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ORIGINAL INVESTIGATION

Social instigation and aggression in postpartum female rats: role of 5-Ht_{1A} and 5-Ht_{1B} receptors in the dorsal raphé nucleus and prefrontal cortex

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Abstract
Rationale 5-HT_{1A} and 5-HT_{1B} receptor agonists effectively reduce aggressive behavior in males that has been escalated by social instigation. Important sites of action for these drugs are the receptors in dorsal raphé nuclei (DRN) and the ventral–orbital prefrontal cortex (VO PFC). DRN and VO PFC areas are particularly relevant in the inhibitory control of escalated aggressive and impulsive behavior.
Objectives The objectives of this study are to assess the anti-aggressive effects of 5-HT_{1A} (8-OH-DPAT) and 5-HT_{1B} (CP-93,129) receptor agonists microinjected into DRN and VO PFC, respectively, and to study the aggressive behavior in postpartum female Wistar rats using the social instigation protocol to increase aggression.
Methods and Results 8-OH-DPAT (0.56 μg) in the DRN increased aggressive behavior in postpartum female rats. By contrast, CP-93,129 (1.0 μg) microinjected into VO PFC decreased the number of attack bites and lateral threats. 5-HT_{1A} and 5-HT_{1B} receptor agonists differed in their effects on non-aggressive activities, the former decreasing rearing and grooming and the latter increasing these acts. When 8-OH-DPAT was microinjected into DRN and CP-93,129 was microinjected into VO PFC in female rats at the same time, maternal aggression decreased. Specific participation of 5-HT_{1B} receptors was verified by reversal of the anti-aggressive effects using the selective antagonist SB-224,289 (1.0 μg).
Conclusions The decrease in maternal aggressive behavior after microinjections of 5-HT_{1B} receptor agonists into the VO PFC and DRN of female postpartum rats that were instigated socially supports the hypothesis that activation of these receptors modulates high levels of aggression in a behaviorally specific manner, due to activation of 5-HT_{1B} receptors at the soma and terminals.

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Introduction

Postpartum aggression in female rodents represents a species-typical adaptation, and escalations beyond this level may model excessive aggression that is of clinical concern. In this sense, postpartum females were used as a model of naturally heightened aggression. In rats, maternal aggressive behavior occurs more frequently from days 3 to 12 after delivery, and during this period, females show intense care directed at the pups (Consiglio and Bridges 2009; Erskine et al. 1978).

In order to enhance the translational value, this type of aggression in postpartum females was escalated by social instigation to engender levels of aggression exceeding the normal species-typical responses. The social instigation procedure has proven to be a highly effective way to increase aggressive behavior in male animals by provoking or instigating a territorial resident through the close proximity of an opponent who cannot be attacked (Potegal 1991). The exposure of an experimental subject to a potential rival for a short time prior to the actual confrontation engenders intense levels of aggression, as originally described in mice (Lagerspetz and Hautojarvi 1967; Tellegen and Horn 1972). For example, male mice, rats, and hamsters initiate attacks with very short latency and at high frequency when tested with an intruder in their home cage or in an unfamiliar locale after having been provoked previously by an opponent (De Almeida and Miczek 2002; Fish et al. 1999; Potegal 1991). Instigation specifically increases aggressive behavior and does not activate locomotion, feeding, or sexual behavior (Lagerspetz and Hautojarvi 1967; Potegal and Tenbrink 1984; Potegal 1991). Even after removal of the instigating stimulus, high levels of aggression persist in fish and rodents, presumably from increased "aggressive arousal" or "attack readiness" (Potegal 1991). At the neurochemical level, male hamsters and rats that have been instigated to fight are characterized by a long-lasting decrease in serotonin in hypothalamus and in medial prefrontal cortex (Payne et al. 1984; van Erp and Miczek 2000). By contrast, behavioral and neurobiological information on escalated aggressive behavior by female animals is lacking.

The neural circuitry which is related to maternal aggressive behavior involves brain areas such as the periaqueductal gray matter, raphé nuclei, septal area, hypothalamic nuclei and ventral–orbital prefrontal cortex (De Almeida and Lucion 1997; Veiga et al. 2007; for review, see Lonstein and Gammie 2002), and several neurotransmitters are implicated in this type of behavior, prominently serotonin (De Almeida and Lucion 1994, 1997). Brain serotonin also plays a critical role in many impulsive types of aggressive behavior and violence in humans and other species (Caspi et al. 2009; Coccaro 1989; Garattini et al. 1967; Giacalone et al. 1968; Maas 1962; Valzelli 1981). The treatment options of escalated aggression are compromised by the fact that there are no selective pharmacotherapies, most still relying on antipsychotic medications (Volavka 1995, 2002).

Systemic administration of selective 5-HT_{1A} receptor agonists such 8-OH-DPAT, alnespirone, S-15535 (De Boer et al. 2000; De Boer and Koolhaas 2005), and some specific 5-HT_{1B} receptor agonists, such as CP-93,129 and CP-94,253 (De Almeida et al. 2006; Veiga et al. 2007; Bannai et al. 2007), exert efficacious and selective anti-aggressive activity, both on species-typical and on escalated aggression when microinjected into VO PFC or dorsal raphé nucleus (DRN). On the other hand, some 5-HT_{1A} receptor agonists, such as buspirone, flesinoxan, and ipsapirone, decrease aggressive behavior accompanied by undesirable side effects (De Almeida and Lucion 1994; Mos et al. 1992; Olivier et al. 1989a, b, 1990a, b, 1994). Escalated aggression and other types of aggressive behavior are effectively reduced by the stimulation of 5-HT_{1A} and 5-HT_{1B} receptors (De Almeida and Miczek 2002; De Almeida et al. 2006; Fish et al. 1999; Olivier and van Oorschot 2005; Veiga et al. 2007). Highly selective 5-HT_{1A} and 5-HT_{1B} receptor agonists do not significantly alter motor activities in the dose range that decreases aggressive behavior, both at species-typical (De Almeida and Lucion 1997; Joppa et al. 1997) and escalated levels (Centenaro et al. 2008; De Almeida and Miczek 2002; De Boer and Koolhaas 2005; Fish et al. 1999; Veiga et al. 2007). The specific role of these receptors was confirmed by reversal of the anti-aggressive effects using selective 5-HT_{1A} and 5-HT_{1B} antagonists WAY-100,635 and SB-224,289 (Centenaro et al. 2008; De Almeida et al. 2006; De Boer et al. 1999, 2000; Lopez-Mendoza et al. 1998; Miczek et al. 1998).

5-HT_{1A} receptors are located on somata and dendrites in the DRN, where they act as inhibitory autoreceptors (Miquel et al. 1992). The 5-HT_{1A} receptors are also located postsynaptically in limbic areas acting as heteroceptors on non-serotonergic neurons, where they inhibit the release of other neurotransmitters (Barnes and Sharp 1999). The 5-HT_{1B} receptors are located pre- and postsynaptically, the former act as autoreceptors on serotonergic terminals (Boschert et al. 1994; Bonaventura et al. 1998) and the latter are located as heteroreceptors. The prefrontal cortex is a brain region that contains both 5-HT_{1A} and 5-HT_{1B} receptors, specifically in the ventral–orbital region, and this area has been identified as a particularly important site in the inhibitory control of the sub-cortical circuits mediating

aggressive and impulsive behavior (Blair 2001, 2004; Séguin 2004; Cardinal et al. 2004; Kheramin et al. 2005; Veiga et al. 2007). Violent behavior is found in patients with lesions or neurodegenerative disorders in areas of the PFC, suggesting that this area is critical for the control of aggressive behavior (Hawkins and Trobst 1998, 2000; Davidson et al. 2000; Veit et al. 2002; Blair 2004; for review, see Brower and Price 2001).

Initially, we tested the hypothesis that 5-HT_{1B} receptors in serotonergic terminals are critical in the VO PFC for the control of escalated aggressive behavior in postpartum females. To this end, we examined the antiaggressive effects of the 5-HT_{1B} receptor agonist, CP-93,129, after this compound was microinjected into the VO PFC. A further test of this hypothesis was to confirm the specificity of 5-HT_{1B} receptor site as critical for decreasing aggressive behavior by microinjecting the 5-HT_{1B} receptor antagonist SB-224,289 into the VO PFC. We expanded the hypothesis by integrating actions at terminal and somatodendritic receptors as sites of action for the behavioral effects of the receptor 5-HT_{1A} and 5-HT_{1B} agonists, respectively, by microinjecting 8-OH-DPAT into the DRN and CP-93,129VO PFC at the same time. Finally, we sought to determine whether the anti-aggressive effects were the result of activation of pre- or postsynaptic receptors (5-HT_{1A} or 5-HT_{1B}).

Materials and methods

Animals

Nulliparous female Wistar rats (N=114), born and bred at *Universidade do Vale do Rio dos Sinos*, UNISINOS, 3–4 months old and weighing between 250 and 350 g, were maintained on a 12:12-h light:dark cycle, lights on at 4:00 am. After delivery, each litter was culled to eight pups. To test maternal aggressive behavior, the experimental female rats confronted male Wistar rats. Each male intruder was used only once per behavioral test. Females were kept in polycarbonate cages (65×55×25 cm). Intruders were male rats which had a direct confrontation with the residents (n=60) and weighed on average 50 g less than the females. The instigators were the animals that were protected and did not have a direct confrontation with the residents (n=60); they were also on average 50 g smaller than the resident females, and were maintained in groups of five, in standard polycarbonate cages (65×55×25 cm). The instigators were males that were never used as intruders. All of the rats were from the same strain, and all rats were kept in the same room in a temperature-controlled environment (20±2°C) with food and water available ad libitum.

Resident intruder confrontation

On the third postpartum day, females were selected for maternal aggressive behavior and only those displaying more than two bites against an unprotected intruder during a 10-min confrontation were used as subjects. About 30% of females were excluded because they did not meet this criterion. The behavioral test was conducted in the home cage of the female residents. From postpartum days 3 to 12, a high level of aggression is observed in females, and thereafter, aggressive behavior declines (Erskine et al. 1978; Mos and Olivier 1986).

Social instigation

On the fifth postpartum day, the social instigation procedure was implemented. The social instigation consisted of placing a clear perforated glass cylinder (28 cm long, 10 cm in diameter) containing an opponent male ("instigator"), for 5 min in the center of the female resident's home cage. The residents typically threatened the protected instigator and attacked the perforated glass cylinder. In general, rodents initiate attacks with very short latency and high frequency when tested with an intruder in their home cage after having been provoked previously by an opponent (Potegal 1991). The pups remained inside the cage together with their dams during the social instigation and the confrontation with the intruder.

Surgery

On the sixth postpartum day, each female was anesthetized with 100 mg/kg ketamine and 10 mg/kg xylazine intraperitoneally (IP), placed in a stereotaxic frame (David Kopf; Tujunga, CA, USA), and implanted with one or two guide cannulae (22 gauge) fixed with dental cement to the skull. One cannula was aimed at the VO PFC at the right hemisphere: 4.3 mm anterior to bregma, 0.6 mm lateral to the mid-saggital line, 2.1 mm below dura mater. A second cannula was aimed at the DRN at the right hemisphere: −7.8 mm posterior to bregma, 1.6 mm lateral to the mid-saggital line, 5.2 mm below dura mater, tilted in a 20° angle. The coordinates were based on the atlas by Paxinos and Watson (1998). Females remained separated from the pups for 2 h. Experiments were performed in accordance with the current NIH Guide for Animal Care and Use and *Colégio Brasileiro de Experimentação Animal* (COBEA), and they were approved by the Research Committee of the University.

Microinjections

On the ninth postpartum day, the microinjections with agonist and antagonist or vehicle were performed 15 and 30 min

before the resident–intruder test, respectively (Veiga et al. 2007). The naive male intruder was placed into the female's cage, and immediately thereafter, the behaviors were videotaped for 10 min. The solutions were slowly infused over the course of 60 s at a rate of 0.2 μl/min, using a Hamilton syringe connected by tubing to the injecting needle that stayed in situ for a further minute after the microinjection.

Experimental groups:

Experiment 1: The animals were microinjected with CP-93,129 at 0.56 μg/0.2 μl (n=12) or vehicle (saline) (n=9) into the VO PFC 15 min before the confrontation with the intruder.

Experiment 2 The females received two microinjections into the VO PFC. First, the animals were microinjected with 5-HT_{1B} receptor antagonist, SB-224,289 (5.0 μg/0.2 μl) and 15 min later with the 5-HT_{1B} receptor agonist, CP-93,129 (1.0 μg/0.2 μl) (n=12) or vehicle (n=13) or with vehicle plus vehicle (n=12).

Experiment 3 The animals were microinjected with a 5-HT_{1A} receptor agonist, 8-OH-DPAT (0.56 μg/0.2 μl) into DRN and with a 5-HT_{1B} receptor agonist, CP-93,129 (0.1 and 1.0 μg/0.2 μl, n=9) into VO PFC or vehicle and vehicle into DRN and into VO PFC. Both microinjections were performed immediately following each other. The control groups were microinjected with saline. In sequence, the rat was microinjected with 8-OH-DPAT immediately followed by CP-93,129. The behavioral tests occurred 15 min after the microinjections.

The groups studied were as follows:

Vehicle into DRN + vehicle into VO PFC (n=11)
Vehicle into DRN + CP-93,129 (1.0 μg/0.2 μl) into VO PFC (n=10)
8-OH-DPAT (0.56 μg/0.2 μl) into DRN + vehicle VO PFC (n=9)
8-OH-DPAT (0.56 μg/0.2 μl) into DRN + CP-93,129 (0.1 μg/0.2 μl) into VO PFC (n=9)
8-OH-DPAT (0.56 μg/0.2 μl) into DRN + CP-93,129 (1.0 μg/0.2 μl) into VO PFRC (n=9)

Drugs

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 8-OH-DPAT (8-hydroxy-2-(di-n-propylamino) tetralin hydrobromide; Sigma, St. Louis, MO, USA) were dissolved and sonicated in saline solution. The 5-HT_{1B} receptor agonist, CP-93,129 was donated by Pfizer.

Histology

After completion of all behavioral tests, the dams were deeply anesthetized with an overdose of sodium thiopental. Brains were perfused with saline and thereafter with 4% formaldehyde. The brains were removed and fixed in 4% formaldehyde and later cut on a vibratome in 50-micron coronal slices. Locations of the cannula tips were determined via microscopic analysis, and only the animals with an exact localization were used for data analysis (Fig. 1). The animals that were designated as anatomical controls had incorrectly positioned placements. Histological analysis showed that 66 cannula placements were correctly positioned in the target areas in experiments 1 and 2 (Fig. 2), and 48 cannula placements were correctly positioned in the target areas in experiment 3 (Fig. 3). Five animals were anatomical controls in experiment 1 (Fig. 2a), seven in experiment 2 (Fig. 2b), and eight in experiment 3 (Fig. 3a, b).

Behavioral analysis

The resident–intruder confrontations were videotaped and later analyzed by a trained investigator with adequate inter- and intra-observer reliability using The Observer software (version 3.0, Noldus, The Netherlands). De Almeida and Lucion (1997) previously defined the behavioral repertoire of lactating females, including the frequency and duration of aggressive elements such as lateral threat, lateral attack, bite, and pin, and the duration of non-aggressive elements such as sniffing the intruder, grooming, rearing, and walking. Pup care measurements included how long each dam carried, licked, and nursed the pups.

Statistical analysis

After confirming the homogeneity of variance of all data, they were expressed as mean ± SEM. The effect of social instigation on maternal aggressive behavior was analyzed using a paired Student t test, comparing species-typical baseline aggression vs aggression after social instigation.

Data from all three experiments were analyzed using one-way ANOVAs. When a statistically significant F value (p<0.05) was obtained, Newman–Keuls 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 treatment were compared with those from their respective controls using ANOVA. When significant differences were found, Newman–Keuls post hoc tests were performed. The data from the anatomical control animals were compared to those from the vehicle group using a paired Student t test.

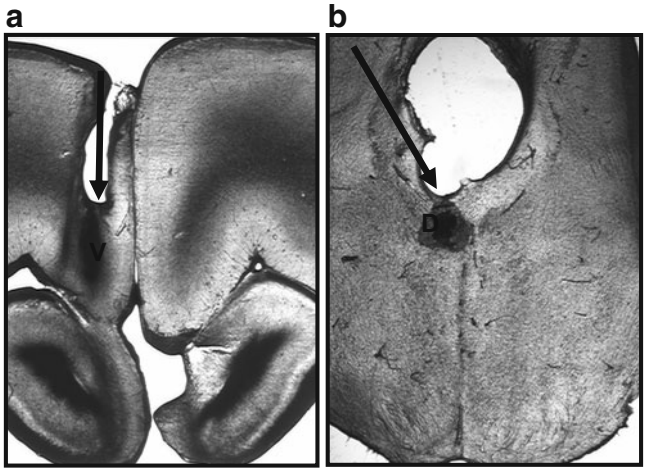

Fig. 1 **a** Photomicrograph showing the placement of the guide cannula and injection in the VO PFC. **b** Photomicrograph showing the placement of guide cannula and injection into DRN (*arrow*)

Results

Heightened aggression after social instigation

Social instigation significantly increased bite frequency in postpartum female rats compared to a non-instigated control group (t (104)=2.87; p<0.004; Fig. 4).

Aggressive behaviors

In experiment 1, CP-93,129 (1.0 μg) microinjected into VO PFC of instigated females decreased the frequency of lateral attack (F(5,77)=4.78; p<0.008; Table 1), lateral threat (F (3,33)=3.62; p<0.05; Table 1), and pinning the intruder (F (5,16)=3.98; p< 0.01; Table 1) as compared to the control

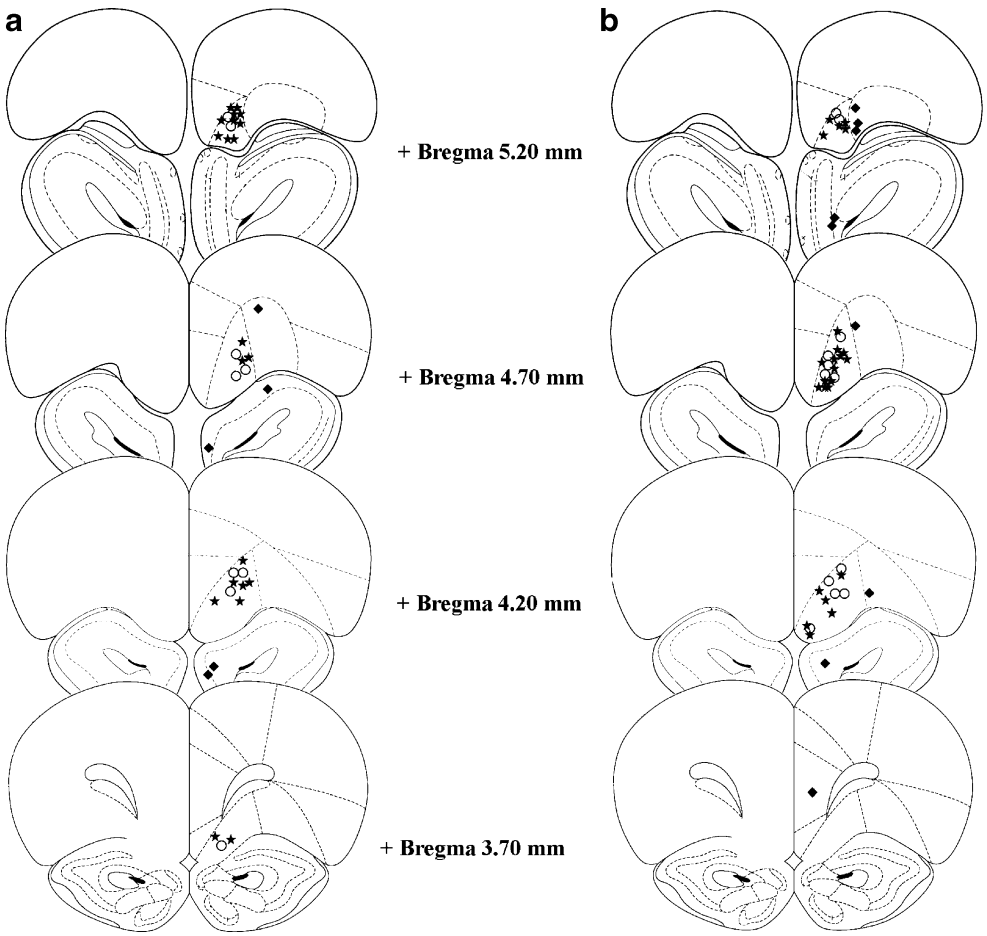

Fig. 2 **a**, **b** Schematic representation of successive coronal sections of the rat brain showing the histological verification of injection placement (n=66) in the ventral–orbital prefrontal cortex (rostral to caudal: 5.20, 4.70, 4.20, and 3.70 mm anterior to the bregma). *VO* ventral–orbital frontal cortex, *LO* lateral orbital cortex, *MO* medial orbital cortex, *Cg3* cingulate cortex, area 3, *Fr2* frontal cortex, area 2, *AI* agranular insular cortex, *VLO* ventrolateral orbital cortex. All the images are from Paxinos and Watson (1998). **a** Experiment 1: *Asterisks* represent the site of CP-93,129 injection and *pen circles* represent the site of vehicle injection. **b** Experiment 2: *Asterisks* represent the site of SB-224,289 injection and *pen circles* represent the site of vehicle injection. *Diamonds* represent off-target injections for CP-93,129, vehicle, or SB-224,289 injections

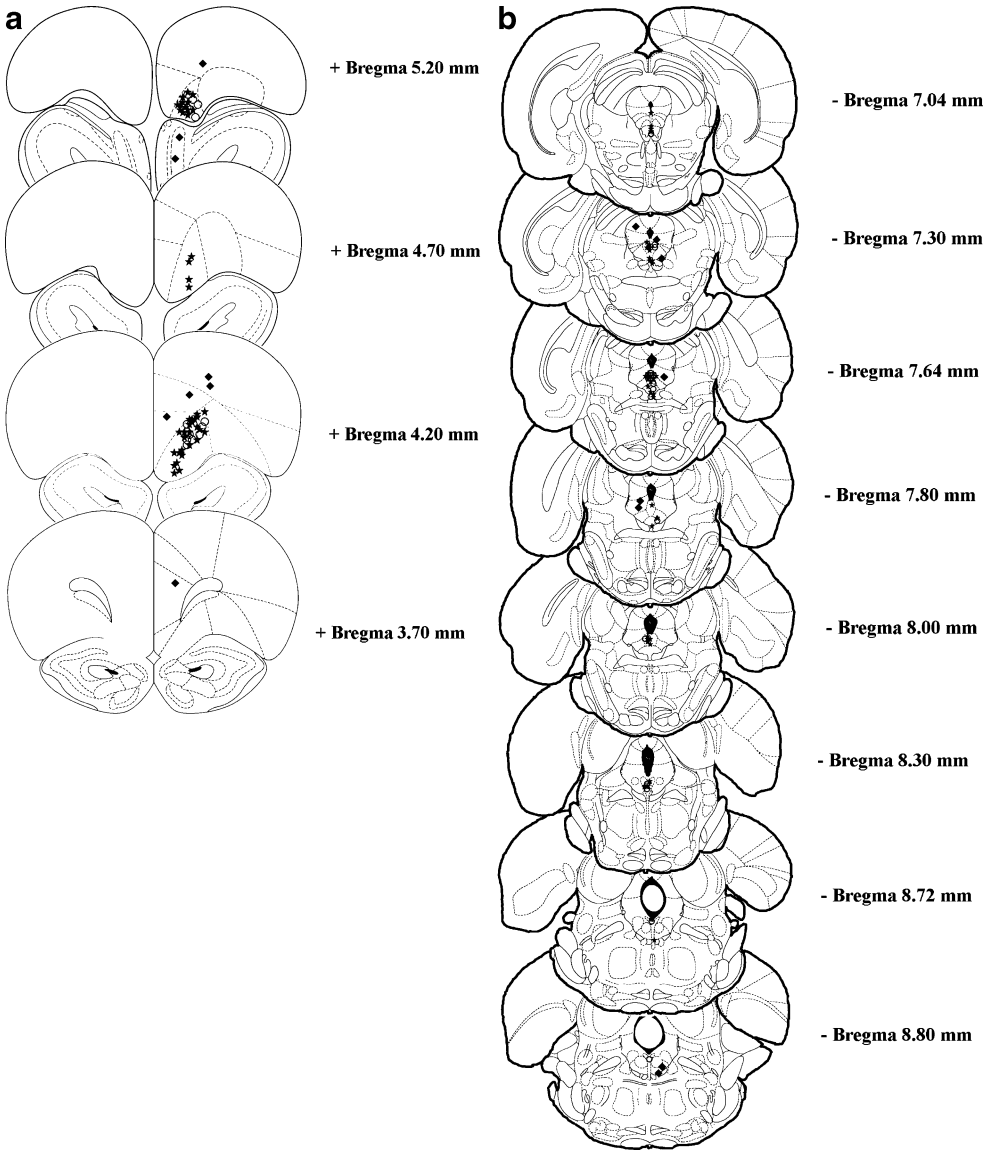

Fig. 3 Experiment 3. **a** Schematic representation of successive coronal sections of the rat brain showing the histological verification of injection placement (n=48) in the ventral–orbital frontal cortex (rostral to caudal: 5.20, 4.70, 4.20, and 3.70 mm anterior to the bregma). *VO* ventral–orbital frontal cortex, *LO* lateral orbital cortex, *MO* medial orbital cortex, *Cg3* cingulado cortex, area 3, *Fr2* frontal cortex, area 2, *AI* agranular insular cortex, *VLO* ventrolateral orbital cortex. *Asterisks* represent the site of CP-93,129 injection and *pen circles* represent the site of vehicle injection. **b** Schematic representation of successive coronal sections of the rat brain showing the histological verification of injection placement (n=48) in the dorsal raphé nucleus (rostral to caudal: −7.04, −7.30, −7.64, −7.80, −8.00, −8.30, −8.72, and −8.80 mm posterior to the bregma). *CG* central gray, *3PC* oculomotor nucleu parvocellular, *Su3* supraoculomotor central gray, *mlf* medial longitudinal fasciculus, *CLi* caudal linear nucleu raphé, *CGLV* central gray, lateral ventral, *CGM* central gray medial, *Me5* mesencephalic trigeminal nucleu. *Asterisks* represent the site of 8-OH-DPAT injection and *pen circles* represent the site of vehicle injection. *Diamonds* represent no target of CP-93,129, vehicle or 8-OH-DPAT injections. All the images are from Paxinos and Watson (1998)

group. The 1.0 μg dose decreased the frequency of lateral attack as compared to 0.56 μg ($F(5,77)=3.03$; $p<0.08$; Table 1). The lower dose of CP-93,129 (0.56 μg) decreased only the frequency of pinning the intruder ($F(5,16)=3.93$; $p<0.01$; Table 1) as compared to the control group. The duration (in seconds) of lateral attack ($F(5,95)=4.86$; $p<0.007$; Table 1), lateral threat ($F(3,34)=3.65$; $p<0.05$; Table 1), and pinning the intruder ($F(4,66)=4.07$; $p<0.01$; Table 1) decreased when CP-93,129 (1.0 μg) was microinjected into VO PFC, as compared to the control group. The lower dose of CP-93,129 (0.56 μg) decreased the duration of pinning the intruder ($F(4,66)=3.34$; $p<0.01$; Table 1) as compared to the control group. When CP-93,129 was microinjected at the 1.0 μg dose outside of the VO PFC, it did not alter any of the aggressive behaviors (Table 1).

In experiment 2, the pretreatment with the 5-HT_{1B} receptor antagonist, SB-224,289, at the 5.0 μg dose antagonized the decrease of frequency of lateral threat and

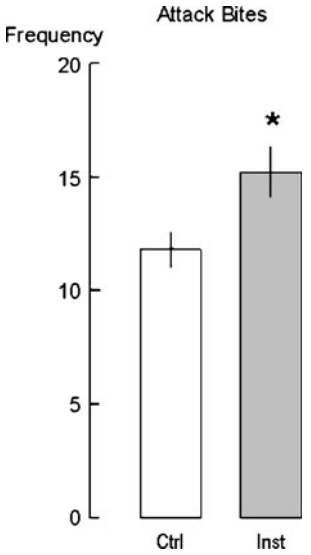

Fig. 4 The effects of instigation (*Inst*) by an intruder on maternal aggressive behavior in resident female rats (N=105 in each group). The aggressive behavior portrayed is the frequency of attack bites towards the male intruder under control (*Ctrl*) and instigation (*Inst*) conditions. *Vertical bars* represent the mean ± SEM. *Asterisk*, $p \leq 0.004$

pinning the intruder produced by CP-93,129 (Table 1). The frequency of lateral attacks was not altered as compared to control group (Table 1). There were no significant effects on aggressive behaviors after the microinjections of vehicle and SB-224,289 into VO PFC (Table 1). The duration (in seconds) of lateral threat and pinning the intruder produced by CP-93,129 too was antagonized after the pretreatment with the 5-HT_{1B} receptor antagonist, SB-224,289 at the 5.0-μg dose (Table 1). The duration of lateral attacks was not altered as compared to control group (Table 1).

In experiment 3, microinjections of 8-OH-DPAT at the 0.56 μg dose into the DRN followed by vehicle into VO PFC significantly increased the frequency ($F(3,45)=4.13$; $p<0.01$, Fig. 5a) and the duration ($F(3,48)=4.06$; $p<0.01$, Fig. 5a) of lateral attacks as compared to the vehicle group. Microinjections of 8-OH-DPAT into DRN (0.56 μg) followed by vehicle into the VO PFC also increased the frequency ($F(3,34)=3.50$; $p<0.01$, Fig. 5b) and the duration ($F(3,32)=3.56$; $p<0.01$, Fig. 5a) of bites directed at the

Table 1 Behaviors during aggression in postpartum female rats

Parameter	CP-93,129 doses (μg/0.2 μl)				Vehicle	SB-224,289 (5.0 μg/0.2 μl)		Ac
	Vehicle (n=9)	0.56 (n=12)	1.0 (n=8)	Ac (n=5)	+Vehicle (n=12)	+Vehicle (n=13)	+CP-93,129 (n=12)	(n=7)
Latency to attack	28.0±7.4	76.4±11.1[b]	21.5±12.2[a]	52.3±9.6	86.0±21.0	64.7±21.3	68.6±31.5	44.6±18.7
Frequency								
Lateral attack	12.0±2.4	8.3±1.5	2.7±1.1[c]	9.8±3.6	8.5±1.3	5.5±1.0	10.2±1.8	10.0±4.9
Bite the body	4.6±2.1	3.5±1.1	2.0±1.1	5.6±4.2	1.4±0.8	2.1±0.8	2.0±0.6	3.1±2.0
Lateral threat	6.1±1.7	4.2±1.2	0.9±0.5[d]	6.4±2.9	1.2±0.4	2.2±0.7	2.8±0.8	5.0±3.4
Pin	4.6±1.1	1.4±0.9 [d]	0.1±0.1 [d]	2.2±1.5	0.2±0.2	0.1±0.1	0.9±0.4	0.8±0.4
Duration aggressive behaviors								
Lateral attack	9.30±1.98	5.35±1.27	1.76±0.7 [d]	7.84±3.21	6.17±1.34	4.04±0.86	7.49±1.65	7.77±4.11
Bite the body	3.82±1.81	2.19±0.75	1.87±0.93	6.24±5.57	0.81±0.46	1.26±0.53	1.05±0.35	3.50±2.51
Lateral threat	10.02±2.83	6.06±2.24	1.21±0.81[d]	18.42±8.35	2.60±1.03	3.36±1.33	4.55±1.53	9.68±7.31
Pin	20.71±7.02	5.89±3.56	0.81±0.81[c]	9.50±5.85	0.80±0.80	0.32±0.24	4.27±2.61	1.80±0.90
Duration non agressive behaviors								
Sniffing	170.4±30.6	160.2±13.8	84.2±20.7[c]	246.3±35.6	194.2±17.8	185.1±17.3	203.2±28.8	214.6±35.3
Pup care	6.9±4.0	1.4±0.8	16.3±10.5	4.1±1.9	1.7±0.9	1.9±1.4	1.8±1.4	2.6±1.3
Walking	98.4±14.5	138.6±17.5	91.6±12.3	95.9±10.1	85.0±13.9	113.3±9.8	135.3±8.9[f]	107.6±16.3
Rearing	11.5±5.5	21.0±3.6	43.4±14.0[d]	19.62±4.0	11.1±3.0	29.4±6.8[g]	12.6±2.3	6.9±2.3
Grooming	53.3±13.0	69.9±14.2	37.2±10.8	59.1±20.6	44.0±14.7	59.5±12.2	43.4±8.0	56.2±15.0

Data expressed in mean ± SEM

Ac anatomical controls

[a] $p<0.01$, compared to 0.56 group

[b] $p<0.01$, compared to vehicle group

[c] $p<0.05$, compared to vehicle and 0.56 groups

[d] $p<0.05$, compared to vehicle group

[e] $p<0.05$, compared to veh + veh and SB + vehicle group

[f] $p<0.01$, compared to veh + veh group

[g] $p<0.01$, compared to veh + veh and SB + CP group

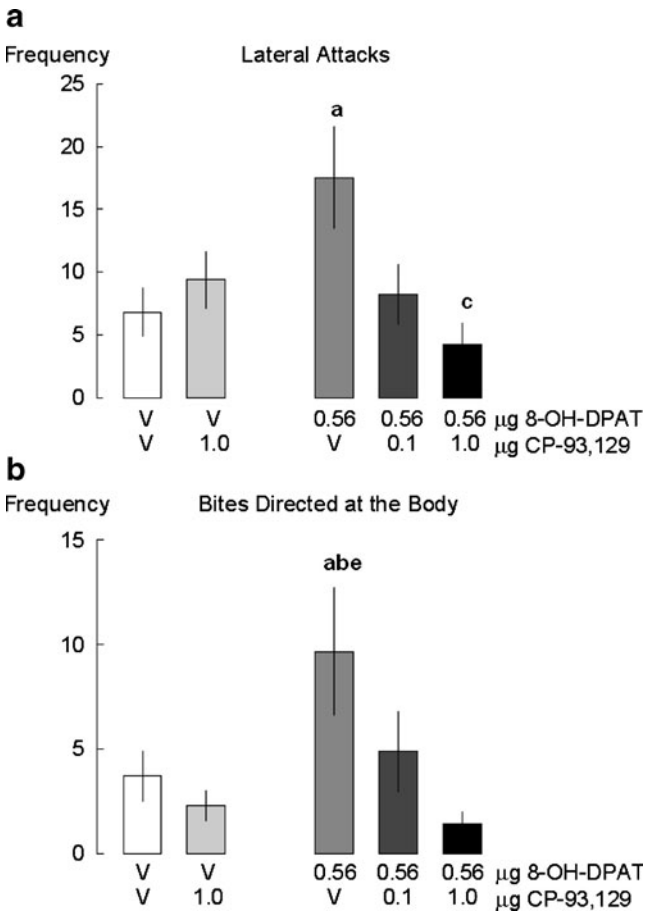

Fig. 5 Effects of 5-HT_{1A} receptor agonist 8-OH-DPAT in the dorsal raphé nucleus and of 5-HT_{1B} receptor agonist CP-93,129 in the VO PFC on escalated aggressive behavior. **a** Frequency of lateral attacks. **a** $p \leq 0.05$ compared to Veh + Veh; **c** $p \leq 0.05$ compared to 8-OH + Veh. **b** Frequency of bites, directed at the body of the intruder after vehicle microinjection followed immediately by a second vehicle, vehicle followed immediately by CP-93,129 (1.0 μg/0.2 μl), 8-OH-DPAT (0.56 μg/0.2 μl), followed immediately by vehicle, 8-OH-DPAT (0.56 μg/0.2 μl) followed immediately by CP-93,129 (0.1/0.2 μl), and 8-OH-DPAT (0.56 μg/0.2 μl) followed immediately by CP-93,129 (1.0 μg/0.2 μl), respectively. *abe* $p \leq 0.05$ compared to Veh + Veh; Veh + CP 1.0 and 8-OH+CP 1.0. *Vertical bars* represent the mean ± SEM

intruder's body as compared to vehicle group. By contrast, microinjections of 8-OH-DPAT into the DRN (0.56 μg) followed by CP-93,129 (1.0 μg) into VO PFC decreased the frequency ($F(3,45)=4.89$; $p<0.01$; Fig. 5a, b) and the duration ($F(3,48)=4.97$; $p<0.01$, Fig. 5a, b) of lateral attacks and also decreased the frequency ($F(3,34)=4.63$; $p<0.01$; Fig. 5a, b) and the duration ($F(3,32)=4.58$; $p<0.01$, Fig. 5a) of bites directed at the intruder's body as compared to 8-OH-DPAT (0.56 μg) + vehicle. The frequency and the duration of lateral threats was not changed in any of the groups after microinjections of 8-OH-DPAT + vehicle or 8-OH-DPAT (0.56 μg) + CP-93,129 (0.1 μg) or 8-OH-DPAT (0.56 μg) + CP-93,129 (1.0 μg) (see Table 2).

Non-aggressive behaviors

In experiment 1, microinjection of 1.0 μg CP-93,129 into VO PFC significantly decreased the duration of sniffing the intruder and the duration of rearing when compared to the control group. The other behaviors, such as interacting with pups, walking, and grooming, were not altered by any dose of CP-93,129 (Table 1).

In experiment 2, only the duration of rearing was decreased after the microinjection of SB-224,289 plus vehicle as compared to this measure in the control group (Table 1). The treatment with SB-224,289 + CP-93,129 changed the duration of non-aggressive behaviors such as walking and rearing as compared to SB-224,289 + vehicle. All the other non-aggressive behaviors remained unchanged as compared to the measures in the control group (Table 1).

In experiment 3, none of the non-aggressive behaviors, such as walking, rearing, and grooming, were changed by the microinjections of 8-OH-DPAT into the DRN and CP-93,129 into the VO PFC (Table 2).

Discussion

The current experiments provide evidence that stimulation of the 5-HT_{1A} somatodendritic autoreceptors in the DRN via the agonist 8-OH-DPAT significantly increases aggressive behavior by postpartum females, while activation of 5-HT_{1B} receptors in the VO PFC has anti-aggressive effects. The current study is the first to demonstrate increased aggressive behavior in postpartum females with microinjection of 8-OH-DPAT in the DRN after social instigation. Moreover, this appears to be the first evidence for functionally opposing roles of receptor subtypes within the 5-HT_1 family, at least with regard to aggressive behavior by postpartum females.

Contrary to the aggression-escalating effects in the present experiments after 8-OH-DPAT microinjection into the DRN, 8-OH-DPAT and alnespirone microinjections into the DRN diminished aggressive behavior in male rats (Mos et al. 1993). De Almeida and Lucion (1997) microinjected 8-OH-DPAT (0.2 and 2.0 μg) directly into the median raphé nucleus and found a decrease in aggression during the postpartum period of female Wistar rats. By contrast, microinjection of 8-OH-DPAT (0.2–2.0 μg) into the medial septal area increased postpartum aggressive behavior (De Almeida and Lucion 1997).

8-OH-DPAT increased important elements of aggressive behavior by postpartum females due to action on serotonergic neurons in the DRN; it causes an auto-inhibition via action on the 5-HT_{1A} autoreceptors (Sprouse and Aghajanian 1987). The activation of 5-HT_{1A} receptors by 5-HT leads to an opening of potassium channels causing a hyperpolarization

Table 2 Behaviors during aggression in postpartum female rats

Parameter	Vehicle		8-OH [0.56]			Ac
	+ Vehicle (n=11)	+ CP-93 [1.0] (n=10)	+ Vehicle (n=9)	+ CP-93 [0.1] (n=9)	+ CP-93 [1.0] (n=9)	(n=8)
Latency to attack	97.8±40.3	48.0±14.9	52.0±13.0	71.4±29.4	47.1±26.0	26.4±12.5
Frequency						
Lateral attack	6.8±2.0	9.4±2.3	17.5±4.1[b]	8.2±2.4	4.2±1.8[a]	11.6±3.8
Bite the body	3.7±1.2	2.3±0.7[a]	9.6±3.0[b]	4.8±1.9	1.4±0.6[a]	10.5±4.1
Lateral threat	1.4±0.8	1.2±1.0	2.5±1.4	1.6±1.1	1.5±0.8	1.5±1.2
Duration aggressive behaviors						
Lateral attack	5.01±1.61	7.47±2.05	14.14±3.90[b]	6.45±2.04	2.42±1.09[c]	9.12±3.28
Bite the body	2.66±0.99	1.54±0.57[a]	7.46±2.59[b]	3.46±1.37	0.97±0.44[a]	8.25±3.57
Lateral threat	1.31±0.87	1.51±1.40	4.96±3.21	2.38±1.88	5.86±4.05	1.50±1.23
Duration non aggressive behaviors						
Walking	103.4±12.4	91.3±14.4	87.8±15.0	132.0±30.5	139.6±21.9	102.1±24.0
Sniffing	199.8±17.8	212.4±27.2	238.0±21.4	180.7±21.9	172.7±28.0	155.8±29.3
Pup care	20.9±14.0	3.2±1.9	30.5±28.3	29.9±29.5	8.3±6.3	97.7±50.0
Rearing	16.0±4.6	4.5±1.1	15.6±4.2	13.2±6.4	16.5±6.9	8.4±2.7
Grooming	53.1±13.1	77.4±8.8	57.4±13.6	84.4±20.3	49.5±9.7	52.3±19.1

Data expressed in mean ± SEM

Ac anatomical controls

[a] $p<0.05$, compared to 8-OH + Veh group

[b] $p<0.05$, compared to Veh + Veh group

[c] $p<0.01$, compared to 8-OH + Veh group

(Sprouse and Aghajanian 1987) and inhibition of the impulse flow in serotonergic cells (Sinton and Fallon 1988; Sprouse and Aghajanian 1986, 1987; Vandermaelen et al. 1986) and the release of 5-HT in terminal areas (Adell et al. 1993; Bosker et al. 1994; Casanovas et al. 1997; Kreiss and Lucki 1994; Sharp et al. 1989), including the prefrontal cortex. In particular, 5-HT_{1A} autoreceptors on DRN show an important role in the physiologic control by ascending serotonergic pathways, attenuation of the excessive activation from 5-HT neurons by excitatory afferences from various structures in the brainstem (Descarries et al. 1982; Jacobs and Azmitia 1992; Baumgarten and Grozdanovic 1997; Ferreira and Menescal-de-Oliveira 2009). Using the current microinjection technique, it is likely that, with the 8-OH-DPAT-induced diminished impulse flow of serotonin to the prefrontal cortex, CP-93,129 diminished aggressive behavior by acting primarily presynaptically.

By contrast, CP-93,129 reduced the offensive elements of maternal aggressive behavior such as the frequency of lateral attacks and the number of bites directed toward the intruder's body (Haney et al. 1989), as well as the duration of lateral attacks and bites (Table 1). On the other hand, no changes were detected in the defensive nature of the female's response, most prominently quick frontal attacks, which have been interpreted most often in terms of a fear or anxiety response towards the intruder (De Almeida and Lucion 1997; Neumann et al. 2010). Our previous studies have also demonstrated that CP-93,129 primarily modifies the offensive elements of maternal aggression (Veiga et al. 2007). The 5-HT_{1B} receptor agonist CP-93,129 reduced maternal aggressive behavior at the highest dose (1.0 μg), and even at the lower 0.1-μg dose had a tendency to decrease the maternal aggressive behavior when microinjected into the VO PFC. The two vehicle microinjections plus CP-93,123 did not have the same effects on the socially instigated lactating females, which also received two instead of one microinjection. All animals received two injections, a potentially more stressful procedure. Interference with aggressive behavior due to this more stressful procedure is another possibility to explain the differential outcomes in the studies from Veiga et al. (2007) and the present one (see De Castilhos et al. 2006; Padovan and Guimarães 2004). Also, seasonal and between-group variability could have accounted for this difference since the two experiments were performed several months apart, confirming earlier observations (Padovan and Guimarães 2004). This anti-aggressive effect was particularly evident in the experimental group that showed very high levels of aggressive behavior after microinjection of 8-OH-DPAT (0.56 μg) in the DRN followed immediately by the

microinjection of CP-93,129 (1.0 μg) into the VO PFC, and as detected by the duration of lateral attacks and bites of the intruder's body (Table 2). However, a significant decrease in aggression was evident in the group microinjected with vehicle followed by CP-93,129 (1.0 μg) into VO PFC. This decrease was significant for the measures of lateral attacks, attack bites, and lateral threats. The non-aggressive behaviors such as locomotion and social investigation were not altered, providing further evidence for the behavioral specificity of the role of 5-HT_{1B} receptors in the modulation of maternal aggressive behavior. CP-93,129 and SB-224,289 are compounds with high affinity for the 5-HT_{1B} receptor (pK_i=8.1 and pK_i=8.2, respectively), when compared with other subtypes of the 5-HT_1 receptor family (Centenaro et al. 2008; Roberts et al. 2001). Systemic or intracerebral administration (Bannai et al. 2007; Centenaro et al. 2008; De Boer and Koolhaas 2005) of CP-93,129 have been shown to exert potent anti-aggressive effects, without modifying other types of non-aggressive behavior.

The relatively few studies on neural mechanisms mediating maternal aggressive behavior (Consiglio et al. 2005; De Almeida and Lucion 1997; Factor et al. 1993; Ferreira et al. 1987; Hansen and Ferreira 1986, Giovenardi et al. 1998; Insel 1986; Lonstein and Gammie 2002; Nelson and Trainor 2007; Russel and Leng 1998; Svare 1990) implicate the mediodorsal region of the thalamus, peripeduncular nucleus of the lateral midbrain (PPN), septum, paraventricular and medial hypothalamus, and amygdala. The defensive nature of the postpartum female's response, most prominently frontal attacks, has been interpreted most often in terms of a fear or anxiety response towards the intruder. Previously, we showed that the 5-HT_{1B} receptors in the VO PFC have an important role in maternal aggressive behavior (Veiga et al. 2007).

The respective roles of 5-HT_{1A} and 5-HT_{1B} receptors in modulating aggressive behavior remain a source of debate and conflicting evidence (De Almeida and Lucion 1997; Millan et al. 1997; Mos et al. 1993; Sanchez and Hyttel 1994; Sijbesma et al. 1991). Consistent with the present results, there is evidence that the anti-aggressive effects of 5-HT_{1A} receptor stimulation are caused via activation of the 5-HT postsynaptic receptors (Sijbesma et al. 1991; Mos et al. 1992, 1993; Olivier and van Oorschot 2005). Microinjections of CP-93,129 or CP-94,253 into the DRN exert potent anti-aggressive effects, which can be obtained by action at multiple sites, somatodendritic autoreceptors, presynaptic terminal autoreceptors, and postsynaptic heteroreceptors (Bannai et al. 2007; Faccidomo et al. submitted). Studies with 5-HT_{1B} full and partial receptor agonists such as CP-94,253, eltoprazine, TFMPP, zolmitriptan, and anpirtoline have consistently shown anti-aggressive effects, regardless of the basal levels of aggressive behavior (De Almeida and Miczek 2002; Miczek et al. 2002; Mos et al. 1992; Olivier and Mos 1986), which can be mediated by somatodendritic autoreceptors (Bannai et al. 2007, Faccidomo et al. submitted) or postsynaptic heteroreceptors (De Almeida et al. 2001).

However, some studies emphasize 5-HT_{1A} autoreceptors as the relevant site for the antiaggressive effects of BMY-7378 (White et al. 1991), NAN-190 (Sanchez et al. 1996), and, particularly, S-15535 (De Boer and Koolhaas 2005; Millan et al. 1997). Other studies have shown that maternal aggressive behavior in rats was decreased after systemic administration of 5-HT_{1A} receptor agonists such as ipsapirone, 8-OH-DPAT, fluprazine, and buspirone and by DOI, a5-$HT_{2A/C}$ receptor agonist (Ferreira et al. 2000; Lonstein and Gammie 2002; Olivier et al. 1985, 1986, 1995), and by the SSRI fluvoxamine (Lonstein and Gammie 2002).

In summary, CP-93,129, when microinjected into the region of the VO PFC of postpartum female rats that were provoked socially, acting either on presynaptic terminal 5-HT_{1B} autoreceptors or on postsynaptic heteroreceptors, reduced aggressive behavior. On the other hand, the activation of the somatodendritic 5-HT_{1A} autoreceptors via the local microinjection of 8-OH-DPAT into the DRN increased aggressive behavior in postpartum female rats. It is possible that 5HT_{1B} receptors in VO PFC participate in enhancing maternal responsivity, including maternal aggression and pup care, rather than aggression itself. On the other hand, the defensive nature of the female's response, most prominently frontal attacks, may involve fear or anxiety responses towards the intruder, contrasting with pup care (Table 1).

Further experiments are necessary to assess the role of 5-HT_{1A} and 5-HT_{1B} receptor agonists in the DRN and in the VO PFC, respectively in male aggression to assess potential sex differences in rodents and primate species. As complement to the current neuropharmacological studies of the VO PFC and the DRN, we are currently assessing the activation of neurons in these areas as indicated by c-Fos during an aggressive confrontation in female rats (Veiga et al. in preparation). Furthermore, it is important to learn to what extent social instigation induces genomic and non-genomic changes in 5-HT_{1A} or 5-HT_{1B} receptor expression.

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