CHAPTER 4.2

Nonpeptide vasopressin V_{1b} receptor antagonists

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Abstract: Arginine vasopressin (AVP) is critical for adaptation of the hypothalamo–pituitary–adrenal axis during stress through its ability to potentiate the stimulatory effect of CRF. This observation, taken together with the identification of AVP receptors (e.g. V_{1b}) in limbic structures has led to the idea that this peptide may provide a good opportunity for pharmacological treatment of stress-related disorders. The availability of an orally active nonpeptide V_{1b} receptor antagonist has allowed to verify this hypothesis. Studies in animals have shown that the V_{1b} receptor antagonist, SSR149415, is able to attenuate some but not all stress-related behaviors in rodents. While the antidepressant-like effects of the compound was comparable to that of reference antidepressants, the overall profile displayed in anxiety tests was different from that of classical anxiolytics, such as benzodiazepines. While the latter were active in a wide range of anxiety models, the AVP antagonist showed clear-cut effects only in particularly stressful situations. Moreover, SSR149415 blocked several endocrine (i.e. ACTH release), neurochemical (i.e. noradrenaline release) and autonomic (i.e. heart rate) responses following acute stress exposure in rats. It is noteworthy that SSR149415 was devoid of central effects not related to emotionality. Altogether, these findings suggest that blockade of central V_{1b} receptors may represent a new therapeutic strategy for the treatment of depression and some forms of anxiety disorders.

Introduction

The treatment of stress-related disorders remains an active area of research and drug discovery focuses more and more on the involvement of neuroactive peptides in the modulation of emotional behaviors. The rapid advances in the understanding of gene structure and regulation of gene expression, the determination of peptide sequences, the characterization of their receptors, and the successful synthesis of both peptide and nonpeptide receptor ligands have increased the attraction for neuropeptides. Among these, corticotropin-releasing factor (CRF), cholecystokinin and tachykinins (substance P, and neurokinin A and B) have been the most extensively studied, but the involvement of other neuroactive peptides such as neurotensin, oxytocin and arginine

vasopressin (AVP) has also been considered (Rowe et al., 1995; Griebel, 1999; Aguilera and Rabadan-Diehl, 2000; Bale et al., 2001). Specific and highly potent nonpeptide receptor antagonists have been discovered and developed for AVP (Serradeil-Le Gal, 1998; Thibonnier et al., 2001; Serradeil-Le Gal et al., 2002). One of them has been tested in animal models of anxiety and depression, and as will be shown below, it produced positive effects in these procedures, although its profile differed from those observed with classical anxiolytics and antidepressants (Fig. 1).

Evidence that arginine vasopressin is involved in the regulation of stress response

The nonapeptide AVP, synthesized in the hypothalamic paraventricular (PVN) and supraoptic nuclei, is well known for its role on hydromineral balance, but there is also clear evidence that the peptide plays an important role as a neurotransmitter in the brain (Engelmann et al., 1996) and as a regulator of

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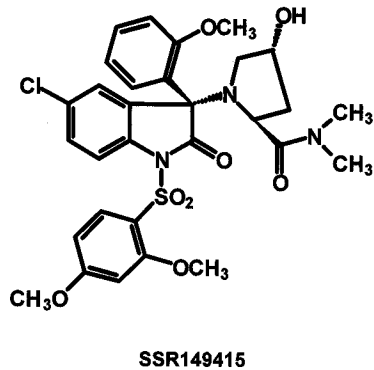
SSR149415

Fig. 1. Chemical structures of SSR149415 ((2S, 4R)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-*N*,*N*-dimethyl-2-pyrrolidine carboxamide, isomer(-)).

pituitary adrenocorticotropin (ACTH) secretion (McCann and Brobeck, 1954; Antoni, 1993; Aguilera, 1994). AVP is critical for adaptation of the hypothalamo–pituitary–adrenal (HPA) axis during stress through its ability to potentiate the stimulatory effect of CRF. Both acute and repeated stresses (e.g., restraint, foot shocks) stimulate release of AVP from the median eminence into the pituitary portal circulation and increase expression of the peptide in parvocellular neurons of the PVN (for a recent review, see Aguilera and Rabadan-Diehl, 2000).

Extrahypothalamic AVP-containing neurons have been characterized in the rat, notably in the medial amygdala and the bed nucleus of the stria terminalis, which innervate limbic structures such as the lateral septum and the ventral hippocampus (De Vries and Buijs, 1983; van Leeuwen and Caffé, 1983; Caffé et al., 1987). In these latter structures, AVP was suggested to act as a neurotransmitter, exerting its action by binding to specific G protein-coupled receptors, i.e., V_{1a} and V_{1b} (Lolait et al., 1995; Vaccari et al., 1998; Young et al., 1999), which are widely distributed in the central nervous system (CNS), including the lateral septum, cortex and hippocampus (Morel et al., 1992; Lolait et al., 1995; Tribollet et al., 1999). The presence of this AVP network suggests a modulatory role of the peptide in limbic functioning. Earlier research has demonstrated that locally applied AVP affects learning and memory, flank marking, hibernation and paternal behavior (De Wied, 1965, 1970;

Koob and Bloom, 1982; Dantzer and Bluthe, 1992; Alescio-Lautier et al., 1993; Engelmann et al., 1996).

The neuroanatomical distribution of AVP and its receptors has also prompted speculation about their functional role in emotional processes leading to studies that investigated the behavioral action of centrally infused peptide V_1 receptor antagonists in animal models of anxiety. For example, the intraseptal application of the mixed $V_{1a/b}$ receptor antagonist $d(CH_2)_5Tyr(Et)VAVP$ was found to produce anxiolytic-like effects in the elevated plus-maze test in rats (Liebsch et al., 1996). Moreover, infusion of an antisense oligodeoxynucleotide to the V_{1a} subtype mRNA into the septum of rats has been shown to reduce anxiety in the elevated plus-maze (Landgraf et al., 1995). Furthermore, AVP-deficient rats (i.e. Brattleboro) displayed attenuated conditioning freezing responses (Stoehr et al., 1993). Although there is no direct evidence that AVP or AVP receptor ligands may modulate anxiety or depression in humans, a recent clinical finding showed that AVP release was significantly correlated with anxiety symptoms in healthy volunteers after anxiogenic drug challenge (Abelson et al., 2001). It is reported in this study that volunteers with the highest levels of AVP also showed higher levels of respiratory distress and cognitive anxiety. Abnormalities in AVP levels or receptor activity have been detected in depression (Purba et al., 1996; van Londen et al., 1997; Zhou et al., 2001) and obsessive-compulsive disorder, but have not yet been studied in other anxiety disorders. Moreover, there is evidence suggesting that HPA axis dysregulation in depression may be associated with a shift towards increased vasopressinergic control of the axis (Holsboer and Barden, 1996; Dinan et al., 1999). In this context, it can be hypothesized that AVP receptor antagonists may represent potential agents for the treatment of stress-related disorders.

Behavioral effects of nonpeptide AVP receptor antagonists in animal models of anxiety and depression

Initially, peptide AVP receptor antagonists were developed, but their usefulness was limited because of their peptide nature, poor access to the brain following systemic administration and poor oral

bioavailability (Manning and Sawyer, 1993). Recently, several classes of nonpeptide antagonists of AVP receptors (i.e., V_{1a} and V_{1b}) have been discovered by random screening (Paranjape and Thibonnier, 2001; Thibonnier et al., 2001; Serradeil-Le Gal et al., 2002) and have allowed assessment of the potential therapeutic applications of selective blockade of AVP binding sites in stress-related disorders.

Effects of selective blockade of V_{1b} receptors

The first nonpeptide antagonist at the V_{1b} receptor, SSR149415, has been described recently (Serradeil-Le Gal et al., 2002). The compound displays high affinities for both native and recombinant human and rat V_{1b} receptors (human: $K_i = 4.2$ and $1.5\,nM$, respectively; rat: $K_i = 3.7$ and $1.3\,nM$, respectively), 60- and 800-fold selectivity for human and rat V_{1b} as compared to V_{1a} receptor, displayed weak affinity

at V_2 and OT receptors, and was inactive in more than 90 binding assays for neurotransmitters and peptides. In vivo, SSR149415 did not modify the V_{1a}-mediated vascular response following AVP administration and had no effect on diuresis in rats. It is a potent antagonist at the V_{1b} receptor as shown by its ability to inhibit AVP-induced Ca^{2+} increase in CHO cells expressing the human or rat V_{1b} receptor ($K_i = 1.26$ and $0.73\,nM$, respectively), and AVP-induced ACTH secretion in corticotroph cells in rats. The effects of SSR149415 were investigated in a variety of procedures based on stress-induced changes in behavioral, endocrine, neurochemical, and autonomic nervous system parameters.

Profile in animal models of anxiety

In traditional screening tests for anxiolytics, such as conflict paradigms (e.g., punished drinking procedure

Table 1. Summary of the pharmacological properties of the V_{1b} receptor antagonist, SSR149415, in rodents. Comparison with diazepam and fluoxetine.

Tests	MED or *ED_{50}, mg/kg, po, (ip) or §sc		
	SSR149415	Diazepam	Fluoxetine
Drinking conflict test in rats	(3)	(1)	(> 20)
Elevated plus-maze in rats	10	3	(> 10)
Fear-potentiated startle in rats	3	1	NT
Light/dark test in mice	(1)	(1)	(> 20)
Four-plate test in mice	3	1	NT
Social interaction in gerbils	10	(0.1)	> 10
Mouse defense test battery	1	1	(5)**
Social defeat stress in mice	0.3	4	(20)
Conditioned fear stress in mice	10	(2)	NT
Distress vocalizations in rat pups§	10**	1	3
Distress vocalizations in guinea pig pups	(20)	NT	(3)
Forced-swimming in rats	10	NA	10
Chronic mild stress in mice	(10)**	NA	(10)**
Chronic subordination stress in rats	10**	NA	10**
Isolation-induced aggression in mice	1	NT	NT
Restraint-induced physiological changes in rats	30	(2)	NT
Restraint stress-induced ACTH release in rats	(10)	NT	NT
Tail pinch stress-induced NE release in rats	(10)	NT	NT
EEG in rats	> 30	(1)	NT
Traction test in mice	> 100	6*	NT
Rotarod in mice	> 100	9*	NT
Morris water maze in mice	> 30	1	NT
Morris water maze in rats	> 30	10	NT

MED = minimal effective dose; NA = not applicable; NT = not tested; **After repeated treatment. Data are from Serradeil-Le Gal et al., 2002; Blanchard et al., 2002; Griebel et al., 2002a; 2002c, or unpublished.

in rats and four-plate test in mice) or exploratory-based models (e.g., elevated plus-maze in rats and light/dark choice task in mice), SSR149415 elicited anxiolytic-like activity following acute peripheral administration (Table 1) (Serradeil-Le Gal et al., 2002; Griebel et al., 2002a; 2002c). Interestingly, the V_{1b} receptor antagonist yielded positive effects in models where antidepressants, which are traditionally used in the long-term treatment of anxiety disorders, were either inactive or sometimes potentiated even further anxiety-related responses after single dosing. Importantly, SSR149415 was devoid of central effects not related to emotionality. When the drug was administered up to 100 mg/kg (po), it did not significantly modify performance of mice in the rotarod and traction tests. Neither did the drug modify sleep patterns following EEG analysis or impair learning in the Morris water maze up to 30 mg/kg (po) in mice or rats (Table 1) (Griebel et al., 2002a). Clearly, these findings have a direct bearing on the issue of the behavioral selectivity of any changes observed in the stress models.

The anxiety-reducing potential of SSR149415 was confirmed in atypical models, such as the fear-potentiated startle paradigm in rats and the mouse defense test battery (MDTB). The former measures conditioned fear by an increase in the amplitude of a simple reflex (the acoustic startle reflex) in the presence of a cue previously paired with an electric footshock. This paradigm offers a number of advantages as an alternative to most animal tests of fear or anxiety because it involves no operant and is reflected by an enhancement rather than a suppression of ongoing behavior (Davis et al., 1993). A variety of clinically effective anxiolytics block fear-potentiated startle in rats. SSR149415 attenuated dose-dependently fear-potentiated startle (Griebel et al., 2002c). It is important to note that the magnitude of the anxiolytic-like action of SSR149415 in these models was always less than that of the BZ anxiolytic diazepam, which was used as a positive control. Whether this may indicate a less efficacious anxiolytic-like potential of V_{1b} receptor antagonists compared to BZs, or suggests that these compounds may have a different spectrum of therapeutic activity in anxiety disorders than BZs remains to be determined. Results obtained with SSR149415 in the MDTB may, however, be relevant to this

issue (Table 1). As mentioned above, this procedure provides a model capable of responding to, and differentiating anxiolytic drugs of different classes through specific profiles of effect on different measures (Griebel and Sanger, 1999). Here, SSR149415 failed to modify significantly risk assessment, a behavior which has been shown to be particularly sensitive to BZs, i.e., generalized anxiety disorder (GAD), but it produced clear-cut effects on defensive aggression, a behavior which is claimed to be associated with certain aspects of stress disorders following traumatic events (Blanchard et al., 1997), thereby suggesting that V_{1b} receptor antagonists may be useful in these conditions rather than in GAD (Griebel et al., 2002a).

This idea was examined further by using several rodent procedures based on behavioral changes produced by traumatic events (social defeat, separation or unavoidable electric shocks) (Fig. 2). In the social defeat stress-induced anxiety paradigm in mice, SSR149415 completely antagonized the heightened emotionality in the elevated plus-maze produced by prior (stressful) exposure to an aggressive isolated resident (Fig. 2C). Conditioned fear stress induced by exposure to an environment paired previously with foot shock dramatically decreases locomotor activity. These effects of stress are attenuated by a variety of psychoactive drugs, including traditional (e.g., BZs) and atypical (e.g., 5-HT_{1A} receptor agonists, 5-HT reuptake inhibitors, tricyclics) anxiolytics (Kitaichi et al., 1995; Hashimoto et al., 1996; Inoue et al., 1996; Maki et al., 2000). Stress-induced hypolocomotion was also antagonized by SSR149415 (Fig. 2D). When rat and guinea pig pups are removed from their litter and separated from their mother, they rapidly emit sonic or ultrasonic distress calls, respectively. These stress responses are reduced by a variety of anti-anxiety drugs, including classical and atypical agents (Molewijk et al., 1996; Olivier et al., 1998). When SSR149415 was tested in these models, it produced a dose-dependent decrease in both sonic and ultrasonic vocalizations (Figs. 2AB). Altogether, these latter findings show clear-cut effects of the V_{1b} receptor antagonist in all models and comparable efficacy as reference compounds, thereby strengthening the idea that a V_{1b} receptor antagonist may be useful in conditions associated with exposure to traumatic events.
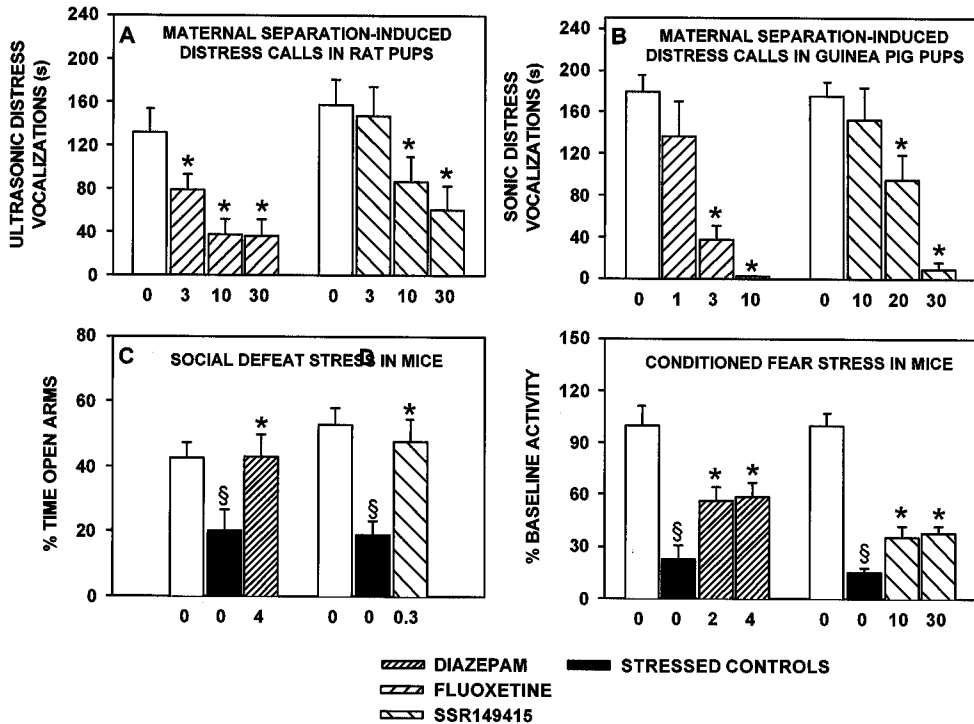
Fig. 2. Effects of the V_{1b} receptor antagonist, SSR149415, in several rodent procedures based on behavioral changes produced by traumatic stress events. (A & B) *Maternal separation-induced distress calls*: Rat or guinea pig pups are removed from their litter and separated from their mother. They rapidly emit sonic or ultrasonic distress calls, respectively. (*C*) *Social defeat stress*: Mice were placed in the cage of a resident male aggressor, which was selected for high levels of aggression. After the intruder mouse has been defeated by the resident aggressor it was tested in the elevated plus-maze. Social stress increased levels of anxiety as shown by the reduction in time spent in open arms (black bars). (*D*) *Conditioned fear stress*: Mice were stressed by exposing them to an environment paired previously with foot shock. Stress dramatically decreased locomotor activity (black bars). SSR149415 was administered subcutaneously (−30 min) (A), intraperitoneally (−30 min) (B) or orally (−60 min) (C & D). Data represent mean ± S.E.M. *$P < 0.05$ (vs controls); § $P < 0.05$ (vs nonstressed controls). Adapted from Griebel et al. (2002a; 2002c).

Profile in animal models of depression

The potential antidepressant-like effects of V_{1b} receptor blockade were investigated in several procedures, including the forced-swimming test in rats, the chronic mild stress model in mice and the chronic subordination stress paradigm in rats. Results from the forced-swimming test showed that SSR149415 produced dose-dependent antidepressant-like activity as it decreased dramatically immobility time (Griebel et al., 2002a). These effects were comparable to those observed with the reference antidepressants, fluoxetine and imipramine. Importantly, the finding that the antidepressant-like effects of SSR149415 were still present, albeit at a higher dose, in hypophysectomized rats, indicates that this action does

not necessarily involve pituitary–adrenal axis blockade, thereby suggesting that extrahypothalamic V_{1b} receptors may play a role in these effects (Griebel et al., 2002a).

The antidepressant potential of SSR149415 was confirmed in both chronic models of depression. The chronic mild stress (CMS) test is based on the procedure originally designed by Willner et al. (1992) for rats, and adapted for mice by Kopp et al. (1999). It consists of the sequential application of a variety of mild stressors, including restraint, forced swimming, water deprivation, pairing with another stressed animal, each for a period of between 2 and 24 h, in a schedule that lasts for three weeks, and is repeated thereafter. Parallels between human depression and chronically stressed animals have been

drawn on the reduction of the efficiency with which even the smallest tasks (e.g., washing and dressing in the morning) are accomplished in depressed patients, leading to the inability to maintain minimal personal hygiene, and the decrease in grooming behavior seen in stressed animals. In this latter case there is a degradation of the physical state of the coat, consisting of a loss of fur and dirty fur. Moreover, CMS mice display increased emotionality and a weak ability to cope with aversive situations.

Repeated administration of SSR149415 for 39 days in CMS animals reversed the degradation of the physical state, anxiety, despair, and the loss of coping behavior produced by stress (Griebel et al., 2002a). The antidepressant-like effects of SSR149415 in the CMS were confirmed in a subsequent experiment using a slightly modified version of this test. As was observed in the first study, SSR149415 again reversed the degradation of the physical state (Fig. 3A). It is noteworthy that at the end of the 7-week stress
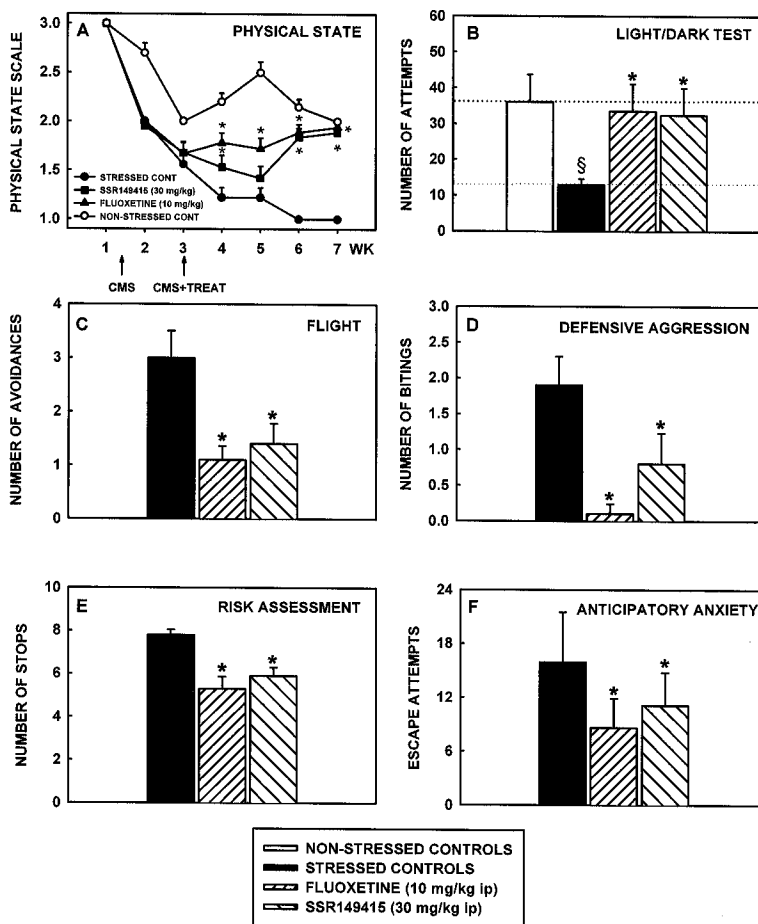

Fig. 3. Effects of repeated administration of the V_{1b} receptor antagonist, SSR149415, and the 5-HT reuptake inhibitor, fluoxetine, on chronic mild stress-induced (A) degradation of the physical state of the coat of animals, (B) anxiogenic-like behavior in the light/dark tests, and (C-F) increased defensiveness as measured in the defense test battery when mice are confronted with a rat. Flight responses were measured when the rat first approached the mouse; risk assessment was observed when mice were chased by the rat; defensive aggression occurred upon forced contact with the rat; and mice displayed anticipatory anxiety after the removal of the rat from the test arena. The chronic mild stress protocol consists of the sequential application of a variety of mild stressors, including restraint, forced swimming, water deprivation, pairing with another stressed animal, in a schedule that lasts for three weeks, and is repeated thereafter. The drugs were administered intraperitoneally once a day for four weeks. Data represent mean ± S.E.M. *$P < 0.05$ (vs stressed mice); § $P < 0.05$ (vs nonstressed mice).

period, animals treated with SSR149415 displayed a comparable physical state as nonstressed controls. In addition, the drug was able to prevent the stress-induced increase in anxiety levels in the light/dark test (Fig. 3B), and reduced defensive reactions in the MDTB, as did the prototypical antidepressant, fluoxetine (Fig. 3C-F).

To investigate further the antidepressant potential of V_{1b} receptor blockade, SSR149415 was tested in the chronic subordination stress model in rats (Blanchard et al., 2002). Effects were compared to those obtained with fluoxetine in this test. In mixed-sex rat groups, consistent asymmetries in offensive and defensive behaviors of male dyads are associated with the development of dominance hierarchies. Subordinate males can be differentiated from

dominants on the basis of both agonistic and nonagonistic behaviors, wound patterns and weight changes. Their behavior changes suggest chronic defensiveness and are also broadly isomorphic to many of the symptoms of depression (Blanchard et al., 1993). Drug administration began on day 3, after determination of dominance, and continued twice daily until day 14. Males treated with fluoxetine typically showed more weight loss (data not shown) and wounding than vehicle controls (Fig. 4A). Together with previous data, this was hypothesized to reflect reduced defensiveness in the presence of the dominant. SSR149415 dose groups showed higher weight loss (data not shown) and wounding relative to vehicle controls (Fig. 4A). Interestingly, on average over 3 days, vehicle subordinate controls
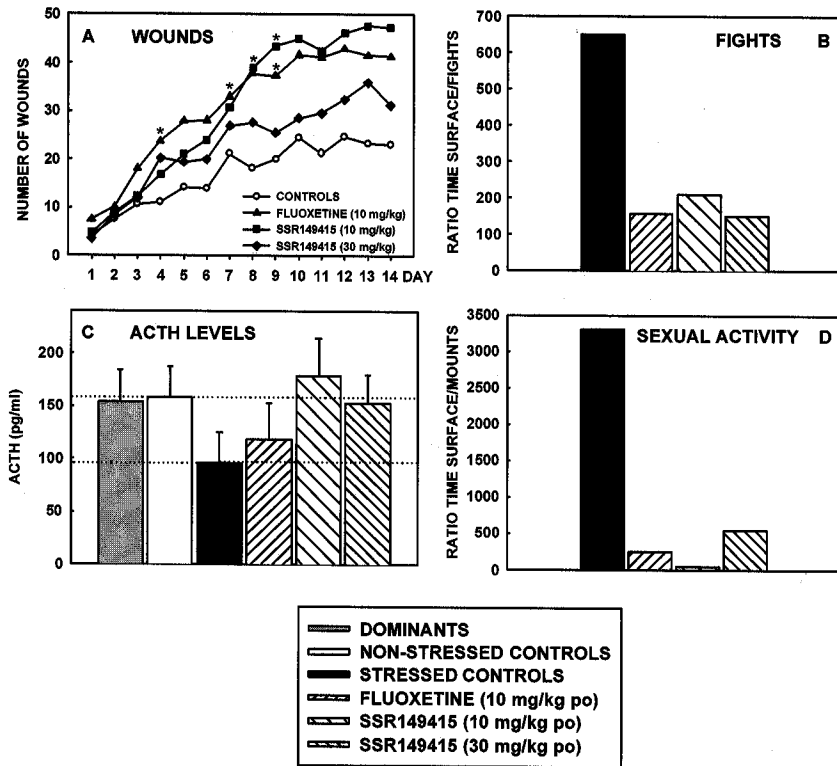

Fig. 4. Effects of repeated administration of the V_{1b} receptor antagonist, SSR149415, and the 5-HT reuptake inhibitor, fluoxetine, on subordinate male rats in visible burrow systems (VBS). The VBS is a semi-natural habitat with an open "surface" area and tunnels/chambers. In mixed-sex VBS group fighting is intense and subordinate males are strongly stressed, thereby leading to behavioral changes in these animals which are broadly isomorphic to many of the symptoms of depression. These changes include decreases in (A & B) fighting behavior with a dominant rat as expressed by the (A) number of wounds and (B) ratio time spent on the open surface area together with the dominant rat to the number of fights; ACTH levels (C), and sexual behavior as expressed by the time spent on the open surface area to the number of female mounts (D). The drugs were administered orally twice a day for 2 weeks. *$P < 0.05$. Adapted from (Blanchard et al., 2002).

had one fight with the dominant about every 650 seconds of surface time when the subordinate was present with the dominant. In contrast, fluoxetine-treated subordinates had one fight with the dominant about every 155 seconds of surface time when both a fluoxetine-treated subordinate and the dominant were present. Animals treated with SSR149415 were very similar to the fluoxetine group with reference to this derived behavioral measure, with one attack received during each 210 (10 mg/kg) and 150 (30 mg/kg) seconds of subordinate/dominant surface time (Fig. 4B). These data provide considerable confirmation of the hypothesis suggested by the wound count data, that some aspect of the behavior of the fluoxetine- and SSR149415-treated subordinates was unusually provocative of attack by the dominant. All subordinate drug treatment male groups made more mounts per unit surface time than controls (Fig. 4D). Plasma ACTH levels were reduced in vehicle subordinates compared to dominants. Whereas fluoxetine-treated males showed slightly higher plasma ACTH levels than vehicle subordinates, the SSR149415-treated groups showed plasma ACTH levels that were comparable to those of nonstressed controls, suggesting normalization of this HPA axis parameter change (Fig. 4C). Overall, the effects of SSR149415 and fluoxetine were comparable, confirming the antidepressant-like potential of the V_{1b} receptor antagonist.

Effects on neuroendocrine, neurochemical and autonomic markers of the stress response

Disruptions in homeostasis (i.e., stress) place demands on the body that are met by the activation of two systems, the HPA axis and the sympathetic nervous system (SNS). Stress-induced activation of the HPA axis and the SNS results in a series of endocrine and neural adaptations known as the "stress response". A challenge to homeostasis initiates the release of CRF from the hypothalamus, which in turn results in release of ACTH into the general circulation. ACTH then acts on the adrenal cortex provoking the release of glucocorticoids into blood. These latter act in a negative feedback fashion to terminate the release

of CRF. Dysregulation of this negative feedback results in excessive levels of the three key hormones of the stress response, and is implicated in a variety of stress-related disorders (Chrousos and Gold, 1998; McEwen, 2000). It has been reasoned that a good strategy for short-circuiting the deleterious effects of stress would be to prevent CRF, ACTH or glucocorticoids from exerting their actions (Holsboer, 1999; Steckler et al., 1999). We therefore tested the ability of SSR149415 to prevent restraint stress-induced elevation of ACTH levels and the synergistic action between AVP and CRF on ACTH release in corticotroph cells in rats. Results showed that the V_{1b} receptor antagonist inhibited both stress-induced ACTH secretion (Fig. 5A) and the release of the stress hormone following combined AVP and CRF challenge (Serradeil-Le Gal et al., 2002) (Fig. 5B).

There is considerable evidence for a relationship between noradrenergic (NA) brain systems and behaviors associated with stress and anxiety (Bremner et al., 1996a; 1996b; Koob, 1999). The majority of NA neurons are located in the locus coeruleus, with projections throughout the cerebral cortex and multiple subcortical areas, including hippocampus, amygdala, thalamus, and hypothalamus. This neuroanatomical formation of the NA system makes it well suited to rapidly and globally modulate brain function in response to changes in the environment, as occurs during the presentation of stress. Stress exposure is associated with an increase in firing of the locus coeruleus and with associated increased release of NA in brain regions, which receive NA innervation. For example, tail pinch stress in rats has been shown to produce a dramatic increase in the release of NA in the prefrontal cortex (Funk and Stewart, 1996) (Fig. 5C), an effect which could be prevented by prior administration of anti-stress drugs, such as the CRF_1 receptor antagonists, antalarmin and SSR125543A (Steinberg et al., 2001; Griebel et al., 2002b). Similarly, the V_{1b} receptor antagonist, SSR149415, significantly reduced the evoked NA release following tail pinch stress (Griebel et al., 2002c) (Fig. 5D).

The autonomic stress response consists notably of significant elevations of blood pressure and heart rate, associated with increased body temperature
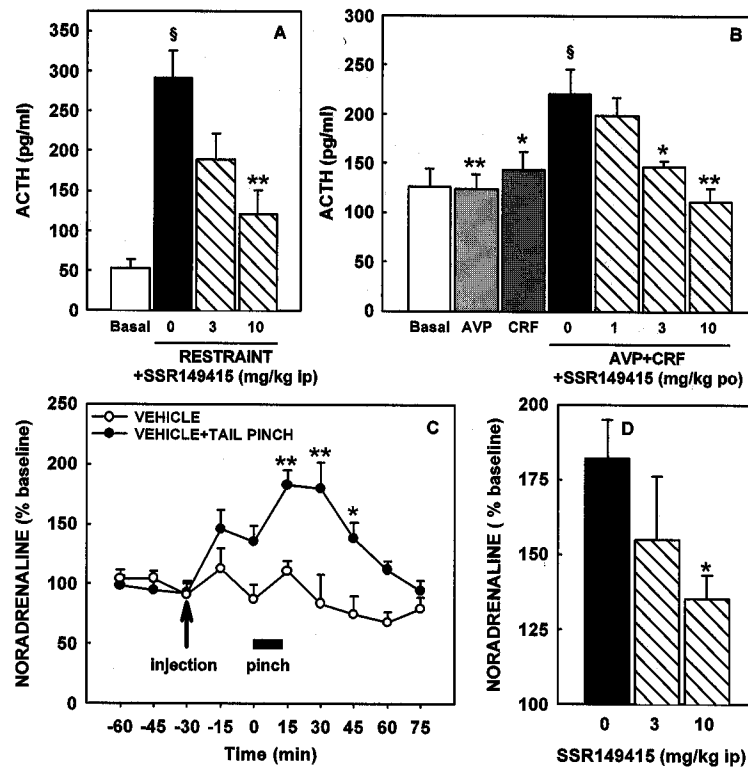
Fig. 5. Effects of the V_{1b} receptor antagonist, SSR149415, on neuroendocrine (ACTH) and neurochemical (cortical norepinephrine release) markers of the stress response produced by (A) 15 min restraint; (B) coadministration of AVP and CRF; and (C & D) tail pinch. SSR149415 was administered intraperitoneally 30 min prior to restraint or tail pinch, and orally 60 min before AVP and CRF infusion. Data represent mean ± S.E.M. *$P < 0.05$, **$P < 0.01$ (vs controls); § $P < 0.05$ (vs baseline levels of ACTH). Adapted from (Serradeil-Le Gal et al., 2002; Griebel et al., 2002c).

(Sgoifo et al., 1999; Oka et al., 2001). For example, immobilization stress produces a marked and transient increase in heart rate accompanied by hyperthermia (Fig. 6). The cardiovascular stress response was diminished but not prevented by administration of SSR149415, while stress-induced hyperthermia was not affected by the V_{1b} receptor antagonist (Fig. 6AC). Interestingly, the BZ diazepam displayed a different profile on the autonomic stress response, as it failed to modify the cardiovascular response, but almost completely abolished hyperthermia (Fig. 6BD). The difference between SSR149415 and diazepam on the autonomic stress response is unclear, but emphasizes further the idea that the V_{1b} receptor antagonist is endowed with anti-stress properties that are different from those of classical anxiolytics, such as BZs.

Conclusion

The very complexity of the stress response would appear to provide multiple opportunities for intervention, but treatment strategies are often centered on the amelioration of symptoms rather than attempting to short-circuit the stress response. Recent efforts have begun to focus on the development of pharmacological agents that can attenuate the stress response itself, rather than the symptoms associated with stress. AVP, together with CRF, is a pivotal mediator in the body's response to stress and its dysregulation has been linked to a variety of disorders. As described above, AVP exerts its actions in the CNS by binding to the V_{1b} receptor, and the pharmacological blockade of this receptor might be expected to prevent the effects of stress.
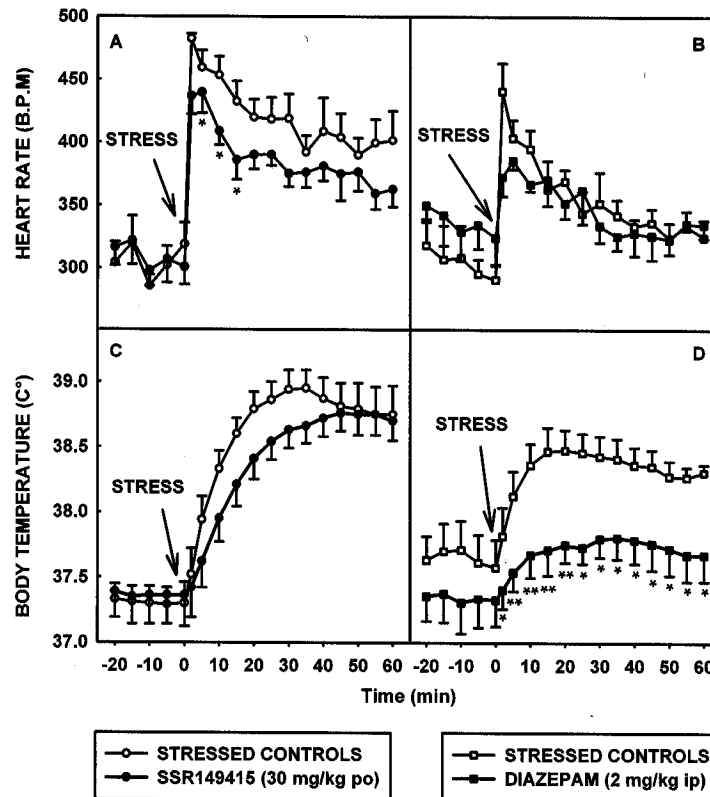
Fig. 6. Effects of the V_{1b} receptor antagonist, SSR149415, on autonomic markers of the stress response produced by restraint as measured by radiotelemetry. It consists notably of significant elevations of blood pressure and heart rate. SSR149415 and diazepam were administered 60 and 30 min prior to restraint, respectively. Data represent mean ± S.E.M. * $P < 0.05$, **$P < 0.01$ (vs stressed controls).

Studies using SSR149415 targeted to specific regions such as the amygdala, septum or hippocampus, are in progress. They should help to clarify the involvement of the V_{1b} receptor in anxiety and depression. In conclusion, the development of nonpeptide V_{1b} receptor antagonists opened a new era for examining the role of AVP in animal models of stress, and may provide a novel avenue for the treatment of affective disorders.

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