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ORIGINAL INVESTIGATION

Social instigation and aggressive behavior in mice: role of 5-HT_{1A} and 5-HT_{1B} receptors in the prefrontal cortex

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Abstract
Rationale Social instigation is used in rodents to induce high levels of aggression, a pattern of behavior with certain parallels to that of violent individuals. This procedure consists of a brief exposure to a provocative stimulus male, before direct confrontation with an intruder. Studies using 5-HT_{1A} and 5-HT_{1B} receptor agonists show an effective reduction in aggressive behavior. An important site of action for these drugs is the ventral orbitofrontal cortex (VO PFC), an area of the brain which is particularly relevant in the inhibitory control of aggressive and impulsive behavior.
Objectives The objectives of the study are to assess the anti-aggressive effects of 5-HT_{1A} and 5-HT_{1B} agonist receptors [8-hydroxy-2-(di-*n*-propylamino) tetralin hydrobromide (8-OH-DPAT) and CP-93,129] in the VO PFC of socially provoked male mice. To confirm the specificity of the receptor, 5-HT_{1A} and 5-HT_{1B} antagonist receptors (WAY-100,635 and SB-224,289) were microinjected into the same area, in order to reverse the agonist effects.
Results 8-OH-DPAT (0.56 and 1.0 μg) reduced the frequency of attack bites. The lowest dose of CP-93,129 (0.1 μg) also decreased the number of attack bites and lateral threats. 5-HT1A and 5-HT1B receptor agonists differed in their effects on non-aggressive activities, the former decreasing rearing and grooming, and the latter, increasing these acts. Specific participation of the 1A and 1B receptors was verified by reversal of anti-aggressive effects using selective antagonists WAY-100,635 (10.0 μg) and SB-224,289 (1.0 μg).
Conclusions The decrease in aggressiveness observed with microinjections of 5-HT_{1A} and 5-HT_{1B} receptor agonists into the VO PFC of socially provoked mice, supports the hypothesis that activation of these receptors modulates high levels of aggression in a behaviorally specific manner.

Keywords Aggression · Social instigation · Serotonin · 5-HT_{1A} receptor · 5-HT_{1B} receptor · Prefrontal cortex

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Introduction

Aggression can be a biologically adaptive behavior, important in acquiring resources, maintaining dominance, and establishing social hierarchy (Miczek et al. 2002). However, in human and veterinary clinics, aggression can be a significant problem because escalated aggression may result in serious damage to others. This situation is aggravated by the fact that there are no selective pharmacological treatment options (Volavka 1995).

Under specific conditions, laboratory animals can exhibit high levels of aggression, a pattern of behavior with certain aspects that are similar to those of violent individuals (Fish et al. 1999; de Boer and Koolhaas 2005). Social instigation is one of the procedures used in rodents to increase aggressive behavior. It consists of exposing the resident animal to a rival that can be seen, heard, and smelled, but it is protected by a screen and cannot be expelled from the home cage of the resident (Potegal 1991; De Almeida et al. 2005). Hamsters, mice, and rats start attacks with a very short latency and high frequency after social instigation (Potegal 1991; Fish et al. 1999; De Almeida and Miczek 2002).

Pharmacological agents that act on 5-HT_{1A} and 5-HT_{1B} receptors may induce a more pronounced reduction in aggressive behavior than the current treatments with antipsychotic medications, β-adrenergic blockers, and selective serotonin reuptake inhibitors (Volavka 1995; Fish et al. 1999; Caldwell and Miczek 2008). Selective 5-HT_{1A} receptor agonists such 8-hydroxy-2-(di-*n*-propylamino) tetralin hydrobromide (8-OH-DPAT), alnespirone, S-15535 (Joppa et al. 1997; De Boer et al. 2000; De Boer and Koolhaas 2005), and some specific 5-HT_{1B} receptor agonists such as CP-93,129, CP-94,253, and anpirtoline (Fish et al. 1999; Veiga et al. 2007) have efficacious anti-aggressive activity, both on species—typical and in escalated aggression. The role of these receptors in aggressive behavior was convincingly confirmed with selective 5-HT_{1A} receptor antagonist WAY-100,635 and 5-$HT_{1D/B}$ receptor antagonist GR-127935, which effectively blocked the anti-aggressive effects of the agonists (Lopez-Mendoza et al. 1998; Miczek et al. 1998b; Fish et al. 1999; De Boer et al. 1999; 2000; De Almeida et al. 2001). However, it is important to note that 5-HT_{1A} and 5-HT_{1B} agonists have been shown to exert contrasting effects on drug taking, sexual behavior, and food intake (Simansky and Vaidya 1990; Crabbe et al. 1996; Parsons et al. 1998; Larsson and Ahlenius 1999).

The prefrontal cortex is a brain region that contains a moderate density of 5-HT_{1A} and 5-HT_{1B} receptors, and it has been identified as particularly important in the inhibitory control of the subcortical circuit mediating aggressive and impulsive behavior (De Almeida et al. 2005; Blair 2004). Patients with orbital and medial prefrontal cortex lesions exhibit impulsive and aggressive behavior, showing lack of control and unawareness of the implications of their actions (Grafman et al. 1996; Anderson et al. 1999; Davidson et al. 2000). Thus, impulsive aggression may be related to a dysfunction of inhibitory projections from the orbital/medial prefrontal cortex to the amygdala, which can result from a neurochemical abnormality that may involve serotonin (Davidson et al. 2000; Best et al. 2002).

The current study aims to verify whether 5-HT_{1A} and 5-HT_{1B} agonists microinjected specifically into ventral orbitofrontal cortex may reduce the escalated aggressive behavior in socially provoked mice. Besides, the study intends to confirm the specificity of the receptor involved in the modulation of the aggressive behavior with the microinjection of selective 5-HT_{1A} and 5-HT_{1B} antagonist receptors (WAY-100,635 and SB-224,289, respectively) into the same brain area.

Materials and method

Animals

Subjects were adult male mice CF1, *Mus musculus*, (acquired from FEEPS, Porto Alegre, RS, Brazil), weighing from 40 to 50 g. The mice were cared for in accordance with the guidelines of the National Institute of Health (NIH) and Colégio Brasileiro de Experimentação Animal (COBEA). Firstly, the animals were divided into "residents" (n=110), "intruders" (n=110), and "instigators" (n=50). Each resident was housed in clear polycarbonate cages (28×17×14 cm) with a female (n=110) from the same strain. Intruders and instigators were maintained in groups of ten, in standard polycarbonate boxes (46×24×15 cm). All mice were in the same room under 12:12 h light/dark cycle (lights on at 06:00 hours), in a temperature-controlled environment (20±2°C) with food and water available ad libitum. The animals were tested during the light phase of the photo cycle from 09:00 to 16:00 hours.

Resident–intruder confrontations

Resident males were allowed to acclimate for 21 days with their female cagemate in the laboratory environment. After this period, each resident was submitted to successive confrontations with a male intruder (three times a week with intervals of at least 24 h) to establish the baseline of aggressive behavior. In these tests, female and pups were removed and a male intruder was placed into the home cage of residents. Each behavioral test lasted 5 min, and if no attack bite occurred, the experimental session was terminated at 5 min (Miczek and O'Donnell 1978). Only the animals that delivered more than ten bites, were included in the experiment. If the resident was attacked, the intruder was substituted immediately. According to Winslow and Miczek (1984) during the first confrontations the levels of aggression from the resident mice were more variable than after some tests (usually six or seven confrontations with the same intruder).

Social instigation

Once aggressive behavior towards the intruder was reliably displayed at stable levels, the first social instigation was

performed. This procedure consisted of removing the female and pups and placing a clear perforated cylinder (18×6 cm) containing an instigator in the center of resident's cage for 5 min (Fish et al. 1999), followed by an interval of additional 5 min. At the end of this period, a male intruder was inserted in the resident's box, without any protection, allowing direct contact between the two animals. Each behavioral test lasted 5 min and was videotaped.

Surgery

The next day, each resident mouse was anesthetized with ketamine and xylazine (100 and 10 mg/kg body weight intramuscularly, respectively), placed in a stereotaxic frame and implanted with a 26-gauge guide cannula (Plastics One, USA). The cannula was aimed at the ventral orbitofrontal cortex (VO PFC) in the left hemisphere using the following coordinates: 2.3 mm anterior to bregma, 0.6 mm lateral to the mid-sagittal line, and 1.0 mm below the dura mater, based on Paxinos and Franklin (1997). After surgery, an obdurator (33-gauge; Plastics One, USA) was inserted to prevent cannula blockage, and the animals were properly warmed until recovery from the surgery.

Microinjections and behavioral analysis

After 72 h of recovery from surgery, microinjections of 5-HT_{1A} and 5-HT_{1B} agonists and antagonists or vehicle were accomplished. For the microinjections, the obdurator was removed and a 33-gauge injector (Plastics One, USA) was inserted through the guide cannula. The injector was 1.0 mm longer than the guide cannula, allowing for the introduction of the drug 2 mm below the dura mater, into the target area. Solutions were slowly infused for a period of 2 min, using the injector connected via a polyethylene tube (P20) to a Hamilton syringe fitted into a pump (WPI-Sp 210 iv syringe pump, model 210, USA). The injector was left in situ for 30 additional seconds after microinjection, allowing the complete diffusion of the solution and preventing backflow.

8-OH-DPAT or CP-93,129 in different doses (0.1, 0.56, and 1.0 μg/0.2 μl) or vehicle (saline solution 0.9%) was administered 15 min before the behavioral tests. Likewise, for a 5-min period, a protected instigator was placed in the center of the resident's cage, followed by an interval of 5-min. After that, an intruder was inserted (without any protection) in the resident's cage, and the behavior of the animals was recorded for 5 min. Each animal received only one of the doses.

In another group of animals, WAY-100,635 (10.0 μg/0.2 μl dose) or SB-224,289 (1.0 μg/0.2 μl dose) was microinjected 30 min before 8-OH-DPAT (1.0 μg/0.2 μl), CP-93,129 (0.1 μg/0.2 μl), or vehicle, respectively. Again, residents were submitted to a social confrontation 5 min after the last injection. In this experiment, the animals received two microinjections, the first microinjection with the specific antagonist and the other with the agonist. The vehicle used for the two antagonists was physiological saline solution.

The resident–intruder confrontations after microinjections were videotaped and later analyzed by a trained investigator using The Observer software (version 3.0, Noldus, The Netherlands). The behavioral repertoire, previously defined for Miczek and O'Donnell (1978), included frequency of aggressive elements such as sniffing the intruder, sideways threat, attack bite, pursuit, tail rattle, and duration of non-aggressive elements such as grooming, rearing, and walking.

Drugs

8-OH-DPAT (Sigma, St. Louis, MO, USA), CP-93,129 (1,4-dihydro-3-[1,2,3,6-tetrahydro-4-pyridinyl]-SH-pyrrolo [3,2-b] pyridine-5-one dihydrochloride; Pfizer, Groton, CT, USA) and WAY-100,635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl]-*N*-(2, pyridinyl) cyclohexanecarboxamide trihydrochloride; Wyeth-Ayerst, Princeton, NJ, USA) were dissolved in 0.9% saline. SB-224,289 (2,3,6,7-tetrahydro-1*p*′-methyl-5-{2′-methyl-4′-[(5-methyl-1,2,4-oxadiazole-3-yl) biphenyl-4-yl)] carbonyl} furo [2,3-f] -indole-3-spiro-4′-piperidine oxalate; Pfizer, Groton, CT, USA) was dissolved with the aid of sonication in 0.9% saline and was gently warmed.

Histological analysis

At the end of the experiment, all resident mice were deeply anesthetized (ketamine and xylazine) and intracardially perfused with 0.9% saline and 0.4% paraformaldehyde (PFA). Brains were removed and fixed in 0.4% PFA until sliced on a vibratome in 60-μm thick coronal sections. The slices were placed on gelatinized slides and examined by a microscope interfaced to a computer. The location of the guide cannula was verified through images of brain slices captured with specific software (Neuro Image Pró 1.0). Mice with placements outside VO PFC served as anatomical controls and were analyzed separately.

Statistical analysis

All data were expressed as mean±SEM. The effect of social instigation on aggressive behavior was analyzed using a paired Student *t* test, comparing species-typical baseline aggression versus aggression after social instigation.

Dose–effect data from each agonist (8-OH-DPAT and CP-93,129) and antagonist (WAY-100,635 and SB-

224,289) were separately analyzed using a one-way analysis of variance (ANOVA). When there were statistically significant F values ($p \leq 0.05$), Bonferroni post hoc tests were conducted comparing drug treatments with the corresponding vehicle group.

Regarding non-aggressive motor behaviors, the data from all groups with agonist and antagonist treatments were compared with those from their respective controls using ANOVA. When significant differences were found, Bonferroni post hoc tests were accomplished.

Results

Heightened aggression after social instigation

Social instigation significantly increased the aggressive behavior of all mice when compared to their species-typical aggression baseline, as indicated by the increase in frequency of attack bites (t (109)= 2.92; p= 0.004; Fig. 1). The baseline of the aggressive behaviors was expressed by the average of the last three resident–intruder confrontations tests.

Histological verification

Histological analysis showed that among all the animals studied, 96 presented injections correctly positioned in the target area (Fig. 2). The remaining animals (n= *14*) were included in the anatomical control group (not on target).

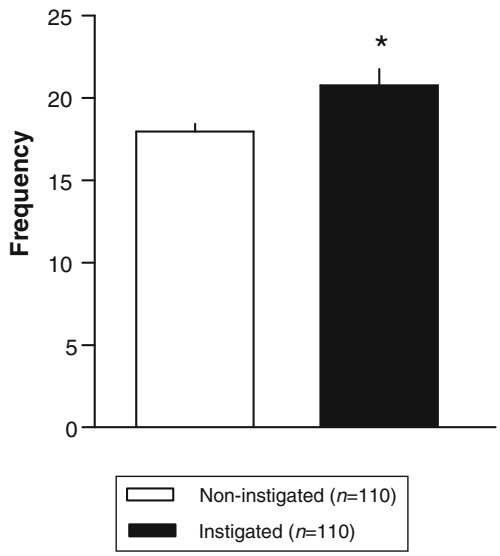


Fig. 1 The effects of social instigation on aggression in the resident male mice. The aggressive behavior portrayed is the frequency of attack bites towards the male intruder. *Vertical bars* represent the mean±SEM. *$p \leq 0.05$

Dose–effects of 8-OH-DPAT and CP-93,129 on instigation-heightened aggression

8-OH-DPAT microinjected into VO PFC reduced the frequency of attack bites at the 0.56- and 1.0-μg doses (F (4,32)= 4.26; p= 0.007; Fig. 3a and Table 1) compared to the control group. The frequency of sideways threat (Fig. 3b), sniffing the intruder, and tail rattling were unchanged compared to the control group (Table 1). Moreover, the effective dose of 8-OH-DPAT (1.0 μg) microinjected outside of VO PFC did not alter aggressive behaviors (Table 1).

The lowest dose of CP-93,129 (0.1 μg) exerted significant anti-aggressive effects when microinjected into VO PFC. Specifically, CP-93,129 reduced the frequency of attack bites (F(4,35) = 2.92; p= 0.03; Fig. 4a and Table 1) and sideways threat (F(4,35)= 3.03; p= 0.02; Fig. 4b and Table 1) compared to the control group. The frequency of sniffing the intruder and tail rattling was unchanged compared to the control group (Table 1). Aggressive elements remained unaltered with the dose (0.1 μg) microinjected outside of VO PFC (Table 1).

Dose–effects of 8-OH-DPAT and CP-93,129 on non-aggressive behaviors

The frequency and duration of walking, grooming, and rearing were not significantly different with any of the 8-OH-DPAT and CP-93,129 doses studied when compared to the control group (Table 1). The results of 5-HT_{1A} and 5-HT_{1B} receptor agonists showed only subtle alterations in some elements of motor activity when compared to the vehicle group (Fig. 5a,b,c). However, the two drugs differ significantly from each other when the duration measures from animals microinjected with 8-OH-DPAT were compared to those from the animals microinjected with CP-93,129 (Fig. 5a,b,c,d).

Antagonism/combination studies

Pretreatment with WAY-100,635, a selective 5-HT_{1A} receptor antagonist (10 μg), antagonized the reduction in the frequency of attack bites produced by 8-OH-DPAT (F (2,17)= 0.29; p= 0.74; Fig. 3a and Table 2). Sideways threat (Fig. 3b), sniffing the intruder, and tail rattling were not significantly modified when compared to the values from the control group (Table 2). No significant effects on aggressive and non-aggressive behaviors were found after microinjections of vehicle or WAY-100,635 plus vehicle in VO PFC (Table 2). The duration of walking, grooming, and rearing remained unaltered by pretreatment with WAY-100,635 and 8-OH-DPAT compared to the control group (Table 2).

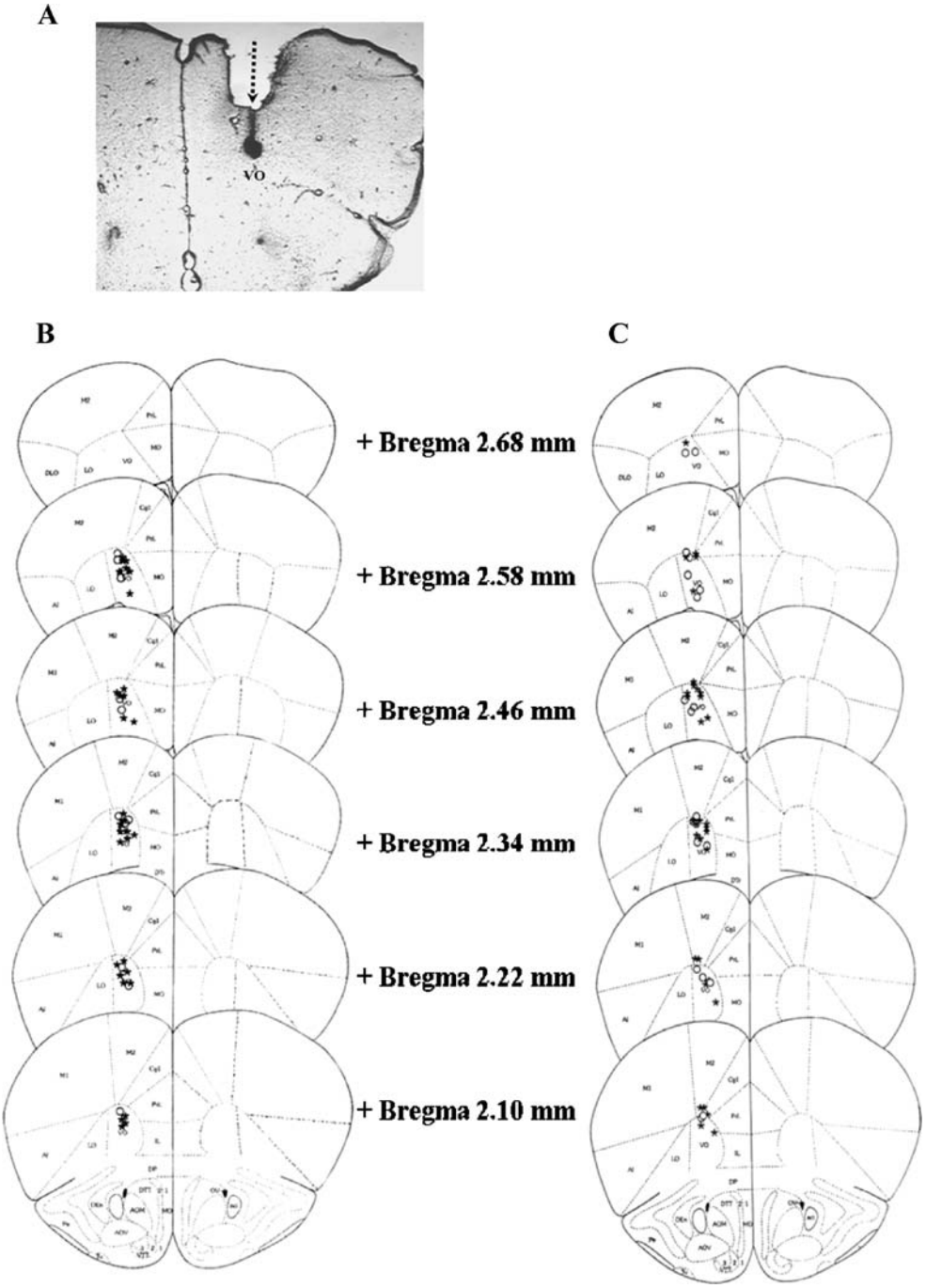


Fig. 2 **a** Photomicrograph showing the correct placement of guide cannula and injection at VO PFC region. **b**, **c** Schematic representation of successive coronal sections of the mouse brain showing the histological verification of injection placement ($n=96$) in the ventral orbital frontal cortex (rostral to caudal: 2.68, 2.58, 2.46, 2.34, and 2.22 mm anterior to the bregma). *VO* Ventral orbital frontal cortex, *Cgl* Cingulate cortex, area 1, *Prl* prelimbic cortex, *MO* medial orbital cortex, *LO* lateral orbital cortex. All the images are from Paxinos and Franklin (1997). **b** *Asterisks* represent the site of 8-OH-DPAT injection or vehicle and *open circles* represent the site of WAY-100,635 injection. **c** *Asterisks* represent the site of CP-93,129 injection or vehicle and *open circles* the site of SB-224,289 injection or vehicle

Pretreatment with selective 5-HT_{1B} receptor antagonist SB-224,289 (1.0 μg/0.2 μl) completely blocked the decrease in the frequency of attack bites and sideways threat produced by CP-93,129 compared to the control group ($F(2,17)=1.71$; $p=0.21$; Fig. 4a and Table 2; $F(2,17)=1.52$; $p=0.24$; Fig. 4b and Table 2). Sniffing the intruder and tail rattling were unchanged compared to the control group (Table 2). No significant effects on aggressive and non-aggressive behaviors were found after microinjections of vehicle or SB-224,289 plus vehicle into VO PFC (Table 2). Moreover, pretreatment with SB-224,289 and CP-93,129 did not reduce the duration of non-aggressive elements, such as walking, grooming, and rearing when compared to the control group (Table 2).

Discussion

The present study confirms that social instigation is an experimental procedure that increases significantly the

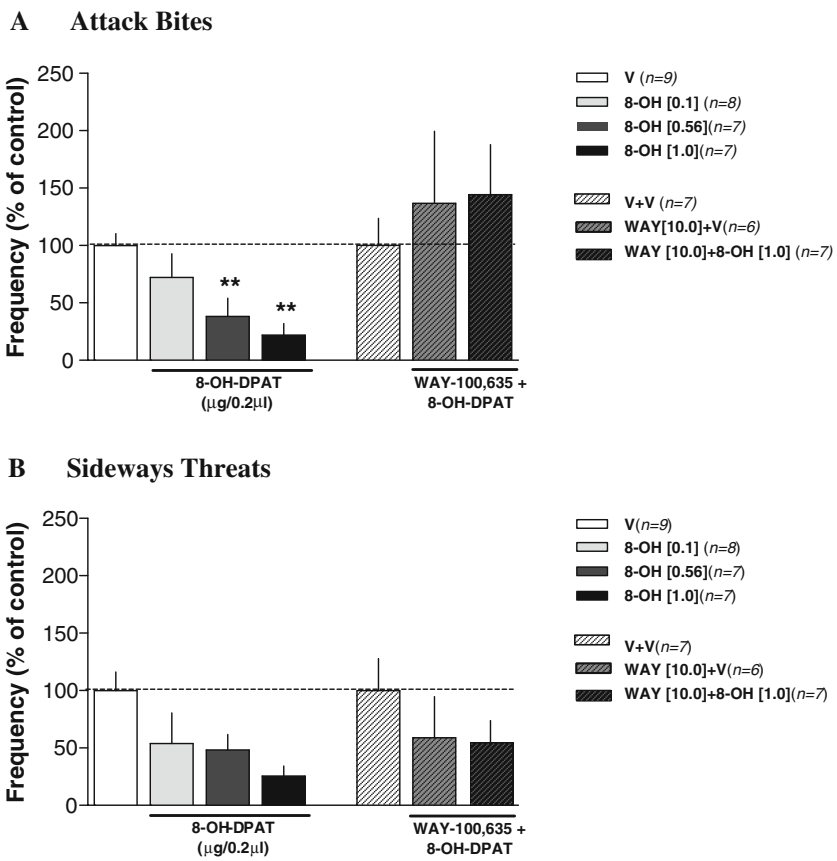


Fig. 3 Effects of 5-HT_{1A} receptor agonist and antagonist on instigation-heightened aggression. **a** Frequency of attack bite after 8-OH-DPAT at different doses (0.1, 0.56, and 1.0 μg /0.2 μl) and after pre-treatment with WAY-100,635 (10.0 μg/0.2 μl) plus vehicle and 8-OH-DPAT (1.0 μg/0.2 μl), respectively. **b** Frequency of sideways threats after 8-OH-DPAT at different doses (0.1, 0.56, and 1.0 μg/0.2 μl, respectively) and after pretreatment with WAY-100,635 (10.0 μg/0.2 μl) plus vehicle and 8-OH-DPAT (1.0 μg/0.2 μl), respectively. *Vertical bars* represent the mean±SEM. **$p \leq 0.001$

levels of aggression. In addition, the results demonstrate that 8-OH-DPAT and CP-93,129 exert significant anti-aggressive effects when microinjected into VO PFC of instigated animals. The 0.56 and 1.0 μg doses of 8-OH-DPAT significantly reduced the frequency of attack bites. The lowest dose of CP-93,129 (0.1 μg) decreased the frequency of attack bites and sideways threats compared to the control group, showing a more potent anti-aggressive effect than 8-OH-DPAT. The frequency of behaviors such as tail-rattles, and in the case of the 8-OH-DPAT, also sideways threats, did not decrease in the same manner as attack bite frequency. The treatments reduced only the consummatory aspects of aggression (the last behavioral elements in the sequence), but social activity was not affected. This pattern by 5-HT_{1A} and 5-HT_{1B} receptor agonists was not found with any other drug used that can decrease aggressive behavior such as antipsychotics, benzodiazepines, alcohol, psychostimulants, antidepressants, anticholinergics, antihistaminergics, and anticonvulsants (Olivier and Oorschot 2005). Importantly, the specific participation of these receptors was confirmed by reversal of anti-aggressive effects using selective antagonists WAY-100,635 and SB-224,289.

In relation to motor activities, there was no significant effect with 5-HT_{1A} receptor agonist or 5-HT_{1B} receptor agonist when compared to control group, but just a trend. However, the two compounds differ from each other in their effects on rearing, grooming, walking, and in the total time spent in non-aggressive behaviors. The current results on these behavioral elements are in concordance with the contrasting effects of these 5-HT receptor agonists on sexual behavior (Larsson and Ahlenius 1999), food intake (Simansky and Vaidya 1990), and drug taking (Parsons et al. 1998; Crabbe et al. 1996) were found.

Aggressive confrontations induce c-*fos* activation in the prefrontal cortex, and this activation was especially strong in mice selected for high aggressive behavior (Halász et al. 2006; Haller et al. 2006). Medial and orbital regions of prefrontal cortex have been clearly related with the modulation of impulsive aggression, while dorsolateral region appears to play a minor role (Grafman et al. 1996; Blair 2004). In humans, anatomical evidence exits for a general deficit of prefrontal cortex in several psychiatric conditions, which are characterized by the inability to inhibit aggressive and impulsive behavior (Best et al. 2002). For example, patients with antisocial personality disorder who displayed impulsive aggression showed an 11% reduction in the volume of prefrontal cortex, and murderers exhibit a general reduction in glucose metabolism within the prefrontal cortex (Raine et al. 1994, 2000).

Table 1 Latency to attack bite, frequency of aggressive and duration of non-aggressive behaviors after microinjection of 5-HT_{1A} and 5-HT_{1B} receptor agonists (8-OH-DPAT and CP-93,129, respectively)

Parameter	8-OH-DPAT doses (μg/0.2 μl)					CP-93,129 doses (μg/0.2 μl)				
	V[a] (*n*=9)	No[b] (*n*=6)	0.1 (*n*=8)	0.56 (*n*=7)	1.0 (*n*=7)	V[a] (*n*=8)	No[b] (*n*=8)	0.1 (*n*=10)	0.56 (*n*=7)	1.0 (*n*=7)
Latency										
First attack bite (s)	14.8±8.2	85.1±43.7	68.4±37.4	93.3±53.3	164.8±52.6	10.0±6.1	8.8±2.6	25.9±15.9	32.6±22.6	46.0±32.3
Frequency										
Attack bites	22.0±2.2	12.1±3.6	15.8±4.5	8.4±3.4**	4.8±2.1**	24.0±2.3	23.5±3.7	11.9±2.4*	20.4±3.6	15.7±3.9
Sideways threat	10.6±1.9	6.6±2.8	5.7±2.8	5.1±1.4	2.7±0.9	30.2±3.7	26.6±3.8	14.5±2.9*	24.8±3.8	18.8±4.8
Sniff	6.3±1.4	12.6±2.5	14.3±2.7	11.7±2.9	13.5±2.0	11.1±3.2	4.7±0.8	13.5±3.6	6.4±3.1	5.1±2.0
Tail rattle	11.8±1.5	5.1±2.0	8.1±2.0	9.5±2.6	18.1±5.1	14.5±3.4	17.1±4.1	20.9±4.0	23.5±6.7	15.8±3.9
Duration										
Groom (s)	6.6±1.3	2.3±1.2	4.1±0.8	3.2±0.9	5.3±2.9	17.1±4.3	21.3±5.2	26.3±7.2	13.0±4.4	17.5±5.2
Rear (s)	13.9±4.7	5.6±1.5	9.0±2.6	3.0±0.8	10.1±2.2	20.3±7.1	22.1±10.5	12.2±3.0	40.7±21.0	40.6±15.7
Walk (s)	69.2±11.7	74.2±5.4	81.2±20.1	47.6±12.2	63.1±6.6	35.2±3.4	34.3±5.4	32.7±5.1	34.3±5.3	35.8±10.3

Data expressed in mean±SEM
*$p<0.05$
**$p\leq0.001$
[a] Vehicle
[b] No target

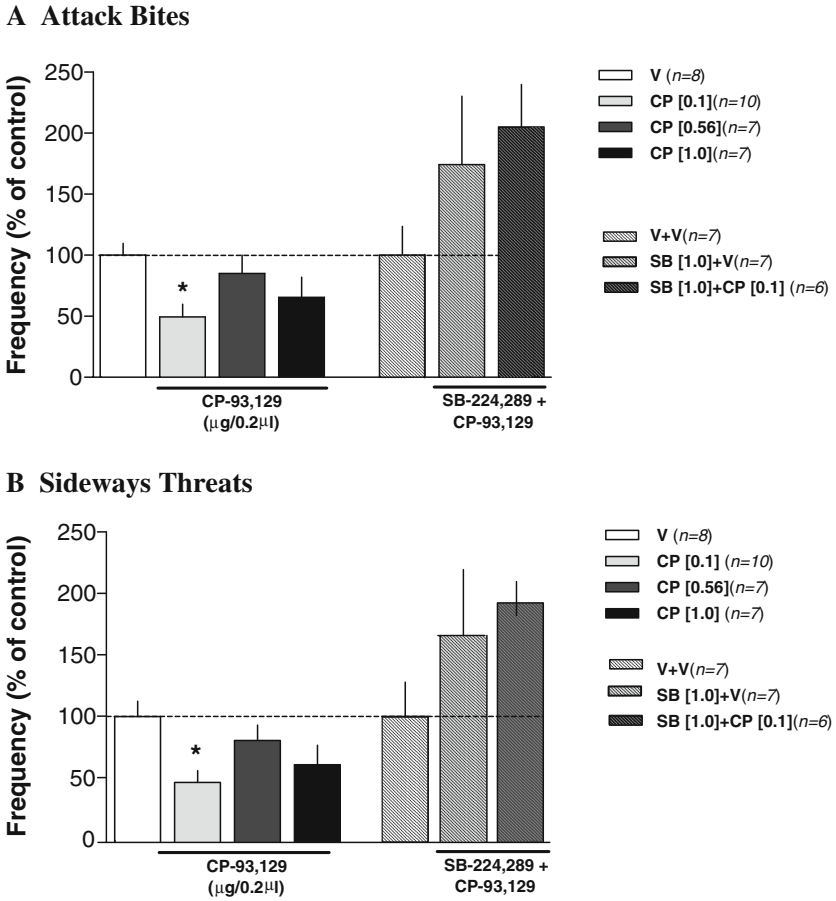
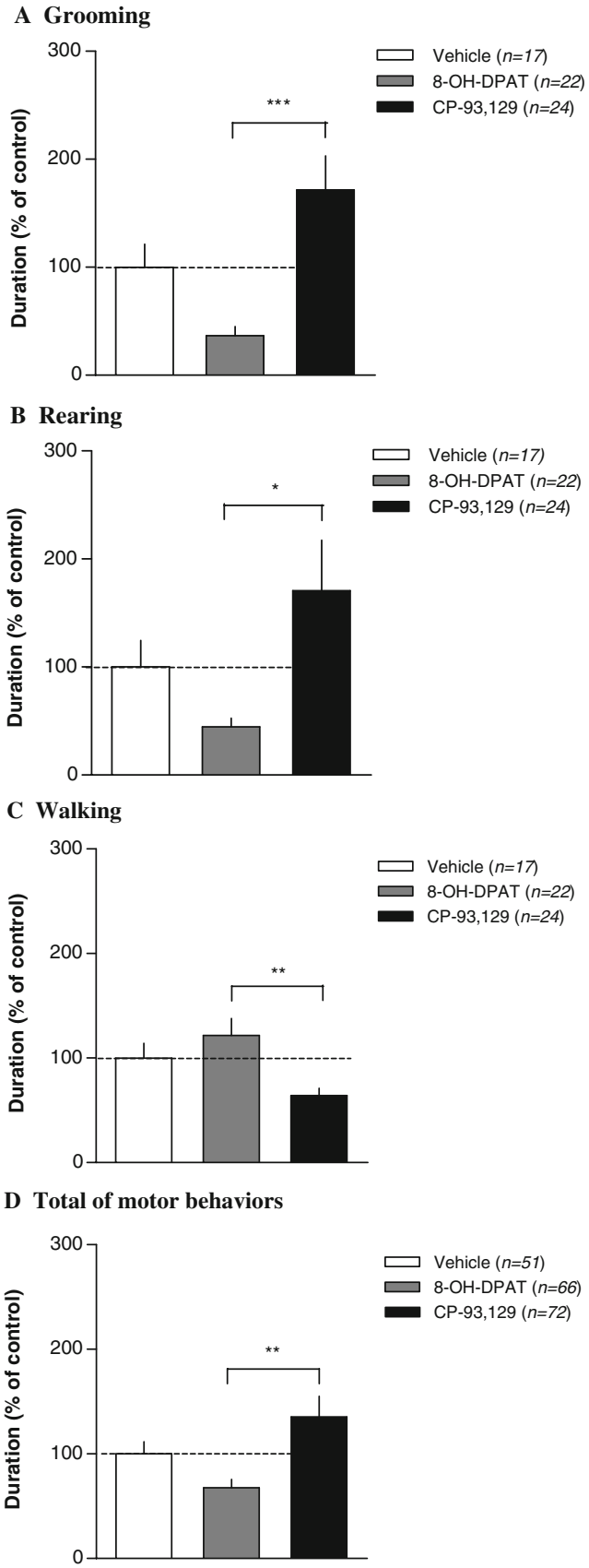


Fig. 4 Effects of 5-HT_{1B} receptor agonist and antagonist on instigation-heightened aggression. **a** Frequency of attack bite after CP-93,129 at different doses (0.1, 0.56, and 1.0 μg/0.2 μl) and after pretreatment with SB-224,289 (1.0 μg/0.2 μl) plus vehicle and CP-93,129 (0.1 μg/0.2 μl), respectively. **b** Frequency of sideways threats after CP-93,129 at different doses (0.1, 0.56, and 1.0 μg/0.2 μl) and after pretreatment with SB-224,289 (1.0 μg/0.2 μl) plus vehicle and CP-93,129 (0.1 μg/0.2 μl), respectively. *Vertical bars* represent the mean±BSEM. *$p\leq0.05$



◀ **Fig. 5** Duration of motor activities after 5-HT_{1A} and 5-HT_{1B} receptor agonist microinjections in all doses. **a** Duration of grooming after microinjections of vehicle, 8-OH-DPAT, and CP-93,129. **b** Duration of rearing after microinjections of vehicle, 8-OH-DPAT, and CP-93,129. **c** Duration of walking after microinjections of vehicle, 8-OH-DPAT, and CP-93,129. **d** Total duration of motor activities after microinjections of vehicle, 8-OH-DPAT, and CP-93,129. *Vertical bars* represent the mean±SEM. *$p \leq 0.05$, **$p \leq 0.001$, ***$p \leq 0.0001$

8-OH-DPAT ($pK_i = 8.7$) is consistently used in studies characterizing the behavioral effects of 5-HT_{1A} receptors, including also those on aggressive behavior. WAY-100,635, the 5-HT_{1A} receptor antagonist, has higher specificity for this receptor subtype ($pKi = 9.0$). When given systemically, 8-OH-DPAT, flesinoxan, and partial agonists such buspirone and ipsapirone effectively and potently decrease aggressive behavior in various animal species ranging from invertebrates, rodents, guinea pigs, primates to humans (Tompkins et al. 1980; Olivier et al. 1989, 1994; Mos et al. 1993; Bell and Hobson 1994; Joppa et al. 1997; De Boer et al. 1999; 2000; Van Der Vegt et al. 2001). However, the most effective doses of these agonists compromise several non-aggressive elements of the behavioral repertoire (Olivier et al. 1989, 1994; Mos et al. 1993; Sanchez et al. 1993; Miczek et al. 1998a, b; Fish et al. 1999; De Almeida et al. 2001).

Previous studies using systemic injections of selective 5-HT_{1B} receptor agonists, zolmitriptan, CP-94,253, and CP-93,129, demonstrate a reduction in the frequency of attacks bites and lateral threats similar to 5-HT_{1A} receptor agonists. The decrease of aggressive behavior after administration of 5-HT_{1B} receptor agonists was observed in species-typical aggression and in several models of heightened aggression (for example, social instigation, frustration procedures, or consumption of moderate doses of alcohol). Importantly, those anti-aggressive effects were highly specific, that is, not accompanied by an increase in behavioral inactivity or sedation (Fish et al. 1999, 2008; De Almeida et al. 2001; Miczek and De Almeida 2001; De Almeida and Miczek 2002; Bannai et al. 2007). CP-93,129 is the agonist with the highest selectivity for 5-HT_{1B} ($pK_i = 8.1$), as well as the antagonist SB-224,289 ($pK_i = 8.2$), when compared to other 5-HT receptor subtypes (Roberts et al. 2001). In the current experiments, CP-93,129 decreased aggressive behavior at the lowest dose, suggesting that 5-HT_{1B} agonist receptors have more potent anti-aggressive effects than agonists acting on 5-HT_{1A} receptors (Miczek et al. 2004; Olivier 2004). Furthermore, we could infer that microinjections of 5-HT_{1B} agonist receptors in VO PFC reduce aggressiveness only in a narrow range of activation, without a systematic dose–effect relation (De Almeida and Lucion 1997).

Table 2 Latency to attack bite, frequency of aggressive and duration of non-aggressive behaviors (in seconds) after microinjection of 5-HT_{1A} and 5-HT_{1B} receptor antagonists (WAY-100,635 and SB-224,289, respectively) into VO PFC, before microinjection of vehicle or 5-HT_{1A} and 5-HT_{1B} receptor agonists (8-OH-DPAT and CP-93,129, respectively)

Behavior	Vehicle	WAY-100,635 (μg/0.2 μl)		SB-224,289 (μg/0.2 μl)	
	+Vehicle (n=7)	+Vehicle (n=6)	+8-OH-DPAT (n=7)	+Vehicle (n=7)	+CP-93,129 (n=6)
Latency					
First attack bite (s)	57.8±27.4	173.6±51.3	122.7±39.9	36.4±15.1	51.9±33.7
Frequency					
Attack bites	10.0±2.3	13.6±6.2	14.4±4.3	17.4±5.6	20.5±3.4
Sideways threat	13.8±3.8	8.1±4.9	7.4±2.7	24.29±7.7	27.0±3.9
Sniff	9.8±2.1	15.8±4.3	13.4±3.3	4.8±2.3	5.5±1.3
Tail rattle	18.1±2.5	8.5±4.3	10.0±3.4	20.5±3.3	26.8±5.6
Duration					
Groom (s)	7.2±2.0	4.5±1.3	3.3±1.2	15.3±6.0	15.7±2.8
Rear (s)	20.1±7.8	13.12±3.8	14.7±5.0	20.2±9.5	21.1±7.9
Walk (s)	46.4±5.6	58.9±9.4	58.6±10.8	37.8±4.6	50.1±4.7

Data expressed in mean±SEM

It is known that both 5-HT_{1A} receptors and 5-HT_{1B} receptors exist as inhibitory autoreceptors on the serotonergic neurons, the first on the dendrites and cell bodies and the last preferentially on the axon terminals (Boschert et al. 1994; Hertel et al. 1999; Riad et al. 2000). 5-HT_{1A} receptors and 5-HT_{1B} receptors are also present as inhibitory heteroreceptors in the serotonin system's terminal fields, on target neurons in several corticolimbic regions related with the modulation of aggressiveness (Brazell et al. 1985; Boschert et al. 1994; Sarhan and Fillion 1999; Riad et al. 2000; De Boer and Koolhaas 2005). Because of this multiple localizations, administrations of 5-HT_{1A} and 5-HT_{1B} receptor agonists in the anti-aggressive doses have dual effects on neurotransmission: by acting at the autoreceptors, they very effectively inhibit neurotransmission on serotonergic neurons (De Boer and Koolhaas 2005). When acting directly at postsynaptic sites, these agonists mimics the effect of 5-HT released, mimicking enhanced 5-HT signaling and inhibit non-serotonergic neurons (De Boer and Koolhaas 2005).

Aggressive arousal seems to be particularly related to the inhibition of brain serotonin, the so-called "5-HT deficiency hypothesis" (De Almeida et al. 2001; Caramaschi et al. 2007). Levels of 5-HIAA have been inversely correlated with aggressive behavior in several studies in rats, mice, and humans (Valzelli and Garattini 1968; Linnoila et al. 1983; Cleare and Bond 1995). Data from 5-HIAA in humans and primates demonstrated that serotonergic deficiency appears to be most readily detected in groups of individuals who exhibit impulsive and violent forms of aggression rather than in individuals with functional forms of aggression (Coccaro et al. 1989; Mehlman et al. 1994; Tuinier et al. 1995; Miczek et al. 2002; De Boer and Koolhaas 2005). The participation of serotonin in adaptive aggressive behavior could differ from its role in violence defined as the pathological form of aggression (De Boer and Koolhaas 2005). The decrease in aggressive behavior after social instigation with 5-HT_{1A} and 5-HT_{1B} agonist receptors in the VO PFC can be hypothesized to be due to stimulation of heteroreceptors, although activation of autoreceptors may also exert anti-aggressive effects (Mos et al. 1993; De Almeida and Lucion 1997; Bannai et al. 2007).

Further supporting evidence comes from other studies using local intracerebral injection in resident male rats (Mos et al. 1992, 1993). Injection of eltoprazine (a mixed 5-$HT_{1A/1B}$ agonist) into the third ventricle, aimed at activating heteroreceptors, led to anti-aggressive effects, whereas injection of eltoprazine into the raphe nuclei (activating somatodendritic autoreceptores) had no effects on aggressive behavior (Olivier and Oorschot 2005). On the other hand, microinjections of 8-OH-DPAT and CP-93,129 at raphe nuclei also decrease aggressive behavior, indicating a possible role for autoreceptors in these agonist effects (Mos et al. 1993; De Almeida and Lucion 1997; Bannai et al. 2007). Studies using the neurotoxin 5,7-dihydroxytryptamine to reduce the number of presynaptic neurons containing 5-HT into the median and dorsal raphé (but not postsynaptic) found that lesions of these neurons do not change the anti-aggressive effects of eltoprazine or zolmitriptan (Sijbesma et al. 1991; De Almeida et al. 2001). However, the neurotoxin technique is limited by incomplete destruction (approximately 60–80%) of ascending presyn-

aptic 5-HT neurons (De Almeida et al. 2001), and possibly, the depletion by 5,7-DHT causes receptor up-regulation, altering the sensitivity of postsynaptic 5-HT receptors (Sijbesma et al. 1991; Frankfurt et al. 1993, 1994; Manrique et al. 1994; Dugar and Lakoski 1997; Van de Kar et al. 1998; De Almeida et al. 2001). Further studies are necessary to delineate the exact site of action of these receptor agonists for their anti-aggressive effects.

Contrary to the serotonin deficiency hypothesis, considerable evidence points to inhibitory and excitatory effects that are mediated by stimulation of serotonin receptor subtypes such as 5-HT2A vs. 5-HT2C as well as 5-HT1A vs. 5-HT1B receptors in specific brain regions resulting ultimately in opposite behavioral changes (Olivier and Oorschot 2005). For example, it remains to be resolved how agonists at 5-HT_{1A} and 5-HT_{1B} receptors decrease serotonin in corticolimbic terminals via action at auto- or heteroreceptors and, at the same time, significantly decrease aggressive behavior (de Almeida and Lucion 1997; Miczek et al. 1998b; Bannai et al. 2007, De Almeida et al. 2006). There are only a few studies that try to establish a parallel between specific brain areas rich in 5-HT_{1B} receptors and an anti-aggressive effect upon activation of a discrete receptor pool. De Almeida and Lucion (1997) found an increase in aggressive behavior after microinjection of 5-HT1A receptor agonist, 8-OH-DPAT into the medial septal area in female rats postpartum, and, Faccidomo et al (2008) have found an increase in aggressive behavior after microinjection of CP-94,253 into the prefrontal cortex (infralimbic area) in male mice with a history of alcohol self-administration.

In conclusion, the anti-aggressive effects observed with microinjections of specific 5-HT_{1A} and 5-HT_{1B} receptor agonists in socially provoked male mice seem to be associated with an enhanced in 5-HT signaling at the prefrontal cortex, most likely due to activation of postsynaptic sites.

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