The Vasopressin V_{1b} Receptor as a Therapeutic Target in Stress-related Disorders

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Abstract: The complexity of the stress response would appear to provide multiple opportunities for intervention, but treatment strategies are often centered on the improvement of symptoms rather than attempting to "treat" the stress response. However, 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. Although CRF, which is the main regulator of the stress system, is the focus of current interest, there is an accumulating body of evidence suggesting that the vasopressinergic system may play an equal role in the regulation of the stress response, and that V_{1b} receptor antagonists may be of potential therapeutic benefit. The availability of SSR149415, the first selective antagonist for the V_{1b} receptor has allowed us to evaluate this hypothesis. SSR149415 is able to attenuate some but not all stress-related behaviors in rodents. While the antidepressant-like activity 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. The latter were active in a wide range of anxiety models, whereas the V_{1b} receptor antagonist showed clear-cut effects only in particularly stressful situations. It is important to note that SSR149415 is devoid of central depressant effects, even at high doses, and does not affect cognitive processes, suggesting a large therapeutic window. Altogether, these findings suggest that V_{1b} receptor antagonists might be useful as a treatment for major depression and stress disorders that result from traumatic events.

Key words: Antidepressant, Anxiety, Anxiolytic, Arginine vasopressin, Depression, SSR149415, Stress, V_{1b} receptor.

1. INTRODUCTION

All the established drug treatments for anxiety disorders and depression target monoamine- and amino acid-mediated neurotransmission, but a close causal relationship between these neurotransmitter mediated mechanisms and the clinical conditions still needs to be established. Today drug discovery in this area is directed towards a variety of neuroactive peptides that play a role in the modulation of emotional behaviors. 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 arginine vasopressin (AVP) has also been considered [1;2].

2. ARGININE VASOPRESSIN: A STRESS HORMONE AND NEUROTRANSMITTER

Following its identification in 1954, AVP, a nonapeptide, was considered the principal factor in the regulation of adrenocorticotropin (ACTH) release [3-5], but following the subsequent elucidation of the structure of CRF, the role of the latter superseded that of AVP. This dominance has been reflected in neuroendocrine studies in depression [6]. However, there is an accumulating body of evidence to support a significant role for AVP in the regulation of pituitary-adrenal activity in health and also in stress-related disorders. In addition to its regulatory activity on ACTH secretion, AVP plays an important role as a neurotransmitter in the brain [7]. AVP is critical for adaptation of the hypothalamo-pituitary-adrenal (HPA) axis during stress through its ability to amplify the stimulatory effect of CRF. Abnormalities in AVP levels or receptor activity have been detected in patients with depression, anxious-retarded depression and obsessive-compulsive disorder [8-11]. For example, increased plasma AVP concentrations have been reported in the hypothalamus and other brain regions of depressed suicide attempters [8;12]. Moreover, there is evidence suggesting that HPA axis dysregulation in depression may be associated with a shift towards increased vasopressinergic control of the axis [13;14]. A recent clinical finding showed that AVP release was significantly correlated with anxiety symptoms in healthy volunteers after anxiogenic drug challenge [15]. It is reported in this study that volunteers with the highest levels of AVP also showed higher levels of respiratory distress and cognitive anxiety. In animal studies, 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

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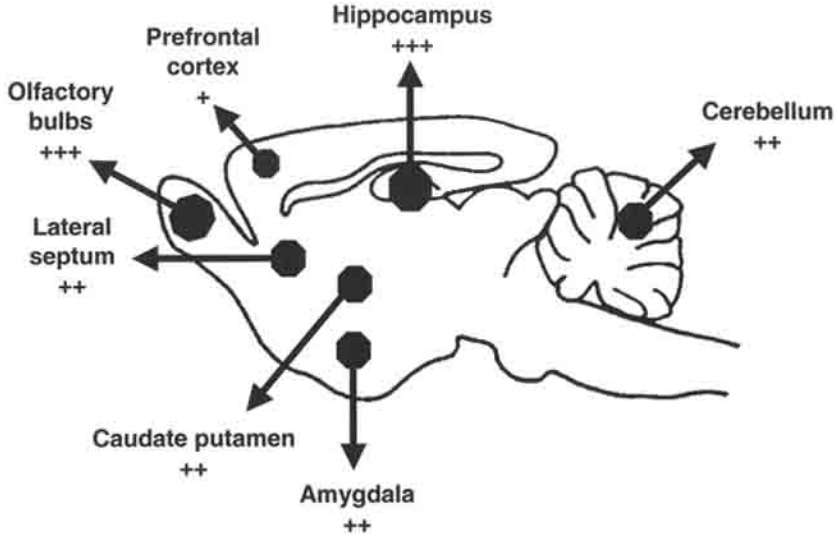


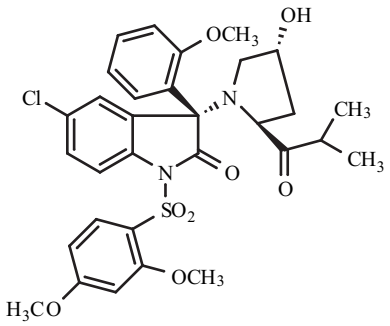
Fig. (1). Distribution of the V_{1b} receptor protein or mRNAs encoding V_{1b} receptors in the rat brain. Adapted from [22;81] and Stemmelin *et al.* (manuscript in preparation).

parvocellular neurons of the PVN (for a recent review, see [2]). Moreover, increased levels of AVP were found in the hypothalamus of rats with high innate anxiety [16]. In this study, pretreatment with a mixed peptide $V_{1a/b}$ receptor antagonist abolished the CRF-stimulated increase in ACTH secretion in dexamethasone-pretreated anxious rats. Interestingly, when these animals were treated chronically with the classical antidepressant, paroxetine, hypothalamic AVP decreased [17]. The authors of this study reported that V_{1a} receptor expression was higher in the lateral septum of high-anxious rats, but remained unchanged following paroxetine challenge. Repeated immobilization stress and repeated hypertonic saline injections were found to produce sustained elevations in AVP V_{1b} receptor mRNA in the pituitary [18], suggesting an upregulation of AVP receptors under chronic stress.

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 [19-21]. 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} [22-24], which are widely distributed in the central nervous system (CNS), including the lateral septum, amygdala, hippocampus and prefrontal cortex [22;25;26] (Fig. (**1**)). The presence of this AVP network suggests a modulator 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 [7;27-31]. More recently, experiments in rats demonstrated that the intracerebroventricular infusion of AVP produced anxiogenic-like activity in the open-field, elevated plus-maze and social interaction tests, and in a procedure based on the suppression of feeding in a novel environment [32]. In contrast, the intra-septal application of the mixed $V_{1a/b}$ receptor antagonist $d(CH_2)_5$Tyr(Et)VAVP was found to produce anxiolytic-like effects in the elevated plus-maze test [33]. Moreover, infusion of an antisense oligodeoxynucleotide to the V_{1a} subtype mRNA into the septum has been shown to reduce anxiety in the elevated plus-maze [34]. Furthermore, AVP-deficient rats (i.e. Brattleboro) displayed attenuated conditioning freezing responses [35]. Taken as a whole these clinical and preclinical findings suggest that AVP receptor antagonists may represent potential agents for the treatment of stress-related disorders [36].

3. SSR149415: THE FIRST NON-PEPTIDE ANTAGONIST AT AVP V_{1b} RECEPTORS

The recent advances in biotechnology which involved notably an optimization of random screening techniques have led to the discovery of several structural series of non-peptide AVP receptor antagonists [37-39]. Among these the selective V_{1b} receptor antagonist, SSR149415 (Fig. (**2**)), has been studied extensively in animal procedures, including anxiety and depression models, thus allowing assessment of the potential therapeutic applications of selective blockade of AVP binding sites in stress-related disorders.



SSR149415

Fig. (2). Chemical structure 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(-)).

3.1. *In vitro* and *In vivo* Biochemical Characterization of SSR149415

SSR149415 displays nanomolar 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 (Table 1), and was inactive in more than 90 binding assays for neurotransmitters and peptides. It is a potent antagonist at the V_{1b} receptor as shown by its ability to inhibit AVP-induced Ca^{2+} increase in Chinese hamster ovary cells expressing the human or rat V_{1b} receptor (K_i = 1.26 and 2 nM, respectively). SSR149415 did not modify the V_{1a}-mediated vascular response in rats following AVP administration up to 10 and 30 mg/kg, ip and po, respectively. Moreover, in Brattleboro rats, a model used for detecting potential agonist antidiuretic activity, SSR149415 had no effect on urine flow rate. Finally, SSR149415 inhibited exogenous and endogenous (subsequent to body water loss) AVP-induced increase in plasma ACTH and antagonized AVP-potentiated ACTH release provoked by exogenous CRF in rats, an effect that lasted for 4 hours [39].

Table 1. Binding Affinity of SSR149415 for Vasopressin and Oxytocin Receptors in Animal and Human Species

	K_i, nM			
	V_{1b}	V_{1a}	V_2	OT
Human				
Hypophysis	4.2 ± 1.1			
CHO	1.5 ± 0.8	91 ± 23	1412 ± 314	
Ltk^-				174 ± 35
Rat				
Hypophysis	3.7 ± 1.3			
CHO	1.3 ± 0.9			
Liver		1050 ± 112		
Kidney			2897 ± 509	
Mammary				270 ± 39

Values represent mean ± S.D. of at least three determinations. Adapted from [39].

3.2. Characterization of SSR149415 in Animal Models of Stress-related Disorders

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 (Table 2). There are few well accepted animal models of psychiatric disorders. However, a number of animal models of anxiety and depression have been proposed, most of which involve exposure of animals to external (e.g. cues previously paired with footshock, novel places, predators, repeated mild stress) or internal (e.g. drug states) stimuli which are assumed to be capable of inducing anxiety or depression in humans. The actual measures taken include for example suppression of previously punished activities, conditioned emotional responses, a range of sonic and ultrasonic vocalizations and social, and exploratory behaviors (for reviews, see [40-43]). Most of these procedures have been subjected to extensive behavioral and pharmacological validations which led to the idea that they may relate to different emotional states, and perhaps that they may model different aspects of human anxiety or depressive disorder [42-44]. A tentative view of the clinical relevance of the tests used to investigate the effects of SSR149415 on emotional processes is given in Table 2.

3.2.1. Effects of SSR149415 in Animal Models of Generalized Anxiety Disorder

In models developed to screen mainly benzodiazepines (BZs), drugs that are effective in the treatment of generalized anxiety disorder (GAD), SSR149415 elicited anxiolytic-like activity following acute peripheral administration, an effect that lasted about 4 hours (Fig. (3)) [39;45;46]. The drug increased significantly punished responding in the four-plate test in mice and in the Vogel conflict paradigm in rats, reduced avoidance behaviors of aversive places in the light/dark test in mice and in the elevated plus-maze in rats, attenuated fear-potentiated startle in rats, and increased active social interaction in gerbils. 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. However, it is important to note that the magnitude of the anxiolytic-like action of SSR149415 in these models was generally less than that of the BZ

Table 2. Tentative view of the Clinical Relevance of the Procedures Used to Investigate the Effects of SSR149415 on Emotional Processes

Generalized Anxiety Disorder	Panic Disorder	Acute Stress Disorder	Major Depressive Disorder
▪ Elevated plus-maze in rats	▪ Flight in the MDTB*	▪ Conditioned fear in mice	▪ Chronic mild stress in mice
▪ Fear-potentiated startle in rats		▪ Defensive aggression in the MDTB*	▪ Chronic social stress in rats
▪ Four plate in mice		▪ Distress vocalizations in rats or guinea pigs	▪ Forced swimming in rats
▪ Light/dark in mice		▪ Restraint-induced ACTH release in rats	
▪ Risk assessment in the MDTB*		▪ Restraint-induced physiological changes in rats	
▪ Social interaction in gerbils		▪ Social defeat in mice	
▪ Vogel conflict in rats		▪ Tail pinch-induced NE release in rats	

*MDTB = Mouse Defense Test Battery

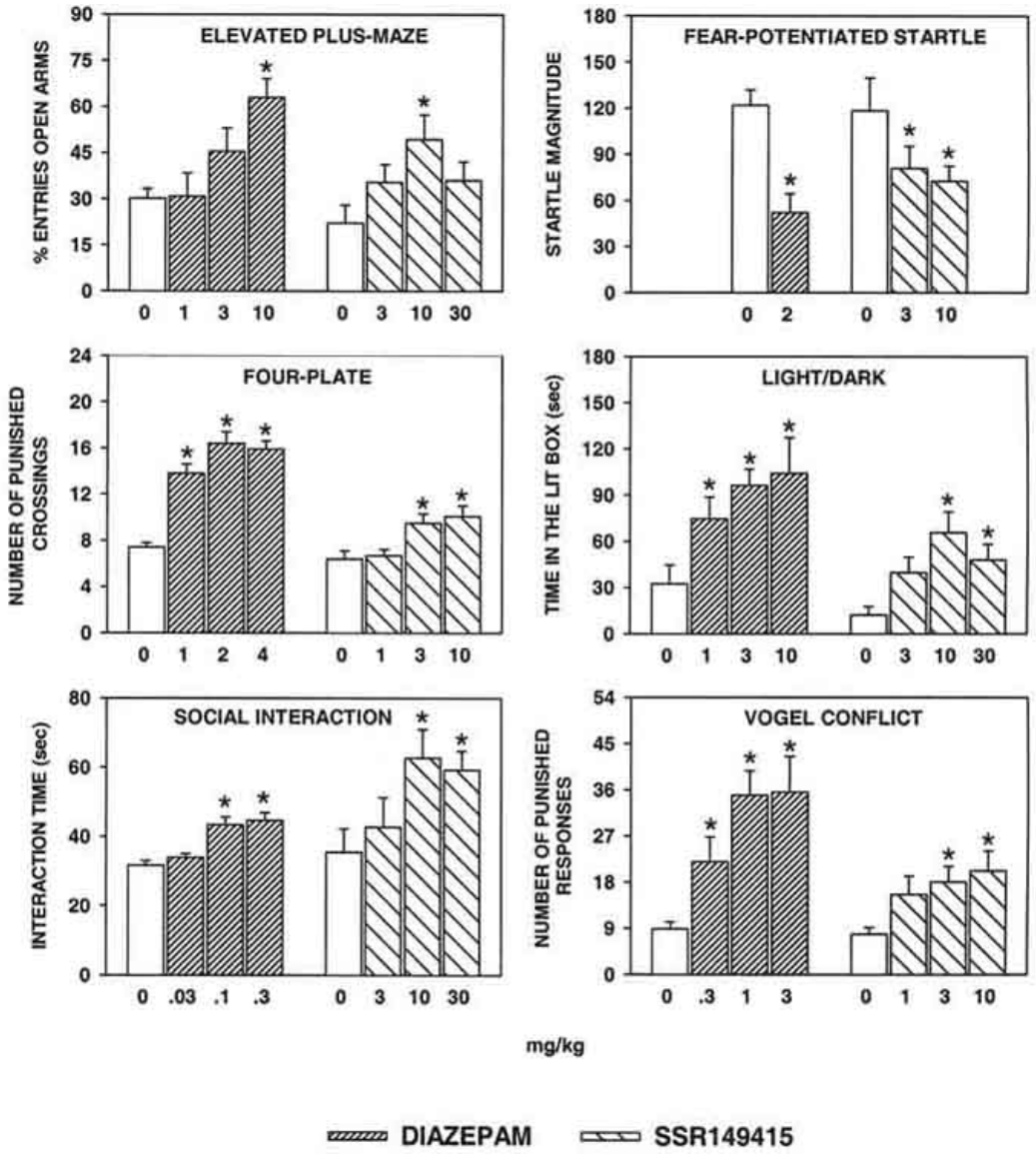


Fig. (3). Comparison of the effects of SSR149415 and diazepam in several rat (elevated plus-maze, fear-potentiated startle and Vogel conflict tests), mouse (four-plate and light/dark test) and gerbil (social interaction) models which have proved to be effective in the screening of drugs developed for the treatment of Generalized Anxiety Disorder. The drugs were administered intraperitoneally (L/D and VC) or orally (EPM, FPS, FP and SI). * $P<0.05$. Adapted from [39;46;60].

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 in GAD, 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 on risk assessment in the mouse defense test battery may, however, be relevant to this issue. This procedure provides a model capable of responding to, and differentiating anxiolytic drugs of different classes through specific profiles of effect on different measures [47]. Here, SSR149415 failed to modify significantly risk assessment [46], a behavior which has been shown to be particularly sensitive to drugs used in the treatment of GAD [48]. This latter result taken together with the findings of reduced efficacy of SSR149415 in classical anxiety tests when compared to BZs, suggest that GAD may not be the primary therapeutic target of V_{1b} receptor antagonists.

3.2.2. Effects of SSR149415 in an Animal Model of Panic Disorder

The high prevalence of panic disorder in the community [49] has stimulated the search for novel treatments for this condition. A direct consequence of this research effort has been the development of a variety of different animal procedures that claim to model certain aspects of a panic attack [44]. Among these, the mouse defense test battery (MDTB) and its flight measures has been shown to be particularly useful as a model of panic disorder as it satisfies some criteria for face, predictive and construct validity

[44;48;50]. When SSR149415 was tested in this procedure, it only weakly affected flight responses [46]. Although the drug decreased significantly the avoidance distance of mice in response to an approaching natural predator (i.e. a rat), it failed to modify the other flight measures (i.e. avoidance frequency and flight speed). Despite the strong predictive validity of the MDTB, it is premature to conclude that V_{1b} receptor antagonists have only limited efficacy in the treatment of panic. Clearly, further experiments using other panic models and perhaps with repeated treatment with SSR149415 (as antipanic drug therapy is always chronic in nature) are necessary to get a more precise idea about the antipanic potential of a V_{1b} receptor antagonist.

3.2.3. Effects of SSR149415 in Animal Models of Acute Stress Disorder

Animal models of acute stress disorder relate to procedures based on behavioral, neurochemical or neuroendocrine changes produced by acute traumatic events (social defeat, separation, restraint, forced confrontation with a natural predator or unavoidable electric shocks) (Table 2). BZ receptor agonists are able to reverse these changes, but several other drug classes, including 5-HT reuptake inhibitors, CRF or substance P receptor antagonists have demonstrated strong ability to counteract the effects of acute stress (e.g. [51-58]).

Results obtained with SSR149415 in these models are shown in Fig. (**4A-H**). In the social defeat paradigm in mice, SSR149415 completely antagonized the heightened emotionality in the elevated plus-maze produced by prior (stressful) exposure to an aggressive isolated resident [46] (Fig. (**4C**)). Conditioned fear stress induced by exposure to an environment paired previously with foot shock dramatically decreases locomotor activity. These effects of stress were attenuated by SSR149415 [59] (Fig. (**4D**)). 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. SSR149415 produced a dose-dependent decrease in both sonic and ultrasonic vocalizations [60] (Fig. (**4AB**)). Results obtained with SSR149415 in the MDTB are in line with these findings as the drug produced a clear-cut reduction in defensive aggression upon forced contact with a natural predator (i.e. a rat) [46] (Fig. (**4E**)), a behavior which is claimed to be associated with certain aspects of stress disorders following traumatic events [48].

Stress-induced activation of the HPA axis, the CNS and the sympathetic nervous system results in a series of endocrine, neurochemical and neural adaptations known as the "stress response". Stressful treatments initiate the release of CRF from the hypothalamus, which in turn results in the 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 (for review, see [61]). Restraint stress in rats has been shown to produce a dramatic increase in ACTH. We therefore tested the ability of SSR149415 to prevent restraint stress-induced elevation of ACTH levels and found that the V_{1b} receptor antagonist inhibited the release of the stress hormone [39] (Fig. (**4F**)) Importantly, SSR149415 selectively blocked stress-induced ACTH release without disturbing basal ACTH release [39]. Moreover, the anti-stress-like effects of SSR149415 may be contingent upon relatively high levels of stress, suggesting that it may be capable of blocking acute stress responses without causing unwanted side-effects due to general suppression of HPA activity (e.g., metabolic abnormalities). There is considerable evidence that stress exposure is associated with an increase in firing of the locus coeruleus and with associated enhanced release of NA in brain regions, which receive NA innervation [62;63]. For example, tail pinch stress in rats has been shown to produce a dramatic increase in the release of NA in the prefrontal cortex [64], an effect which could be prevented by prior administration of anti-stress drugs, such as the CRF_1 receptor antagonists, antalarmin and SSR125543A [52;65]. Similarly, the V_{1b} receptor antagonist, SSR149415, significantly reduced the evoked NA release following tail pinch stress [59] (Fig. (**4G**)). The autonomic stress response consists notably of significant elevations of blood pressure and heart rate [66]. For example, immobilization stress produces a marked and transient increase in heart rate. This cardiovascular stress response was diminished but not prevented by the administration of SSR149415 [59] (Fig. (**4H**)).

Altogether, the findings with SSR149415 in acute stress disorder models show clear-cut effects of the V_{1b} receptor antagonist in a majority of these procedures with comparative efficacy as reference compounds, thereby suggesting the idea that a V_{1b} receptor antagonist may be useful in conditions associated with exposure to traumatic events.

3.2.4. Effects of SSR149415 in Animal Models of Major Depressive Disorder

The potential antidepressant-like properties of SSR149415 were investigated in several procedures, including the forced-swimming test in rats [67], the chronic mild stress model in mice [68;69] and the chronic subordination stress paradigm in rats [70]. Results from the forced-swimming test showed that SSR149415 produced dose-dependent antidepressant-like activity [46]. These effects were comparable to those observed with the reference antidepressant fluoxetine (Fig. (**5A**)).

The antidepressant potential of SSR149415 was confirmed in the chronic mild stress model in mice. This test consists of the sequential application of a variety of mild stressors (e.g. restraint, forced swimming, water deprivation, pairing with another stressed animal) for 7 weeks. It leads to a degradation of the physical state of the coat, increased emotionality and a reduced ability to cope with aversive situations. Repeated administration of SSR149415 for 39 days reversed the degradation of the physical state, anxiety, despair and the loss of coping behavior produced by stress [46]. The antidepressant-like effects of SSR149415 in the chronic mild stress were confirmed in a subsequent study using a slightly modified version of this test. As was observed in the first experiment, SSR149415 again reversed the degradation of the physical state (Fig. (**5B**)). In addition, the drug was able to prevent the stress-induced increase in anxiety levels in the light/dark test as did the prototypical antidepressant, fluoxetine (Fig. (**5C**)).

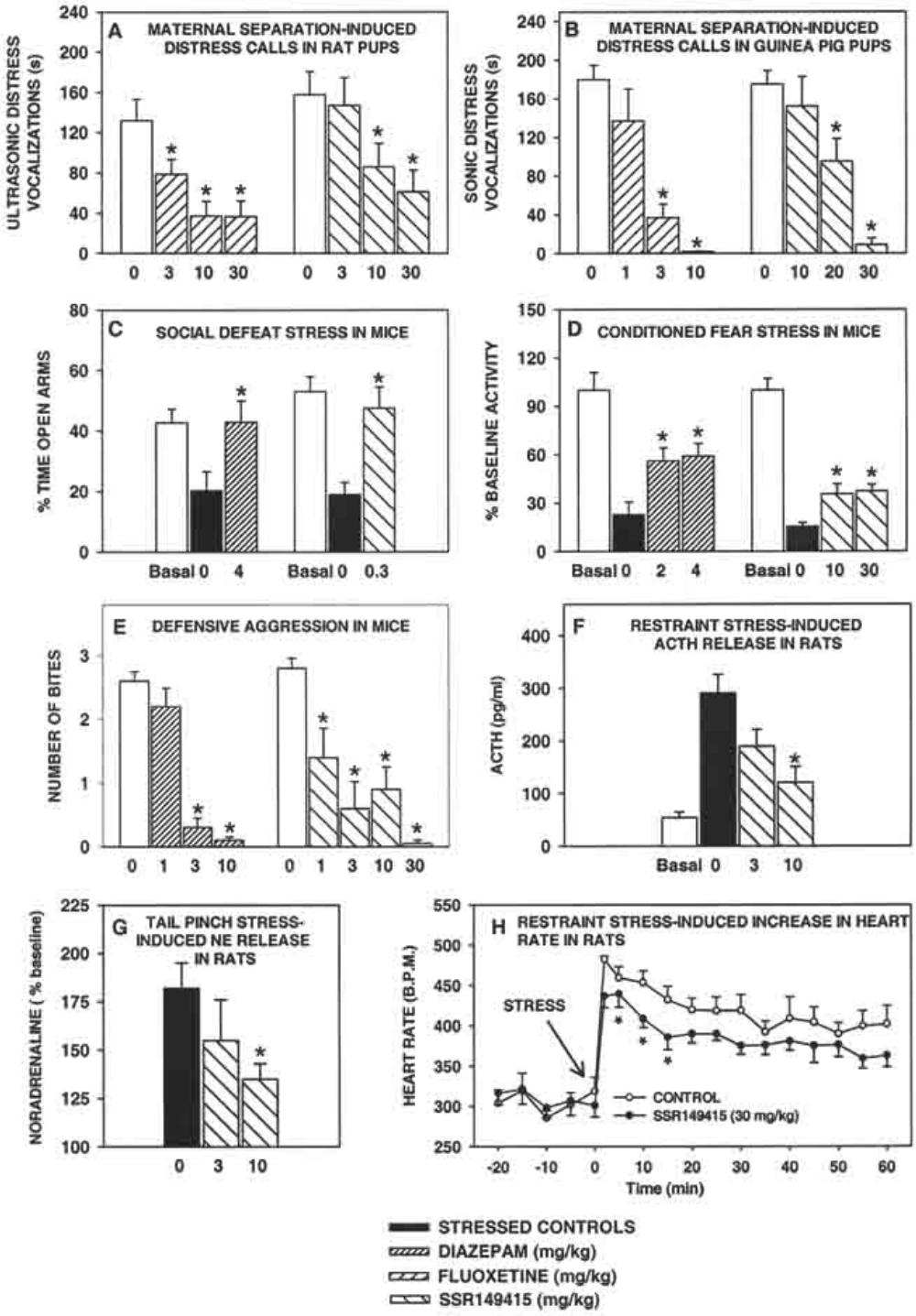


Fig. (4). Effects of SSR149415 in several models of Acute Stress Disorder. The drugs were administered intraperitoneally (maternal separation-induced distress calls in guinea pig pups, conditioned fear stress with diazepam and tail pinch stress-induced NE release), orally (social defeat stress, conditioned fear stress with SSR149415, defensive aggression and restraint stress-induced ACTH release) or subcutaneously (maternal separation-induced distress calls in rat pups). * $P<0.05$ (vs vehicle controls). Adapted from [39;46;59;60].

In the chronic subordination stress model in rats, SSR149415 was administered to subordinate male rats in visible burrow systems (VBS). The VBS is a semi-natural habitat with an open "surface" area and tunnels/chambers [71]. 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 [70].

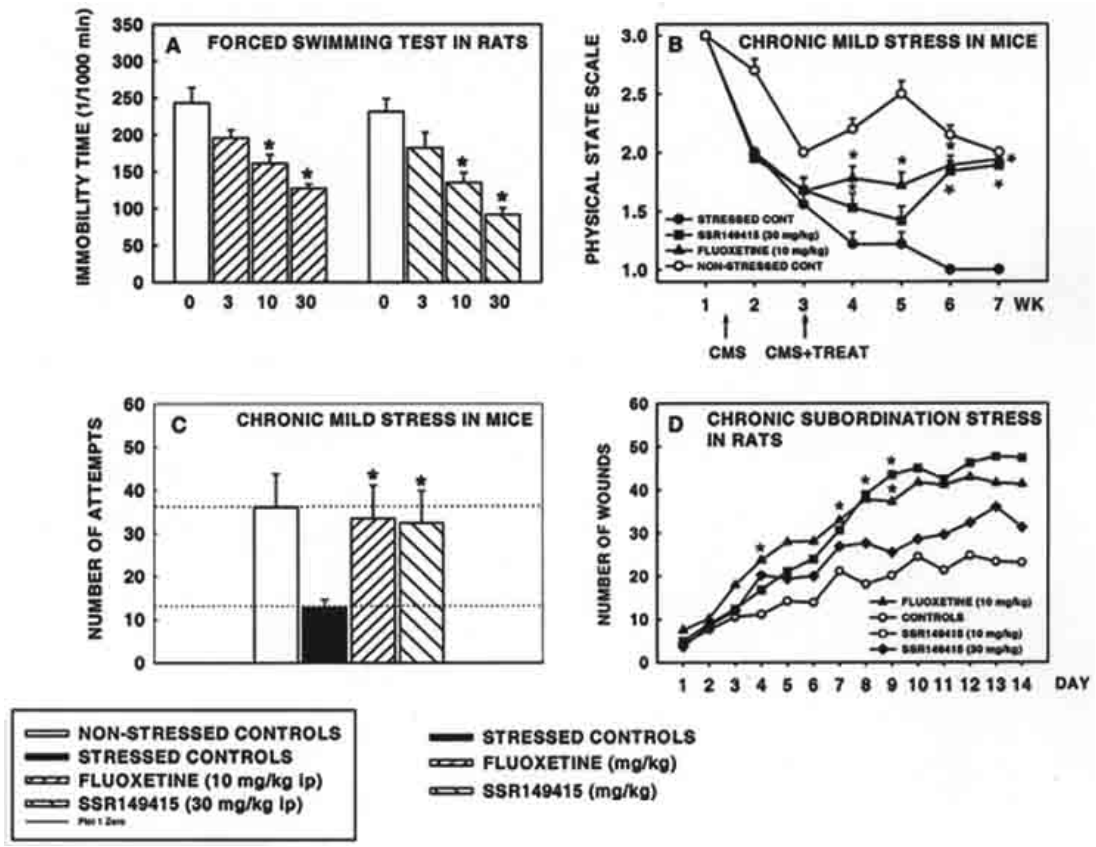


Fig. (5). Comparison of the effects of SSR19415 and fluoxetine in several models of depression. The drugs were administered twice (forced swimming test), once a day for 39 days (chronic mild stress) or twice a day for 14 days (chronic subordination stress). Data represent mean±S.E.M.* P<0.05. Adapted from [46;59;72].

Subordinate animals avoid the surface (preferentially utilized by the dominant) and show inhibition of sexual behavior and approaches to females in the presence of the dominant. Fluoxetine administration to VBS colony subordinates reduced behavioral inhibition such as mounting of females in the presence of the dominant. Dominants showed enhanced attack to fluoxetine-dosed subordinates, as indexed by enhanced wounding on these animals. Males treated with SSR149415 typically showed more wounding than vehicle controls (Fig. (**5D**)). This was hypothesized to reflect reduced defensiveness in the presence of the dominant. Interestingly, on average over 3 days, vehicle subordinate controls had one fight with the dominant about every 650 seconds of surface time when the subordinate was present with the dominant. In contrast, SSR149415-treated subordinates had one fight with the dominant about every 210 (10 mg/kg) and 150 (30 mg/kg) seconds of surface time when both SSR149415-treated subordinate and the dominant were present (data not shown) [72]. These data provide considerable confirmation of the hypothesis suggested by the wound count data, that some aspect of the behavior of 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 (data not shown) [72]. The ACTH response following restraint stress was reduced in vehicle subordinates compared to dominants, a phenomenon that has been described previously [70]. SSR149415-treated groups showed much higher plasma ACTH levels relative to vehicle subordinates, suggesting normalization of this HPA axis parameter change (data not shown) [59]. Overall, the effects of SSR149415 and fluoxetine, which was tested in parallel, were comparable, confirming the antidepressant-like potential of the V_{1b} receptor antagonist.

3.2.5. Effects of SSR149415 in an Animal Model of Offensive Aggression

The above-mentioned finding that SSR149415 reduced markedly defensive aggression upon forced encounter with a threatening predator in the MDTB suggests that the blockade of V_{1b} receptors may affect other aspects of aggression, in particular spontaneous aggressiveness induced by prolonged socio-environmental deprivation or isolation. AVP is implicated in agonistic behavior in a variety of species, including rodents [73;74]. Moreover, in humans increased levels of AVP have been measured in the cerebrospinal fluid of people with a life history of offensive aggression [75]. There is strong evidence that involves the V_{1a} receptor subtype in the modulation of aggression as evidenced notably by the findings that centrally administered peptide V_{1a} receptor antagonists suppress aggression in rats and hamsters [76;77]. More recently, Wersinger and colleagues demonstrated that the V_{1b} receptor subtype plays also a role in the modulation of offensive aggression [78]. They showed

that mice lacking the V_{1b} receptor exhibit reduced aggression in the resident-intruder and neutral arena paradigms. We used the isolation-induced aggression model in mice to assess the potential antiaggressive properties of SSR149415. Results showed that the V_{1b} receptor antagonist significantly reduced the duration of fighting between 4-week isolated mice and intruder mice (Table 3) [45]. However it must be emphasized that the magnitude of these effects was less than that of the tricyclic antidepressant, imipramine. Clearly, further experiments are required to evaluate more precisely the antiaggressive potential of V_{1b} receptor antagonists.

Table 3. Comparison of the Effects of SSR149415 and Imipramine in the Isolation-induced Aggression Paradigm in Mice. Data Represent Mean ± S.E.M.* *P*<0.05. Adapted from [45]

Treatment	Dose (mg/kg)	Duration of fighting (s)
Imipramine	0	53±4
(ip-30 min)	15	12±4*
	30	0.2±0.2*
SSR149415	0	64±6
(po-60 min)	1	36±6*
	3	35±4*

3.2.6. Side Effect Profile of SSR149415

Compounds that affect motor coordination, produce sedation or impair cognitive processes will confound results from behavioral studies, including the anxiety and depression models described above. Therefore we addressed potential side effects of SSR149415 by looking at spontaneous locomotor activity and reported no significant effects up to 100 mg/kg (po). Neither did the drug modify sleep patterns following EEG analysis at 30 mg/kg (po). Studies on the specific role of AVP on cognitive processes are sparse, although the peptide has frequently been implicated in learning and memory (for reviews, see [7;79]). We used the Morris water maze task in mice and rats to investigate potential effects of SSR149415 on spatial memory, but found no effect on either the acquisition of the test or on recalling the platform position after removal. These data are in accordance with the results of Engelmann and colleagues [80], who infused centrally the mixed peptide $V_{1a/b}$ receptor antagonist $d(CH_2)_5$Tyr(Et)VAVP during Morris maze spatial learning. They reported that treatment with this antagonist had no effect on acquisition of the test when compared with controls animals. Overall, the findings of a lack of activity of SSR149415 in models of motor coordination, EEG activity and cognitive processes have a direct bearing on the issue of the behavioral selectivity of any changes observed in the stress models and indicate that the drug is devoid of central effects not related to emotionality.

4. CONCLUSION

Hyperactivity of the HPA axis is one of the key biological abnormalities described in affective disorders such as major depression and post-traumatic stress disorder. Although CRF, which is the main regulator of this stress system, is the focus of current interest, there is an accumulating body of evidence suggesting that the vasopressinergic system may play an equal if not more important role in the HPA hyperactivity observed in stress-related disorders. The demonstration that repeated stress produces sustained elevations in V_{1b} receptor mRNA in the pituitary [18] coupled with the observation that this receptor subtype may be upregulated in depression [14], provides the framework for a novel perspective on potential anti-stress drugs, namely that V_{1b} receptor antagonists may be of potential therapeutic benefit. Now, the availability of SSR149415, the first selective antagonist for the V_{1b} receptor has allowed us to test this hypothesis. Results showed that SSR149415 is able to attenuate some but not all stress-related behaviors in rodents. While the antidepressant-like activity of the compound was comparable

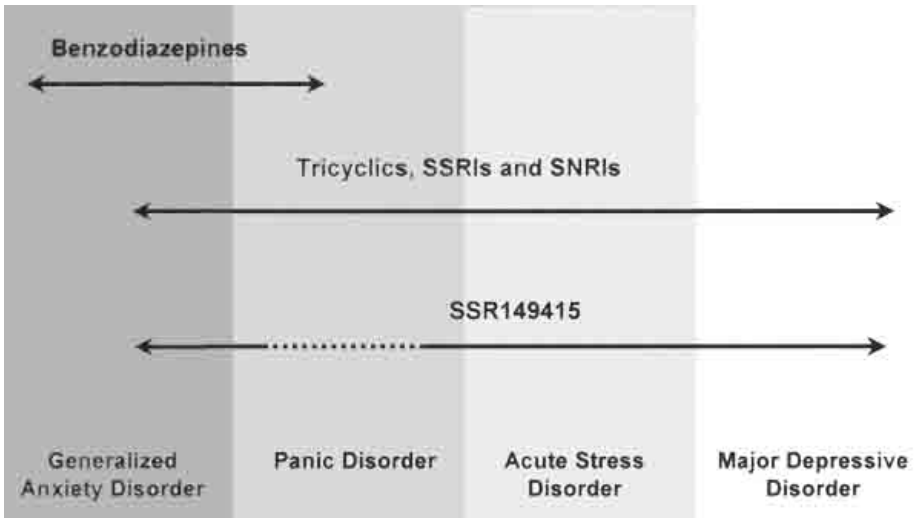


Fig. (6). Expected clinical spectrum of therapeutic activity of the V_{1b} receptor antagonist, SSR149415, in stress-related disorders. SSRI = selective 5-HT reuptake inhibitor; SNRI = mixed 5-HT/noradrenaline reuptake inhibitor.

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 V_{1b} receptor antagonist showed clear-cut effects only in particularly stressful situations, and in tests sensitive to social or aggression cues. This latter finding is in agreement with the known behavioral effects of centrally administered vasopressin. It is important to note that SSR149415 is devoid of central depressant effects, even at high doses, and does not affect cognitive processes, suggesting a large therapeutic window. Consequently, it is unlikely that the FDA will schedule the drug. Altogether these findings suggest that V_{1b} receptor antagonists might be useful as a treatment for major depression and stress disorders that result from traumatic events (Fig. (**6**)).

Although these results might be therapeutically useful, they do not tell us where in the brain SSR149415 acts to reduce anxiety- or depressive-like behaviors. However, the fact that it is still effective in hypophysectomized rats [46] indicates that the effects do not depend on blocking only the hypothalamic V_{1b} receptors. Likely structures involved in these effects include the hippocampus, the lateral septum and amygdala. These regions show abundant expression of V_{1b} receptors [22;81]. To verify these hypotheses, experiments with local injections of SSR149415 in specific brain areas are in progress.

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