**
ANA	48.4±5.6	46.5±5.3	54.2±9.9	38.8±8.8	36.3±6.9	**21.6±4.5**	**9.55±2.8**	**10.1±3.0**
Non-aggressive behaviors								
Groom duration								
AHA	14.9±2.9	13.9±2.0	19.9±10.5	17.7±7.2	10.0±3.3	6.84±2.0	22.1±6.3	17.4±4.9
ANA	13.3±2.0	11.0±1.7	11.8±2.5	11.5±2.8	10.0±4.7	4.61±1.6	10.0±2.6	21.4±6.9
Rear duration								
AHA	71.4±5.9	81.0±5.5	62.8±24.2	51.5±11.6	43.5±12.7	57.9±14.1	80.1±11.5	67.2±16.6
ANA	73.4±5.1	72.8±4.0	80.5±12.8	47.8±6.7	**45.8±11.2**	**40.4±7.6**	**40.8±8.4**	52.0±11.5
Walk duration								
AHA	75.8±2.7	**68.6±1.7**	62.7±9.9	**58.1±4.7**	64.6±3.1	64.4±5.4	**55.6±3.7**	71.3±5.9
ANA	59.5±3.8	57.5±3.5	68.0±6.8	58.7±4.5	68.0±4.6	57.5±5.8	63.5±3.6	68.5±6.2
Contact duration								
AHA	4.76±2.1	3.45±.86	2.55±1.7	10.5±6.4	12.0±5.3	10.3±3.5	11.0±5.3	14.7±8.9
ANA	8.32±1.3	9.07±1.8	17.8±5.6	14.6±3.7	13.6±3.3	20.0±6.6	23.5±6.0	11.9±3.7

Data for each behavior are mean (±SEM). Values that are significantly different from ethanol are expressed in **boldface** ($P<0.05$)

t_{23}=2.68, P<0.013 for 5-HIAA) and in the hippocampus (t_{23}=5.13, P<0.001 for 5-HT; t_{23}=6.22, P<0.001 for 5-HIAA) than vehicle-treated animals. The depletion of total 5-HT in these areas was approximately 60–80% (Table 3). None of the aggressive or non-aggressive behaviors was altered after the lesion (Table 4). However, administration of zolmitriptan (17 mg/kg) and CP-94,253 (10 mg/kg) significantly decreased the frequency of bites, sideways threats, and tail rattles in both groups (Fig. 4 and Table 4). There was no statistically significant interaction between the effect of lesion and drug treatment. In addition, there was no significant cor-

Table 3 Effect of 5,7-DHT on 5-HT and 5-HIAA in cortex and hippocampus

Treatment	Cortex		Hippocampus	
	5-HT	**5-HIAA**	**5-HT**	**5-HIAA**
Vehicle	0.54±0.05	0.13±0.02	1.11±0.15	0.70±0.06
5,7-DHT	**0.22±0.02**	**0.06±0.01**	**0.27±0.07**	**0.24±0.04**

Data are expressed as pmol/g tissue (mean±SEM). Significant values compared with sham are expressed in **boldface** (P<0.0125)

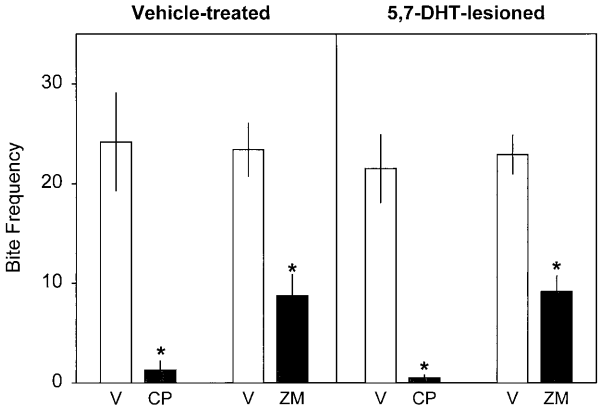

Fig. 4 The effects of zolmitriptan and CP-94,253 on the aggressive behavior of 5,7-DHT lesioned and vehicle-treated mice after surgery. *White vertical bars* represent vehicle trials and *gray vertical bars* represent trials of 17.0 mg/kg zolmitriptan (*ZM*) and 10.0 mg/kg CP-94,253 (*CP*), respectively. The aggressive behavior portrayed is the frequency of attack bites as means±SEM. *Asterisks* indicate statistical significance of drug treatment compared with respective vehicle (P<0.05)

Table 4 Effects of CP-94,253 and zolmitriptan on aggressive and non-aggressive behaviors in 5,7-DHT-lesioned and vehicle-treated mice

Dose (mg/kg)	Vehicle-treated			5,7-DHT-lesioned				
	V	10	17	V	10	17	F	*p*
Aggressive behaviors								
Pursuit frequency								
CP-94,253	0.6±0.5	0.0±0.0		0.5±0.3	0.0±0.0			
Zolmitriptan	0.4±0.2		1.4±0.6	0.7±0.3		0.4±0.2		
Threat frequency								
CP-94,253	28.7±5.5	**2.1±1.5**		21.8±3.8	**0.5±0.3**		41.73	<0.001
Zolmitriptan	20.2±3.2		**10.5±2.7**	17.8±2.0		**10.4±1.6**	124.65	<0.001
Bite frequency								
CP-94,253	24.2±4.9	**1.3±0.8**		21.5±3.4	**0.5±0.3**		50.43	<0.001
Zolmitriptan	23.4±2.6		**8.7±2.1**	22.9±1.9		**9.1±1.5**	22.17	<0.001
Tail rattle frequency								
CP-94,253	38.2±7.7	**3.3±2.1**		33.3±11.5	**1.5±1.3**		24.75	<0.001
Zolmitriptan	36.1±5.2		**23.7±4.7**	34.7±6.5		**17.6±4.1**	22.17	<0.001
Non-aggressive behaviors								
Groom duration								
CP-94,253	10.7±3.5	12.8±1.6		10.8±6.1	14.7±10.0			
Zolmitriptan	10.2±2.7		10.0±3.4	5.2±1.6		**17.0±6.7**	5.94	<0.023
Rear duration								
CP-94,253	86.3±25.5	41.8±14.7		79.5±15.2	17.0±3.9		15.97	<0.003
Zolmitriptan	82.2±17.2		63.4±9.0	68.6±10.0		43.8±8.5		
Walk duration								
CP-94,253	59.9±5.5	60.7±6.9		62.0±4.7	53.7±4.7			
Zolmitriptan	51.2±3.9		45.7±2.1	52.8±2.9		**42.4±3.7**	6.20	<0.02
Contact duration								
CP-94,253	13.9±6.3	34.4±15.4		14.3±9.0	14.5±1.7			
Zolmitriptan	16.4±9.8		15.3±8.5	11.7±3.4		16.9±8.9		

Data for each behavior are mean (±SEM). Values that are significantly different from drug vehicle are expressed in **boldface** (P<0.05)

relation between the degree of 5-HT depletion and the frequency of attack bites. Administration of CP-94,253 (10 mg/kg) significantly decreased the duration of rearing when compared with the sham group (Table 4). Administration of zolmitriptan (17 mg/kg) significantly increased the duration of grooming and decreased walking (Table 4).

Discussion

Aggression is effectively reduced by the administration of agonists with activity at 5-HT_{1B} receptors (Olivier et al. 1989; Sijbesma et al. 1991; Sanchez et al. 1993; Fish et al. 1999). The present studies extend these anti-aggressive effects to zolmitriptan, a 5-$HT_{1B/1D}$ receptor agonist used clinically to treat migraine. Zolmitriptan did not induce motor impairment or stimulation, indicating a high degree of behavioral specificity. Moreover, zolmitriptan's anti-aggressive effects are likely mediated by 5-$HT_{1B/1D}$ receptors, because the 5-$HT_{1B/1D}$ receptor antagonist GR 127935 blocked the effects of zolmitriptan. Destruction of the 5-HT-containing neurons in the raphé area did not alter the anti-aggressive effects of zolmitriptan, suggesting the involvement of post-synaptic receptors.

The remarkable degree of behavioral specificity observed after treatment with zolmitriptan appears to characterize other 5-HT_{1B} receptor agonists such as the arylpiperidines CP-94,253 and anpirtoline (Fish et al. 1999; Miczek and de Almeida 2001). These agents decrease the salient elements of murine aggressive behavior (i.e., sideways threats, attack bites, and tail rattles) without significant effects on non-aggressive motor behaviors including walking, rearing, and grooming. This lack of motor impairment distinguishes 5-HT_{1B} agonists from most 5-HT_{1A} agonists, such as 8-OH-DPAT and flesinoxan, and partial agonists such as buspirone, ipsapirone, and gepirone. These latter agents reduce aggression by inhibiting motor routines that are necessary to perform social behaviors (McMillen et al. 1988; Olivier et al. 1989, 1994; Mos et al. 1993; Sanchez et al. 1993; de Almeida and Lucion 1994, 1997; Miczek et al. 1998a). However, the recently developed 5-HT_{1A} receptor agonists alnespirone and S-15535 may have more specific anti-aggressive effects in rats (De Boer et al. 1999, 2000). Studies with 5-HT_{1A} and 5-HT_{1B} knockout mice also display a number of contrasting behavioral phenotypes (Saudou et al. 1994; Brunner et al. 1999; Zhuang et al. 1999).

At recombinant human 5-HT_1 receptors, zolmitriptan is one of the more selective agents, having a greater affinity for 5-HT_{1B} receptors than for 5-HT_{1A} receptors (pK_i=9.08 vs 6.93; Pauwels et al. 1997). Zolmitriptan also displays a high affinity for 5-HT_{1D} receptors (pK_i=9.66), but there is a relatively small number of 5-HT_{1D} binding sites in rodents (Bruinvels et al. 1993; Hoyer et al. 1994). So far, there is no evidence that implicates the 5-HT_{1D} receptors in the neurobiological control of aggression. This type of receptor has begun to be considered as a pharmacotherapeutic target in psychiatric and other disorders such as schizophrenia, anxiety, and depression (Fuller 1991; Chopin et al. 1994). Evidence for the 5-HT_{1B} receptor as the critical site of action for zolmitriptan derives from the fact that administration of GR 127935, an antagonist with high affinity (about 10 nM) for 5-$HT_{1B/D}$ receptors (Skingle et al. 1996), produced a rightward shift in the dose–effect curve for zolmitriptan. GR 127935 has also been shown to antagonize the effects of 5-HT_{1B} agonists on a variety of behavioral and physiological endpoints (O'Neill et al. 1996; Pauwels et al. 1997; Maurel et al. 1998; Parsons et al. 1998; Fish et al. 1999, 2000; Fletcher and Korth 1999; Harrison et al. 1999; Knobelman et al. 2000). In the present experiment and other pilot experiments, when administered alone and across a range of doses, GR 127935 had no effect on aggressive or locomotor behaviors in adult mice or ultrasonic vocalizations in mouse pups, suggesting that GR 127935 is not acting as a partial agonist (Miczek et al. unpublished data, Fish et al. 1999, 2000).

Evidence suggests that 5-HT_{1B} receptors are involved in many of the effects of alcohol. Administration of 5-HT_{1B} receptor agonists decreases alcohol intake (Maurel et al. 1999; Tomkins and O'Neill 2000) and can substitute for the discriminative stimulus effects of alcohol (Grant et al. 1997; Maurel et al. 1998). Mice lacking the 5-HT_{1B} receptor gene consume more alcohol than wild-type mice and are more sensitive to some of the ataxic effects of alcohol (Crabbe et al. 1996; Boehm et al. 2000; but see Crabbe et al. 1999b; Bouwknecht et al. 2000). Using quantitative trait loci analysis in BXD recombinant inbred mice, the 5-HT_{1B} receptor gene has been identified as a potential candidate gene for alcohol preference (Crabbe et al. 1999a). Polymorphisms in the 5-HT_{1B} receptor gene have also been linked to antisocial personality and alcoholism in humans (Lappalainen et al. 1998; but see Huang et al. 1999). Additionally, the 5-HT_{1B} receptor agonist CP-94,253 decreases the aggression-heightening effects of alcohol at doses lower than those necessary to reduce species-typical aggression (Fish et al. 1999). Unlike CP-94,253, zolmitriptan did not differentially affect alcohol-heightened aggression. Although both compounds act primarily at 5-HT_{1B} receptors, it is possible that activity at other receptor subtypes may account for this differential pattern of effects.

The selective anti-aggressive effects of 5-HT_{1B} receptor agonists have consistently been shown, but evidence on whether this occurs via pre- or postsynaptic receptor mechanisms is conflicting. Support for presynaptic sites of action primarily derives from studies demonstrating that 5-HT_{1B} receptor agonists reduce 5-HT release (Roberts et al. 1997; Knobelman et al. 2000). However, post-synaptic sites of action have been implicated by the observations that 5,7-DHT lesions of the raphé nuclei or para-chlorophenylalanine (PCPA) synthesis inhibition did not alter the anti-aggressive effects of eltoprazine, the anorectic effects of RU 24969, or the inhibitory ef-

fects of *N*-(3-trifluoromethylphenyl)piperazine (TFMPP) on sexual behavior (Kennett et al. 1987; Fernandez-Guasti and Escalante 1991; Sijbesma et al. 1991).

Neurotoxic destruction of the 5-HT neurons by 5,7-DHT often reduces aggression in mice and rats (Pöschlova et al. 1976; File and Deakin 1980; Matte 1982; Sijbesma et al. 1991; Johansson et al. 1999). In the present study, the baseline levels of aggression were not affected by the 5,7-DHT lesion, possibly due to the animals' extensive experience with aggressive behavior prior to the lesion. After lesions of the presynaptic and somatodentric receptors with 5,7-DHT, zolmitriptan and CP-94,253 were still capable of decreasing aggressive behavior. This observation suggests that the anti-aggressive effects of zolmitriptan and CP-94,253 do not require the integrity of the 5-HT neurons. The present neurotoxic lesions in mice spared approximately 20–40% of the ascending 5-HT neurons, and the contribution of pre-synaptic sites to the anti-aggressive effects cannot be eliminated completely. Furthermore, the present 2-µl infusions of 5,7-DHT caused an anatomically widespread degeneration of 5-HT neurons that receive innervation from the dorsal or median raphé nuclei. It is also possible that the 5,7-DHT depletion alters the sensitivity of post-synaptic 5-HT_{1B} receptors, and this may compensate for the reduced pre-synaptic actions of zolmitriptan and CP-94,253. Studies with 5,7-DHT have shown alterations in the sensitivity of the 5-HT_{1A} and 5-HT_{1B} receptors after the neurotoxic lesion (Oberlander et al. 1987; Sijbesma et al. 1991; Dugar and Lakoski 1997; Van de Kar et al. 1998). Receptor upregulation is one hypothesis for increased sensitivity following 5,7-DHT lesions (Weissmann et al. 1986; Oberlander et al. 1987; Sijbesma et al. 1991; Frankfurt et al. 1993, 1994; Manrique et al. 1994), although other changes, such as in signal transduction pathways, are also probable mechanisms. In addition to the currently used doses, studies with further doses of CP-94,253 provided no evidence for a possible leftward shift in dose–effect curves (Nikulina, unpublished observations), as otherwise suggested by studies with the mixed 5-$HT_{1A/1B}$ agonist eltoprazine (Sijbesma et al. 1991).

Given the evolutionary diversity of aggressive behavior and 5-HT receptor subtypes, it will be important to investigate the effects of 5-HT_{1B} receptor agonists in different types of aggression and in primates. Another important experiment is to evaluate the role of pre- and post-synaptic 5-HT_{1B} receptors via microinjection of selective agonists and antagonists into putative sites of action such as the dorsal raphé, pre-frontal cortex, hippocampus, and ventral tegmental area. Studies with the mixed 5-$HT_{1A/1B}$ agonist eltoprazine suggest that the postsynaptic 5-HT_{1B} receptor modulates offensive aggression in male rats (Mos et al. 1992, 1993). If the anti-aggressive effects of zolmitriptan and CP-94,253 are indeed due to action at post-synaptic receptors, then identifying the interactions with other neurotransmitter systems, possibly γ-aminobutyric acid (GABA) and dopamine, could determine the mechanisms through which 5-HT_{1B} receptor agonists specifically decrease aggressive behaviors. Since the $GABA_A$ receptor represents a site through which alcohol heightens aggression (Weerts et al. 1993; Fish et al. 2001), the serotonergic modulation of GABA activity may be particularly critical.

Acknowledgements This research was supported by U.S.P.H.S. research grants AA05122 and DA02632 (KAM, PI), a grant from the Alcoholic Beverage Medical Research Foundation, and CAPES (Brazil) and UNISINOS (Brazil) grants (RMMdeA). The authors would like to thank Mr. J Thomas Sopko for his exceptional technical assistance.

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