Psychopharmacology (2006) 187:237–244
DOI 10.1007/s00213-006-0424-1

ORIGINAL INVESTIGATION

Differential roles of amygdaloid nuclei in the anxiolytic- and antidepressant-like effects of the V1b receptor antagonist, SSR149415, in rats

N. Salomé · J. Stemmelin · C. Cohen · G. Griebel

Received: 23 February 2006 / Accepted: 20 April 2006 / Published online: 2 June 2006

Abstract
Rationale SSR149415 ((2S, 4R)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-*N*,*N*-dimethyl-2-pyrrolidinecarboxamide), the first selective nonpeptide vasopressin V1b receptor antagonist has been shown to induce antidepressant—and anxiolytic-like effects following systemic administration, whereas intraseptal infusion of the drug engender antidepressant—but not anxiolytic-like effects.
Objectives Based on recent evidence that V1b receptors are located within the amygdaloid complex, a structure which is well known for its modulatory role of emotional processes, the possible involvement of the different amygdaloid nuclei in the anxiolytic- and/or antidepressant-like effects of SSR149415 was examined.
Methods Male Sprague-Dawley or Wistar rats were infused with SSR149415 into the central (CeA), the basolateral (BlA), or the medial (MeA) nucleus of the amygdala and tested 10 min after microinjection in the elevated plus-maze or the forced-swimming test, two models typically used for assessing the anxiolytic and antidepressant effects of drugs, respectively.
Results Microinjection of SSR149415 into the BlA (1–10 ng), but not into the CeA or the MeA, increased the percentage of time spent in the open arms of the elevated plus-maze, indicating anxiolytic-like effects. Furthermore, in the forced-swimming test, microinjection of the drug into the CeA (1, 10, and 100 ng), BlA (1–10 ng), or MeA (100 ng) decreased immobility, an effect which is indicative of an antidepressant-like action. Together, these findings indicate that while the antidepressant-like effects of SSR149415 are mediated by different amygdaloid nuclei, its anxiolytic-like effects appear to involve only the basolateral nucleus of the amygdala. Moreover, these results add further evidence to the role of extrahypothalamic vasopressinergic systems in the control of emotional responses.

Keywords SSR149415 · Amygdaloid nuclei · Elevated plus-maze · Forced-swimming test · Anxiety · Depression · Rat · Vasopressin · V1b receptor

N. Salomé · J. Stemmelin · C. Cohen (✉) · G. Griebel
Sanofi-Aventis, Department of Psychopharmacology,
31 avenue Paul Vaillant-Couturier,
Bagneux 92220, France
e-mail: caroline.cohen@sanofi-aventis.com

Introduction

Vasopressin is a key regulator of the hypothalamic–pituitary–adrenal (HPA) axis. During stress exposure, the peptide is released from the median eminence into the pituitary portal circulation where it potentiates the effects of corticotropin-releasing factor (CRF) on adrenocorticotropin (ACTH) release (Aguilera and Rabadan-Diehl 2000). Among the two Gq/11-coupled vasopressin receptors (V1a and V1b) found in the brain, the V1b subtype mediates the pituitary actions of vasopressin (Tanoue et al. 2004). Extrahypothalamic vasopressin-containing neurons have been characterized in the rat, in particular in the medial amygdala and the bed bucleus of the stria terminalis (BNST) (Caffé et al. 1987). More recently, using anti-V1b receptor immunochemistry, V1b receptors were localized in the lateral septum, amygdala, BNST, hippocampal formation, and several cortical areas (Hernando et al. 2001; Stemmelin et al. 2005). This pattern of distribution, along

with the finding that the expression of V1b receptor mRNA increases after chronic stress exposure (Rabadan-Diehl et al. 1997), suggests that vasopressin might exert a modulatory role of the stress response via activation of the V1b receptors located in the pituitary and in extrahypothalamic brain structures.

Recently, the first selective nonpeptide antagonist of the V1b receptor, SSR149415 ((2S, 4R)-1-[5-chloro-1-[(2, 4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-*N*,*N*-dimethyl-2-pyrrolidinecarboxamide), was described (Serradeil-Le Gal et al. 2002). Behavioral studies showed that SSR149415 displayed anxiolytic-like activity in a variety of classical (punished drinking, elevated plus-maze, and light/dark tests) and atypical (fear/anxiety defense test battery and social defeat-induced anxiety) rodent models, and antidepressant-like activity in several acute and chronic models, such as the forced-swimming and chronic mild stress tests (Griebel et al. 2002, 2003). In the forced-swimming test in rats, hypophysectomy did not alter the effect of SSR149415, suggesting that extrahypothalamic V1b receptors may be involved in the antidepressant-like action of SSR149415. In line with this idea are recent findings showing that intraseptal application of the compound produced antidepressant-like effects in the forced-swimming test. However, intraseptal infusion of SSR149415 failed to produce anxiolytic-like activity, suggesting that other brain structures may mediate such effects (Stemmelin et al. 2005).

Among the brain regions that have been suggested to be involved in the pathophysiology of anxiety and depression, the amygdala, which is composed of several functionally distinct nuclei, is of particular interest (Davis and Whalen 2001). In humans, neuroimaging studies using positron emission tomography (PET) or magnetic resonance imaging (MRI) have shown functional and structural abnormalities of the amygdala associated with depression and anxiety disorders (Sheline et al. 1998; Drevets 2001; Massana et al. 2003; Hasting et al. 2004). However, limitations in spatial resolution have precluded implication of specific amygdaloid nuclei in these conditions. In animals, different amygdaloid nuclei have been suggested to be involved in the expression of anxiety-related behaviors (Pesold and Treit 1995; Menard and Treit 1999). For example, the basolateral amygdala (BlA) was shown to play a major role in mediating the anxiolytic-like effects of benzodiazepines in the elevated plus-maze, while the central amygdala (CeA) was involved in mediating anxiolysis of these drugs in the shock-probe burying test or the Geller–Seifter test (Shibata et al. 1982; Kataoka et al. 1987; Green and Vale 1992; Zangrossi and Graeff 1994; Pesold and Treit 1995). Although most of the studies have focused on the CeA and the BlA, a few data suggest that the medial amygdaloid (MeA) nucleus could modulate anxiety-related behavior as well. Microinjection of a 5-HT2B receptor agonist into the MeA produced anxiolysis in the elevated plus-maze and the social interaction tests in rats (Duxon et al. 1995, 1997). More recently, microinjections of a neurokinin-1 receptor antagonist into the MeA were found to block the anxiogenic-like response to immobilization stress in the elevated plus-maze (Ebner et al. 2004). The differential involvement of the amygdaloid nuclei in the modulation of depressive-like behavior is less documented. Gorka et al. (1979) reported that unilateral lesion of the amygdala reduced the effect of systemic injection of imipramine on the duration of immobility in the forced-swimming test. In addition, infusion of imipramine into the CeA-BlA or into the MeA produced antidepressant-like effects in this test (Araki et al. 1984; Duncan et al. 1986). A number of previous studies have suggested that the amygdala is a target region for vasopressin to exert its physiological action. The amygdala contains a substantial number of vasopressinergic neurons and receptors (Caffé and van Leeuwen 1983; Dorsa et al. 1984; Sofroniew 1985; Veinante and Freund-Mercier 1997). More particularly, using anti-V1b receptor immunohistochemistry, the presence of V1b receptors was demonstrated in the amygdaloid complex including the CeA, BlA, and MeA (Hernando et al. 2001; Stemmelin et al. 2005). It is interesting to note that peripheral or intracerebroventricular injection of vasopressin was shown to increase immediate early gene c-*fos* expression in the amygdala (Andrea and Herbert 1993; Wu et al. 1995; Chen and Herbert 1995). It was also demonstrated that swim stress enhances vasopressin release in the amygdala (Ebner et al. 2002), suggesting a close relationship between vasopressin, amygdala, and stress.

In this context, the aim of the present study was to investigate the role of the CeA, MeA, and BlA in mediating the anxiolytic- and antidepressant-like effects of the V1b receptor antagonist, SSR149415, as measured in the elevated plus-maze and forced-swimming tests in rats.

Materials and method

Animals

Male Sprague–Dawley rats (elevated plus-maze; 200–250 g, Iffa Credo, Les Oncins, France) or male Wistar rats (forced-swimming; 200–250 g, Janvier, Le Genest, St-Isle, France) housed in groups of five upon arrival were used. After surgery, they were housed in single cages (20 × 30 × 18 cm) and maintained under a 12:12 LD cycle (lights on at 0700). Food and water was available ad libitum. The behavioral experiments were performed between 0900 and 1500. All experimental procedures described herein were

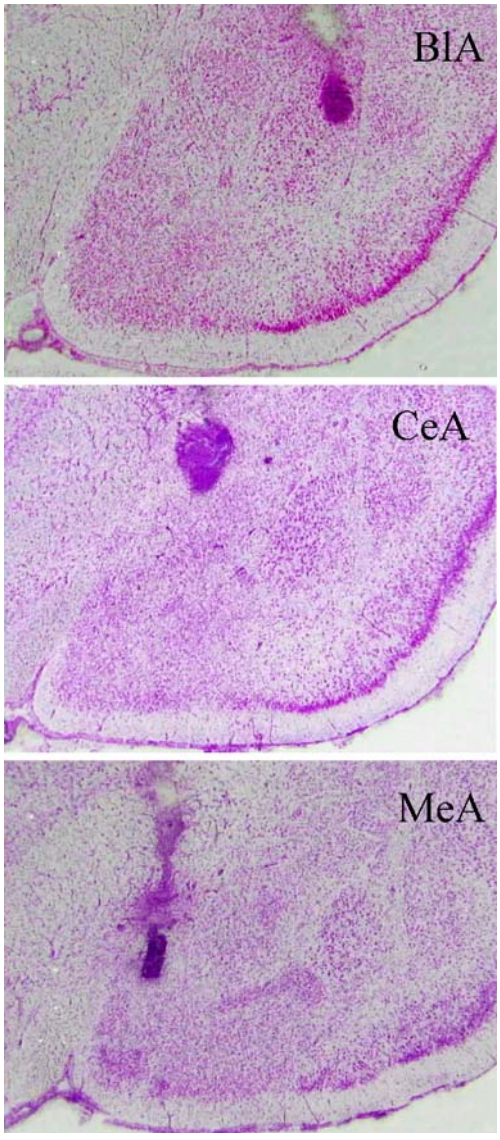

Fig. 1 Position of microinfusion cannula in the BlA, CeA, and MeA on cresyl violet stained brain slices

approved by the Animal Care and Use Committee of Sanofi-Aventis and fully comply with French legislation on research involving laboratory animals.

Surgical procedures

Rats were anesthetized with Zoletil (a mixture of tiletamine 30 mg/kg and zolazepam 30 mg/kg, Virbac, Carros, France, 60 mg/kg, i.p.) and placed in a stereotaxic frame (Kopf Instruments, Tujunga, CA, USA). Two guide cannulae consisting of stainless-steel tubings (26 G, 12 mm, Cooper, London, UK) were implanted in the CeA, BlA, or MeA so as to position the tips at 1 mm above the nucleus (coordinates from bregma: BlA AP −2.8, ML 5.3, V: −7.4; MeA, AP −2.6, ML 4, V −8.0, angle 5°; CeA, AP −2.3, ML 4.2, V −6.0) according to the rat brain atlas of Paxinos and Watson (1998) (Fig. 1). The guide cannulae with obturators were anchored to the skull with two jeweler screws (Plastic One, Ronaoke, VA, USA) and Paladur dental cement (Heraeus Kulzer, Hanau, Germany). After surgery, rats were allowed a 5-day recovery period, during which they were handled twice before testing to verify that the cannulae obturators (A-M Systems, Carlsborg WA, USA) were kept in place.

Behavioral testing

The elevated plus-maze test

The procedure was a modification of that described by Pellow et al. (1985). The apparatus was made of polyvinyl-chloride. It was elevated to a height of 70 cm with two open (50×10) and two enclosed arms (50×10×50) arranged so that the arms of the same type were opposite to each other. The apparatus was equipped with infrared beams and sensors capable of measuring activity in the different arms. The illumination intensity measured in the open arms was 30 lx. Rats were placed in the center of the maze for a free exploration period of 4 min. Results were expressed as the mean ratio of time spent in open arms to total time spent in both open and closed arms (an index of the level of anxiety) and the mean number of entries in closed arms (an index of general locomotor activity). An arm entry was counted when the rat had four feet onto an arm.

The forced-swimming test

The procedure was a modification of that described by Porsolt et al. (1977). Animals were placed in individual glass cylinder (diameter 17 cm, height 40 cm) containing water (height 24 cm, 22°C). Two swimming sessions were conducted (an initial 15-min pretest followed the next day by a 6-min test). The duration of immobility (in second) was measured manually during the 6-min test by an experimenter who was unaware of the drug treatments. Immobility was defined as the minimal movement necessary for the rat to stay afloat.

Drug administration

Ten minute before testing in the elevated plus-maze, rats received a bilateral injection of the drug using stainless-steel microinjection cannulae (31 G Cooper, London, UK) that extended 1 mm beyond the tips of the guide cannulae. In the forced-swimming test, rats implanted with guide cannulae in the CeA received one injection after the first day and another 10 min before to testing. However, due to the occurrence of tissue necrosis with the double injection in some animals that have been excluded from the statistical

Table 1 Group sizes for each experiment

Elevated plus-maze			Forced-swimming test		
Amygdaloid nucleus	Dose (ng)	Number of rats	Amygdaloid nucleus	Dose (ng)	Number of rats
BlA	0	16	BlA	0	20
	0.1	6		0.1	7
	1	8		1	8
	10	10		10	10
CeA	0	16	CeA	0	10
	1	10		0.1	6
	10	7		1	12
	100	14		10	10
				100	11
MeA	0	13	MeA	0	18
	10	13		10	12
	100	9		100	9

analyses, animals implanted with guide cannulae in the BlA and MeA received only one microinjection the day of testing, 10 min before testing. The cannulae were connected by polyethylene tubings (Plastic One, Ronaoke, VA, USA) to microsyringes (Exmire, Ito, Fuji, Japan) mounted on a motorized pump (CMA, Solna, Sweden).

SSR149415, isomer(−), was synthesized by the Medicinal Chemistry Department of Sanofi-Aventis. It was prepared as a solution in physiological saline 0.9% containing DMSO 5% (Sigma, Lyon, France) and Cremophor EL 5% (Sigma, Lyon, France). Aliquots containing 1 mg/0.6 ml SSR149415 were frozen and stored at −20°C. Solutions were infused at a volume of 0.3 µl/side and at a rate of 0.2 µl/min. Cannulae were left in place for an additional minute to avoid reflux of the drugs inside the guide cannulae. During the 2-min infusion, rats were slightly restrained by the experimenter. After injection, obturators were inserted and rats were placed in their home cages. Control animals were injected with the vehicle.

Table 2 Effects of SSR149415 in the elevated plus-maze after bilateral infusion into the BlA, CeA, or MeA

Amygdaloid nucleus	Dose (ng)	Number of closed arm entries (mean±SEM)
BlA	0	12.3±0.9
	0.1	14.8±2.3
	1	12±0.9
	10	9.5±1.1
CeA	0	13.9±0.8
	1	12.6±0.5
	10	13.3±0.9
	100	11.4±1
MeA	0	12.7±0.7
	10	13.6±1
	100	12.1±1.7

Histology and controls

On the day after testing, rats were killed with an overdose of pentobarbital (Virbac, Carros, France, 100 mg/kg, i.p.), and brains were removed and frozen. Brain slices (30 mm) were subsequently cut using a cryostat and stained with cresyl violet. Cases where the tip of one or both cannulae was located outside the CeA, BlA, or MeA were excluded from statistical analysis. Group sizes are given in Table 1.

Statistics

Data were analyzed with one-factor analysis of variance (ANOVA). Significance was set at 0.05. In cases of a significant main effect, post hoc comparisons were performed with a Dunnett's test.

Results

Behavioral testing

Effects of intraamygdala infusion of SSR149415 in the elevated plus-maze. The bilateral infusion of SSR149415 into the BlA modified significantly the percentage of time spent in the open arm without affecting locomotor activity as assessed by the number of entries into the closed arms ($F(3,39)=6.45$, $p<0.01$; $F(3,39)=2.60$, n.s., respectively) (Table 2). Post hoc comparison showed that the doses of 1 and 10 ng of SSR149415 induced a significant increase of the percentage of time spent in the open arms when compared to the control group ($p<0.05$ and $p<0.01$, respectively) (Fig. 2). The bilateral infusion of SSR149415 into the CeA (0.1–100 ng) or the MeA (10–100 ng) did not modify significantly the percentage of time spent in the open arms and the number of entries into the closed arms [$F(3,46)=0.27$ and $F(3,46)=1.69$, respectively, for CeA and $F(2,34)=0.27$ and $F(2,34)=0.45$, respectively for MeA] (Table 2).

Effects of intraamygdala infusion of SSR149415 in the forced-swimming test. The bilateral infusion of SSR149415 into the BlA, CeA, or MeA modified significantly immobility time [$F(4,48)=9.30$, $p<0.001$; $F(3,41)=4.97$, $p<0.01$; $F(2,38)=10.6$, $p<0.01$, respectively]. Post hoc comparisons showed that SSR149415 reduced this behavior at 1 and 10 ng in the BlA, at 1, 10, and 100 ng in the CeA, and at 100 ng in the MeA (Fig. 3).

Discussion

The present study assessed the behavioral effects of local infusion of the selective nonpeptide V1b receptor antago-

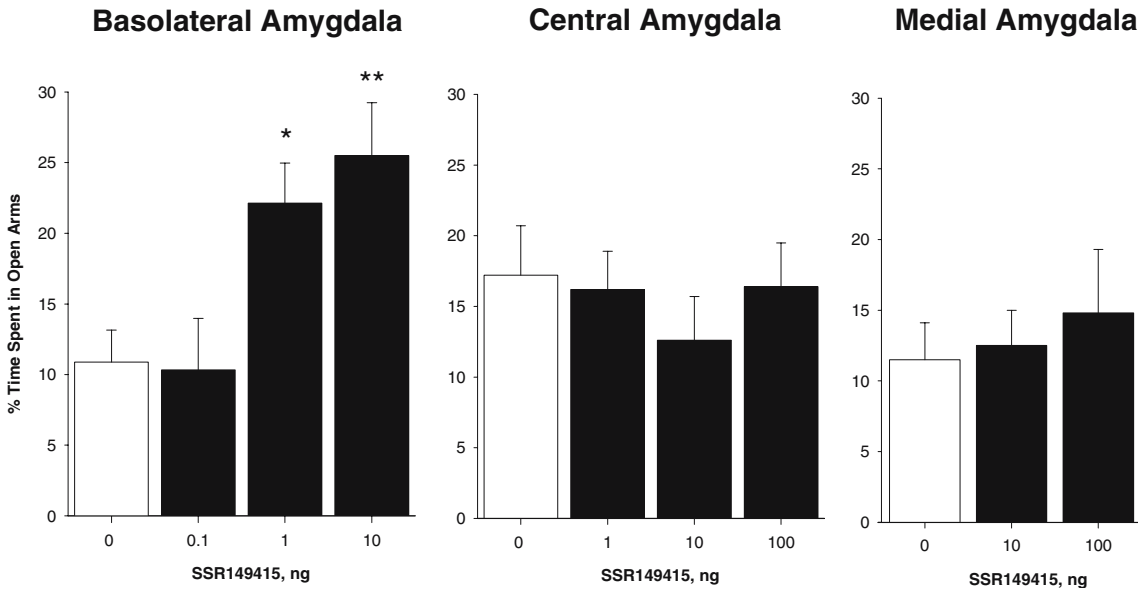

Fig. 2 Percentage of time spent in open arms in the elevated-plus maze after bilateral infusion of SSR149415 into BlA (*left panel*), CeA (*middle panel*), and MeA (*right panel*). Data represent mean±SEM. *$p<0.05$, **$p<0.01$ vs control

nist SSR149415 in distinct amygdaloid nuclei, which have been involved in the modulation of stress-related responses. The results showed that the direct application of this drug into the basolateral nucleus of the amygdala-induced anxiolytic-like effects in the elevated plus-maze, while its infusion into the central, the basolateral and the medial nucleus of this structure produced antidepressant-like effects in the forced-swimming test. This is the first study that investigated the amygdala as a possible site of action of SSR149415. A previous report (Stemmelin et al. 2005) has demonstrated antidepressant-like effects of SSR149415 in the forced-swimming test after microinjection into the lateral septum, whereas a similar treatment failed to modify levels of anxiety in the elevated plus-maze.

The anxiolytic-like activity of SSR149415 when injected into the BlA was not contaminated by motor impairment as indicated by the lack of effect of the drug on the number of entries into the closed arm, a parameter classically related to locomotor activity (Pellow et al. 1985). Moreover, in previous studies where the drug was administered systematically, it did not produce central depressant effects in classical motor tests and EEG experiments up to very high doses (i.e., 100 mg/kg, p.o.) (Griebel et al. 2002). Although SSR149415 may have diffused to other brain regions, it is

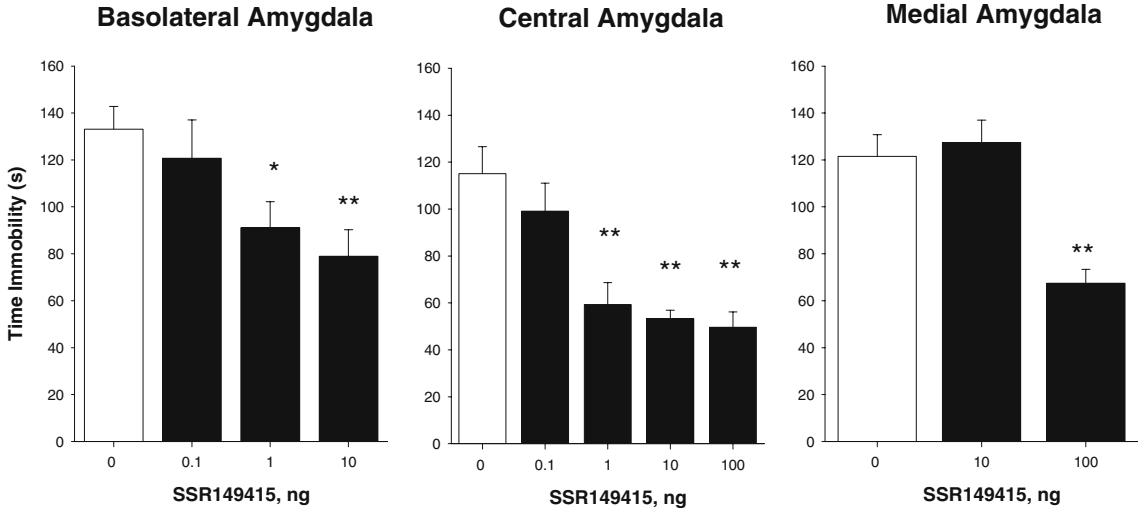

Fig. 3 Effects of SSR149415 in the forced-swimming test after bilateral infusion into BlA (*left panel*), CeA (*middle panel*), and MeA (*right panel*). Data represent mean±SEM. *$p<0.05$, **$p<0.01$ vs control

unlikely that its anxiolytic-like effects were due to the blockade of V1b receptors located in other structures. Firstly, the injection of the compound into adjacent regions (CeA, MeA) had no effect in the elevated plus-maze. Secondly, the total volume of injection, 0.3 μl, was rather small in comparison to the 0.5 μl frequently used (Wilensky et al. 2000; Pesold and Treit 1995; Duxon et al. 1995). Previous studies have shown that the BlA is an important site for mediating the anxiolytic-like effects of drugs in models based on exploratory activity. For example, microinjection of the benzodiazepine, midazolam, or of the 5-HT_{1A} agonist, 8-OH-DPAT, elicited anxiolytic-like effects in the elevated plus- or T-maze (Green and Vale 1992; Pesold and Treit 1995; Gonzalez et al. 1996; Zangrossi et al. 1999). In our experiment, microinjection of SSR149415 into the CeA and MeA did not modify the behavior in the elevated plus-maze. These data are in agreement with previous studies. For example, the CeA has been reported to be mainly involved in the regulation of anxiety-related behavior when subjects were confronted with procedures based on punished responding, such as the Vogel or the Geller–Seifter conflict paradigm (Pesold and Treit 1995, Kataoka et al. 1987). Concerning the MeA, however, it has been shown that injection of the 5-HT_{2B} receptor agonist, BW 723C86, produced anxiolysis in the elevated plus-maze and in the social interaction tests (Duxon et al. 1995, 1997). Overall, our results suggest that in our experimental conditions, only the BlA is an important anatomical locus involved in the modulation of anxiety by SSR19415. Moreover, our study supports a growing body of evidence that subsystems of the amygdala may regulate different aspects of anxiety-related behavior (Killcross et al. 1997). Further investigations need to be performed to study the role of V1b receptors in distinct amygdaloid nuclei in other paradigms, including conflict procedures.

Results obtained in the forced-swimming test indicate that V1b receptors located in the amygdala are critical for mediating the antidepressant-like effects of SSR149415. More particularly, when infused into the CeA, the BlA, or the MeA, the drug produced similar reductions in immobility time as that reported after a systemic administration (Griebel et al. 2002). The involvement of amygdala V1 receptors in the regulation of depressive-like behaviors has been reported previously. Infusion of the mixed V1a/b peptide antagonist d(CH2)5Tyr(Me)AVP into the amygdala using a retrodialysis technique in rats produced antidepressant-like behaviors (Ebner et al. 2002). The amygdala has been implicated in the regulation of depressive-related behavior or in the actions of antidepressant drugs in the forced-swimming test and the olfactory bulbectomized paradigm (Gorka et al. 1979; Duncan et al. 1986; Shibata and Watanabe 1994; Wrynn et al. 2000; Ho et al. 2001; Rutkoski et al. 2002). For example, unilateral lesion of the amygdala reduced the antidepressant-like effects of imipramine on immobility time and microinjection of imipramine into the CeA, BlA, or MeA produced antidepressant-like effects (Gorka et al. 1979; Araki et al. 1984; Duncan et al. 1986). Moreover, acute administration of imipramine or fluoxetine increased the number of Fos immunoreactive neurons in the central and medial amygdala (Duncan et al. 1993; Salchner and Singewald 2002). SSR149415 was apparently less potent when injected into the MeA than into the BlA and CeA. This result is consistent with the locus of action of imipramine and pargyline in the forced-swimming test paradigm (Duncan et al. 1986).

The present results showing that SSR149415 displayed anxiolytic- and antidepressant-like effects after injection into specific amygdaloid nuclei add further evidence to the role of extrahypothalamic vasopressinergic systems in the control of emotional responses. Griebel et al. (2002) have first demonstrated that the antidepressant-like effects of SSR149415 were still present, albeit at a higher dose, in hypophysectomized rats. Recently, Stemmelin et al. (2005) found that SSR149415 injected into the lateral septum engendered antidepressant-like effects. In line with these results, V1b receptors are localized in limbic regions (e.g., septum and amygdala) in which vasopressin release could be stimulated by a variety of stressors (Ebner et al. 1999, 2002; Hernando et al. 2001; Stemmelin et al. 2005; Huber et al. 2005). The precise origin of extrahypothalamic vasopressin remains vague. Thus, vasopressin could be released from local terminals or might travel over long distances (De Vries and Buijs 1983; Landgraf et al. 1995).

In conclusion, this study demonstrated for the first time that the blockade of V1b receptors located in the basolateral amygdala by SSR149415 induced anxiolytic-like effects resembling those observed after systemic administration of the compound. Moreover, this study showed that several brain areas, such as the central, the basolateral, the medial nucleus of amygdala, and, as previously reported, the lateral septum were involved in the antidepressant-like action of the compound. These findings confirm further the hypothesis that the behavioral effects of SSR149415 in stress-related responses involve extrahypothalamic V1b receptors, suggesting that the HPA stress axis does not solely mediate the antistress-like action of this compound.

References

Aguilera G, Rabadan-Diehl C (2000) Vasopressinergic regulation of the hypothalamic–pituitary–adrenal axis: implications for stress adaptation. Regul Pept 96:23–29

Andrea LC, Herbert J (1993) Expression of c-fos in restricted areas of intraventricular infusions of vasopressin and corticotropin-releasing factor. Neuroscience 53:735–748

Araki H, Kawashima K, Aihara H (1984) The difference in the site of actions of tricyclic antidepressants and methamphetamine on the duration of the immobility in the behavioral despair test. Jpn J Pharmacol 35:67–72

Caffé AR, van Leeuwen FW (1983) Vasopressin-immunoreactive cells in the dorsomedial hypothalamic region, medial amygdaloid nucleus and locus coeruleus of the rat. Cell Tissue Res 233:23–33

Caffé AR, van Leeuwen FW, Luiten PG (1987) Vasopressin cells in the medial amygdala of the rat project to the lateral septum and ventral hippocampus. J Comp Neurol 261:237–252

Chen X, Herbert J (1995) Alterations in sensitivity to intracerebral vasopressin and the effects of a V1a receptor antagonist on cellular, autonomic and endocrine responses to repeated stress. Neuroscience 64:687–697

Davis M, Whalen PJ (2001) The amygdala: vigilance and emotion. Mol Psychiatry 6:13–34

De Vries GJ, Buijs RM (1983) The origin of the vasopressinergic and oxytocinergic innervation of the rat brain with special reference to the lateral septum. Brain Res 273:307–317

Dorsa DM, Petracca FM, Baskin DG, Cornett LE (1984) Localization and characterization of vasopressin-binding sites in the amygdala of the rat brain. J Neurosci 4:1764–1770

Drevets W (2001) Neuroimaging and neuropathological studies of depression: implications for the cognitive–emotional features of mood disorders. Curr Opin Neurobiol 11:240–249

Duncan GE, Breese GR, Criswell H, Stumpf WE, Mueller RA, Covey JB (1986) Effects of antidepressant drugs injected into the amygdala on behavioral responses of rats in the forced swim test. J Pharmacol Exp Ther 238:758–762

Duncan GE, Johnson KB, Breese GR (1993) Topographic patterns of brain activity in response to swim stress: assessment by 2-deoxyglucose uptake and expression of Fos-like immunoreactivity. J Neurosci 13:3932–3943

Duxon MS, Beckett SRG, Baxter GS, Blackburn TP, Fone (1995) Intra-amygdala injection of the 5-HT2B receptor agonist BW 723C86 produces anxiolysis on the elevated plus-maze in the rat. Br J Pharmacol 115:105P

Duxon MS, Kennett GA, Lightowler S, Blackburn TP (1997) Activation of 5-HT2B receptors in the medial amygdala causes anxiolysis in the social interaction test in the rat. Neuropharmacology 36:601–608

Ebner K, Wotjak CT, Holsboer F, Landgraf R, Engelmann M (1999) Vasopressin released within the septal brain area during swim stress modulates the behavioural stress response in rats. Eur J Neurosci 11:997–1002

Ebner K, Wotjak CT, Landgraf R, Engelmann M (2002) Forced swimming triggers vasopressin release within the amygdala to modulate stress-coping strategies in rats. Eur J Neurosci 15:384–388

Ebner K, Rupniak NM, Saria A, Singewald N (2004) Substance P in the medial amygdala: emotional stress-sensitive release and modulation of anxiety-related behavior in rats. Proc Natl Acad Sci USA 23:4280–4285

Gonzalez LE, Andrews N, File SE (1996) 5-HT1A and benzodiazepine receptors in the basolateral amygdala modulate anxiety in the social interaction test, but not in the elevated plus-maze. Brain Res 732:145–153

Gorka Z, Ossowska K, Stach R (1979) The effect of unilateral amygdala lesion on the imipramine action in the behavioral despair in rats. J Pharm Pharmacol 31:647–648

Green S, Vale AL (1992) Role of amygdaloid nuclei in the anxiolytic effects of benzodiazepines in rats. Behav Pharmacol 3:261–264

Griebel G, Simiand J, Serradeil-Le Gal C, Wagnon J, Pascal M, Scatton B et al (2002) Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. Proc Natl Acad Sci USA 99:6370–6375

Griebel G, Simiand J, Stemmelin J, Serradeil-Le Gal C, Steinberg R (2003) The vasopressin V1b receptor as a therapeutic target in stress-related disorders. Curr Drug Target CNS Neurol Disord 2:191–200

Hasting RS, Parsey RV, Oquendo MA, Arango V, Mann JJ (2004) Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. Neuropsychopharmacology 29:952–959

Hernando F, Schoots O, Lolait SJ, Burbach JP (2001) Immunohistochemical localization of the vasopressin V1b receptor in the rat brain and pituitary gland: anatomical support for its involvement in the central effects of vasopressin. Endocrinology 142:1659–1668

Ho Y, Liu T, Tai M, Wen Z, Chow RS, Tsai Y, Wong C (2001) Effects of olfactory bulbectomy on NMDA receptor density in the rat brain. Brain Res 900:214–218

Huber D, Veinante P, Stoop R (2005) Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. Science 308:245–248

Kataoka Y, Shibata Z, Yamashita K, Ueki S (1987) Differential mechanisms involved in the anticonflict action of benzodiazepines injected into the central amygdala and mamillary body. Brain Res 416:243–247

Killcross S, Robbins TW, Everitt BJ (1997) Different types of fear-conditioned behaviour mediated by separate nuclei within amygdala. Nature 388:377–380

Landgraf R, Gerstberger R, Montkowski A, Probst JC, Wotjak CT, Holsboer F et al (1995) V1 vasopressin receptor antisense oligodeoxynucleotide into septum reduces vasopressin binding, social discrimination abilities, and anxiety-related behavior in rats. J Neurosci 15:4250–4258

Massana G, Serra-Grabulosa JM, Salgado-Pineda P, Gasto C, Junque C, Massana J, Mercader JM, Gomez B, Tobena A, Salamero M (2003) Amygdalar atrophy in panic disorder patients detected by volumetric magnetic resonance imaging. Neuroimage 19:80–90

Menard J, Treit D (1999) Effects of centrally administered anxiolytic compounds in animal models of anxiety. Neurosci Biobehav Rev 23:591–613

Paxinos G, Watson W (1998) The rat brain in stereotaxic coordinates, 4th edn. Academic, London

Pellow S, Chopin P, File SE, Briley M (1985) Validation of open: closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J Neurosci Methods 14:149–167

Pesold C, Treit D (1995) The central and basolateral amygdala differentially mediate the anxiolytic effects of benzodiazepines. Brain Res 671:213–221

Porsolt R, Le Pichon M, Jalfre M (1977) Depression: a new animal model sensitive to antidepressant treatments. Nature 266: 730–732

Rabadan-Diehl C, Makara G, Kiss A, Lolait S, Zelena D, Ochedalski T et al (1997) Regulation of pituitary V1b vasopressin receptor messenger ribonucleic acid by adrenalectomy and glucocorticoid administration. Endocrinology 138:5189–5194

Rutkoski NJ, Lerant AA, Nolte CM, Westberry J, Levenson CW (2002) Regulation of neuropeptide Y in the rat amygdala following unilateral olfactory bulbectomy. Brain Res 951: 69–76

Salchner P, Singewald N (2002) Neuroanatomical substrates involved in the anxiogenic-like effect of acute fluoxetine treatment. Neuropharmacology 43:1238–1248

Serradeil-Le Gal C, Wagnon J, Simiand J, Griebel G, Lacour C, Guillon G et al (2002) Characterization of (2S,4R)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-*N*,*N*-dimethyl-2-pyrrolidine

carboxamide (SSR149415), a selective and orally active vasopressin V1b receptor antagonist. J Pharmacol Exp Ther 300:1122–1130

Sheline Y, Gado MH, Price JL (1998) Amygdala core nuclei volumes are decreased in recurrent major depression. J Neurosci 22:3251–3261

Shibata S, Watanabe S (1994) Facilitatory effect of olfactory bulbectomy on 2-deoxyglucose uptake in rat amygdala slices. Brain Res 665:147–150

Shibata K, Kataoka Y, Gomita Y, Ueki S (1982) Localization of the site of the anticonflict action of benzodiazepines in the amygdaloid nucleus of rats. Brain Res 234:442–446

Sofroniew MV (1985) Vasopressin- and neurophysin-immunoreactive neurons in the septal region, medial amygdala and locus coeruleus in colchicine-treated rats. Neuroscience 15:347–358

Stemmelin J, Lukovic L, Salome N, Griebel G (2005) Evidence that the lateral septum is involved in the antidepressant-like effects of the vasopressin V1b receptor antagonist, SSR149415. Neuropsychopharmacology 30:35–42

Tanoue A, Ito S, Honda K, Oshikawa S, Kitagawa Y, Koshimizu TA, Mori T, Tsujimoto G (2004) The vasopressin V1b receptor critically regulates hypothalamic–pituitary–adrenal axis activity under both stress and resting conditions. J Clin Invest 113:302–309

Veinante P, Freund-Mercier (1997) Distribution of oxytocin- and vasopressin-binding sites in the rat extended amygdala: a histoautoradiographic study. J Comp Neurol 38:305–325

Wilensky AE, Schafe GE, LeDoux JE (2000) The amygdala modulates memory consolidation of fear-motivated inhibitory avoidance learning but not classical fear conditioning. J Neurosci 20:7059–7066

Wu PH, Lança AJ, Liu JF, Man CF, Kalant H (1995) Peripheral injection of arginine8-vasopressin increases Fos in specific brain areas. Eur J Pharmacol 281:263–269

Wrynn AS, Sebens JB, Koch T, Leonard BE, Korf J (2000) Prolonged c-Jun expression in the basolateral amygdala following bulbectomy: possible implications for antidepressant activity and time of onset. Brain Res Mol Brain Res 76:7–17

Zangrossi H, Graeff FG (1994) Behavioral effects of intra-amygdala injections of GABA and 5-HT acting drug in the elevated plus maze. Braz J Med Biol Res 27:2453–2456

Zangrossi Jr H, Viana MB, Graeff FG (1999) Anxiolytic effect of intra-amygdala injection of midazolam and 8-hydroxy-2-(di-*n*-propylamino)tetralin in the elevated T-maze. Eur J Pharmacol 369:267–270