Non-Peptide Vasopressin V_{1b} Receptor Antagonists as Potential Drugs for the Treatment of Stress-Related Disorders

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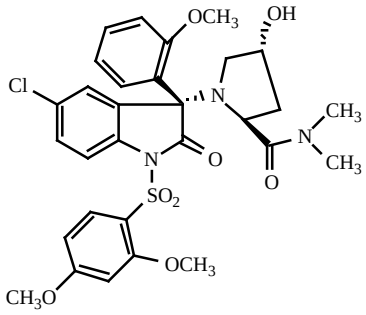
Abstract: Since vasopressin has been shown to be critical for adaptation of the hypothalamo-pituitary-adrenal axis during stress through its ability to potentiate the stimulatory effect of CRF, it has been hypothesized that this peptide may provide a good opportunity for pharmacological treatment of stress-related disorders. The availability of the first orally active non-peptide V_{1b} receptor antagonist, SSR149415, opened a new era for examining the role of vasopressin in animal models of anxiety and depression. In rats, SSR149415 blocked several endocrine (i.e. ACTH release), neurochemical (i.e. noradrenaline release) and autonomic (i.e. hyperthermia) responses following various stress exposures. Moreover, the drug was 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. These latter were highly effective and reliably produced robust effects in most anxiety tests, while SSR149415 showed clear-cut effects only in particularly stressful situations. Experiments with mice or hamsters indicated that V_{1b} receptor blockade is associated with reduced aggressiveness, suggesting that SSR149415 could prove useful for treating aggressive behavior. It is important to note that SSR149415 is devoid of adverse effects on motor functions or cognitive processes, and it did not produce tolerance to its anxiolytic- or antidepressant-like activity. Altogether, these findings suggest that V_{1b} receptor antagonists represent a promising alternative to agents currently used for the treatment of depression and some forms of anxiety disorders.

Key Words: Antidepressant, Anxiety, Anxiolytic, Depression, SSR149415, Stress, V_{1b} receptor, Vasopressin.

1. INTRODUCTION

Benzodiazepines (BZs) and monoamine oxidase/reuptake inhibitors have been the mainstay of drug treatment of anxiety and depressive disorders, over the last 4 decades. However, the problems associated with their use (e.g., abuse liability of BZs or slow onset of action of monoamine reuptake inhibitors) prompted the research for alternative agents that would be useful in these conditions. Today, drug discovery focuses more and more on the involvement of neuropeptides in the modulation of stress-related disorders. 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 nociceptin, oxytocin and vasopressin has also been considered [1-4]. The present paper gives an overview on vasopressin and the first specific and highly potent non-peptide vasopressin V_{1b} receptor antagonist, SSR149415 (Fig. (**1**)) [5]. The drug has been tested in a variety of animal models of anxiety and depression, and as will be shown below, it yielded a profile that differed from that observed with classical anxiolytics and antidepressants.



SSR149415

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

2. VASOPRESSIN, RECEPTOR REGULATION AND THE STRESS RESPONSE

Vasopressin is a nine-amino acid neuropeptide that is synthesized in different hypothalamic nuclei, including the supraoptic, paraventricular and suprachiasmatic nucleus [6, 7] (Fig. (**2**)). Prominent among these are the magnocellular neurons of the hypothalamic paraventricular, supraoptic and accessory magnocellular nuclei, and cell groups whose axons project to the posterior pituitary where the peptide is released directly into the systemic circulation after physiological stimuli, including short-term noxious stimuli [8-10]. Moreover, vasopressin synthesized in parvocellular neurons of the hypothalamic paraventricular nucleus is a regulator of the hypothalamic-pituitary-adrenocortical (HPA) axis [11-13]. The peptide is critical for adaptation of the HPA axis during stress through its ability to potentiate the stimulatory effect of CRF on adrenocorticotropin (ACTH) in the anterior pituitary. Both acute and repeated stresses stimulate release

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of vasopressin from the median eminence into the pituitary portal circulation and increase expression of the peptide in parvocellular neurons of the paraventricular nucleus (for a recent review, see [4]) (Fig. (**3**)). The finding that genetically vasopressin-deficient Brattleboro rats have impaired ACTH response to aversive stimuli [14, 15] provided further evidence for the role of the peptide in stress.

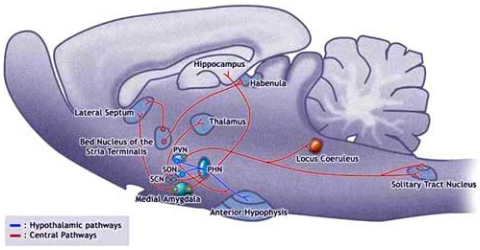

Fig. (2). The main vasopressinergic pathways in the rat brain. PHN = posterior hypothalamic area, PVN = parvocellular paraventricular nucleus, SCN = suprachiasmatic nucleus, SON = supraoptic nucleus of the hypothalamus.

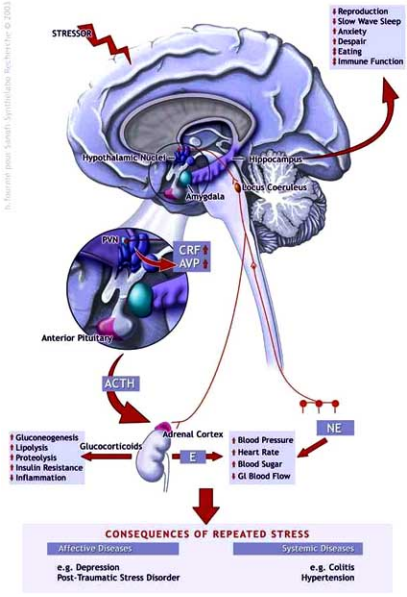

Fig. (3). Schematic representation of the endocrine, behavioral and autonomic responses to stress mediated by vasopressin (AVP), and the consequences of repeated stress. E = epinephrine, NE = norepinephrine, PVN = paraventricular nucleus.

Vasopressin-containing neurons have been characterized in extrahypothalamic structures, including the bed nucleus of the stria terminalis and the medial amygdala [16-18]. They project to the lateral septum, ventral septal nucleus, lateral habenular nucleus, locus coeruleus and ventral hippocampus (Fig. (**2**)). In these latter structures, vasopressin was suggested to exert its biological effects by binding to V_{1a} and V_{1b} (also called V_3) receptors, that activate phospholipases via $G_{q/11}$ proteins [19-21]. Both receptors are widely distributed in the central nervous system, including the lateral septum, cortex and hippocampus [19, 22, 23] (Fig. (**4**)).

The presence of this vasopressin network suggests a modulator role of the peptide in limbic functioning. Extensive animal research has established a role for this peptide in learning and memory processes. Moreover, it is now recognized that centrally released vasopressin is involved in a variety of roles, including social, reproductive and feeding behavior [24-29]. In addition, evidence is emerging that suggests that vasopressin plays an important role in emotional processes. Studies which investigated the behavioral action of central infusion of vasopressin and peptide V_1 receptor ligands in animal models of anxiety have shown that intracerebroventricular infusion of the peptide produced anxiogenic-like activity in rats [30], whereas central application of the mixed $V_{1a/b}$ receptor antagonist $d(CH_2)_5$Tyr(Et)VAVP produced anxiolytic-like effects [31]. In line with these findings are results from a study using an antisense oligodeoxynucleotide mRNA to the V_{1a} subtype which showed that intra-septal infusion of the antisense reduced anxiety in the elevated plus-maze [32]. Furthermore, the vasopressin-deficient rats Brattleboro were found to display attenuated conditioning freezing responses [33], while rats with high innate anxiety showed increased levels of vasopressin in the hypothalamus [34]. Interestingly, chronic treatment with the classical antidepressant, paroxetine, normalized hypothalamic vasopressin levels in these latter rats [35]. Moreover, it was reported in this study that V_{1a} receptor expression was higher in the lateral septum of high-anxious rats, but remained unchanged following paroxetine challenge. In non-stressed rats, immobilization stress and repeated hypertonic saline injections were found to produce sustained elevations in V_{1b} receptor mRNA in the pituitary [36], suggesting an upregulation of this receptor under chronic stress.

Although there is no direct evidence that vasopressin or vasopressin receptor ligands may modulate anxiety or depression in humans, there are several clinical findings that provide substantial evidence for the role of the peptide in stress-related disorders. Plasma levels of vasopressin have been shown to be elevated in patients with major depression [37, 38] and anxious-retarded melancholic depression [39]. Interestingly, in this latter study there was a highly significant correlation between plasma vasopressin and cortisol levels. Moreover, chronic treatment with the classical antidepressant fluoxetine decreased significantly elevated vasopressin levels in major depression [37]. The changes in plasma vasopressin levels in depression may be accompanied by abnormalities in vasopressin receptor activity [40, 41]. Although the involvement of vasopressin in human anxiety behaviors has been much less investigated, one study reported that vasopressin release was significantly correlated with anxiety symptoms (e.g., respiratory distress, cognitive anxiety) in healthy volunteers after anxiogenic drug challenge [42]. Together, these preclinical and clinical findings suggest that vasopressin receptor antagonists may represent effective agents for the treatment of stress-related disorders [43].

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

Initially, peptide vasopressin receptor antagonists were described, but their usefulness was limited because of their peptide nature, poor access to the brain following systemic administration and poor oral bioavailability [44]. The

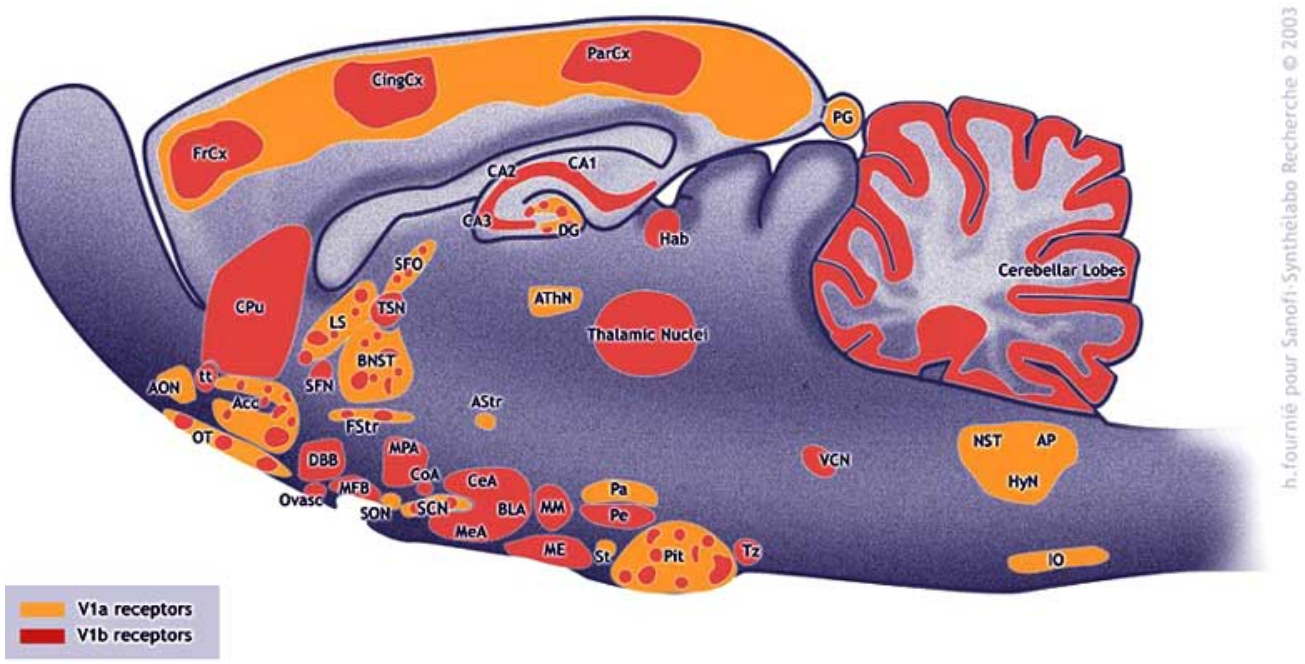

Fig. (4). Distribution of the V_{1a} and V_{1b} receptor proteins or mRNAs encoding V_{1a} or V_{1b} receptors in the rat brain. Adapted from [19, 23, 83, 84] and Stemmelin *et al*. (manuscript in preparation). Acc = Accumbens nucleus, AON = Anterior olfactory nucleus, AP = Area postrema, Astr = Amygdalostriatal area, AthN = Anteroventral thalamic nucleus, BlA = Basolateral amygdala, BNST = Bed nucleus of the stria terminalis, CA1 = Hippocampal field CA1, CA2 = Hippocampal field CA2, CA3 = Hippocampal field CA3, CeA = Central amygdala, CingCx = Cingulate cortex, CoA = Cortical amygdaloid nucleus, Cpu = Caudate/putamen, DBB = Diagonal band of Broca, DG = Dentate Gyrus, FrCx = Frontal cortex, FStr = Fundus striati, Hab = Medial habenula, HyN = Hypoglossal nucleus, IO = Inferior olive, LS = Lateral septum, ME = Median eminence, MeA = Median amygdala, MFB = Medial forebrain bundle, MM = Medial mammillary nucleus, MPA = Medial preoptic area, NST = Nucleus of the solitary tract, OT = Olfactory tubercle, Ovasc = Organum vasculosum laminae terminalis, Pa = Paraventricular hypothalamic nucleus, ParCx = Parietal cortex, Pe = Periventricular hypothalamic nucleus, PG = Pineal gland, Pit = Pituitary gland, SCN = Suprachiasmatic nucleus, SFN = Septofimbrial nucleus, SFO = Subfornical organ, SON = Supraoptic nucleus, St = Stigmoid nucleus, TSN = Triangular septal nucleus, tt = Taenia tecta, Tz = Trapezoid body, VCN = Ventral cochlear nucleus.

compelling preclinical and clinical findings indicated above have driven the search for small molecule vasopressin receptor antagonists that, by peripheral administration, mimic the pharmacological profile of the peptide antagonists. Recently, several classes of non-peptide antagonists of vasopressin receptors (i.e. V_{1a} and V_{1b}) have been discovered by random screening [5, 45-47] and have allowed assessment of their therapeutic potential, notably in stress-related disorders.

SSR149415 ((-)-(2*S*,4*R*)-1-[(3*R*)-5-chloro-1-[(2,4-dimethoxylphenyl) sulfonyl] -3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H* - indol - 3 - yl]- 4 - hydroxy - *N*,*N* - dimethyl - 2-pyrrolidine carboxamide) is the first non-peptide antagonist at the V_{1b} receptor [5] (Fig. (**1**)). It belongs to the [1*H*] - 2,3 dihydroindol-2 one family of vasopressin antagonists. Receptor binding studies demonstrated that SSR149415 has 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 oxytocin (a closely vasopressin-related peptide) receptors, and was found to have minimal affinity (K_i > 10 μM) in more than 90 binding assays for neurotransmitters and peptides. Potent antagonist activity of SSR149415 at the V_{1b} receptor was demonstrated by its ability to inhibit vasopressin-induced Ca^{2+} increase in Chinese hamster ovary cells expressing the human or rat V_{1b} receptor (K_i = 1.26 and 0.73 nM, respectively), and vasopressin-induced ACTH secretion in corticotroph cells in rats [5].

3.1. Profile of SSR149415 in Animal Models of Anxiety/Stress

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. In classical animal models of anxiety, such as conflict paradigms (e.g. punished drinking procedure in rats and four-plate test in mice or gerbils) 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 [5, 48-51]. A summary of the effects obtained with this compound is shown in Table **1**. 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. It is important to note that the magnitude of the anxiolytic-like action of SSR149415 in these models was

Table 1. The Effects of the V_{1b} Receptor Antagonist SSR149415 in Anxiety/Stress Models

Models	Species	Dosing	Activity	Positive control	Reference
Cage switch-induced increase in heart rate	Sprague-Dawley rats (250-300g)	10 and 30 mg/kg, p.o., 120 min	Active at 30	Diazepam inactive	Unpublished
Conditioned fear stress	Mice	10 and 30 mg/kg, p.o., 60 min	Active at 10 and 30	Diazepam at 2 and 4	[51]
Defensive aggression in the MDTB	Swiss mice (10-week old)	1-30 mg/kg, p.o., 60 min	Active at 1, 3, 10 and 30	Diazepam at 1 and 3	[49]
Distress sonic vocalizations	Hartley Guinea pig pups (5-day old)	10-30 mg/kg, i.p., 30	Active at 20 and 30	Diazepam at 3 and 10	[50]
Distress ultrasonic vocalizations	Sprague-Dawley rat pups (7-day old)	3-30 mg/kg, s.c., 30 min	Active at 10 and 30	Diazepam at 1 and 3	[50]
Elevated plus-maze	Sprague-Dawley rats (180-200g)	3-30 mg/kg, p.o., 60 min	Active at 10 and 30	Diazepam at 10	[49]
Flight in the MDTB	Swiss mice (10-week old)	1-30 mg/kg, p.o., 60 min	Active at 30	Diazepam inactive	[49]
Four-plate	Mongolian gerbils	10-30 mg/kg, p.o., 60 min	Active at 10 and 30	Diazepam at 1 and 2	Unpublished
Four-plate	NMRI mice (17-23g)	1-10 mg/kg, i.p., 30 min	Active at 3 and 10	No	[5]
Four-plate	NMRI mice (17-23g)	1-10 mg/kg, p.o., 60	Active at 3 and 10	No	[5]
Light/dark	BALB/c mice (8- week old)	1-30 mg/kg, p.o., 60 min	Active at 1, 10 and 30	Diazepam at 3	[49]
Punished drinking	Sprague-Dawley rats (200-225g)	1-10 mg/kg, i.p., 30 min	Active at 3 and 10	Diazepam at 3	[49]
Restraint stress-induced ACTH release	Sprague-Dawley rats (150-200g)	3 and 10 mg/kg, p.o., 60 min	Active at 10	No	[5]
Risk assessment in the MDTB	Swiss mice (10-week old)	1-30 mg/kg, p.o., 60 min	Inactive	Diazepam at 0.5, 1 and 3	[49]
Social defeat stress	Swiss mice	0.1-3 mg/kg, p.o., 60 min	Active at 0.3, 1 and 3	Diazepam at 4	[49]
Social interaction	Mongolian gerbils (50-60g)	3-30 mg/kg, p.o., 60 min	Active at 10 and 30	Diazepam at 0.1 and 0.3	[51]
Swim stress-induced PS rebound	Sprague-Dawley rats (350-450g)	30 mg/kg, p.o., 60 min	Active at 30	No	Unpublished
Tail pinch-induced NE release	Sprague-Dawley rats	3 and 10 mg/kg, i.p., 30 min	Active at 10	No	[51]
Tail pinch-induced hyperthermia	Sprague-Dawley rats (250-300g)	10 and 30 mg/kg, p.o., 120 min	Active at 30	Diazepam at 1 and 2	Unpublished

MDTB = mouse defense test battery; PS = paradoxical sleep

always less than that of the BZ anxiolytic diazepam, which was used as a positive control.

When, however, anxiety levels were increased by stress treatments, the activity of SSR149415 appeared to be enhanced. This is best exemplified by the findings from the social defeat stress-induced anxiety paradigm in mice, where SSR149415 completely antagonized the heightened emotionality in the elevated plus-maze produced by prior (stressful) exposure to an aggressive isolated resident [49]. Similarly, results obtained with SSR149415 in the mouse defense test battery (MDTB) are relevant to this issue. In this model, mice are directly confronted with a natural threat (a rat) as well as situations associated with this threat. Primary measures taken during rat confrontation include flight, risk assessment and defensive attack [52]. Here, SSR149415 failed to modify clearly flight and risk assessment, two behaviors associated with low levels of stress, but it produced clear-cut effects on defensive attack upon forced contact with the rat [49]. This latter situation is particularly stressful for animals since they have no possibility to escape and confrontation with the threat stimulus is unavoidable. Interestingly, V_{1b} receptor knockout mice (V_{1b}RKO) displayed a comparable behavioral profile in the MDTB as animals treated with SSR149415 [53]. While V_{1b}RKO showed similar flight and risk assessment performances than wild-type mice, they had minimal defensive aggression

reactions upon forced contact with the rat (Fig. (**5**)). This clearly suggests that the V_{1b} receptor plays a crucial role in terminal defensive behaviors such as defensive attack and aggression. The idea that stress levels are important to reveal anxiolytic-like effects of SSR149415 was examined further by using several rodent procedures based on behavioral changes produced by traumatic events. 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 [54, 55]. When SSR149415 was tested in these models, it produced a dose-dependent decrease in both sonic and ultrasonic vocalizations [50].

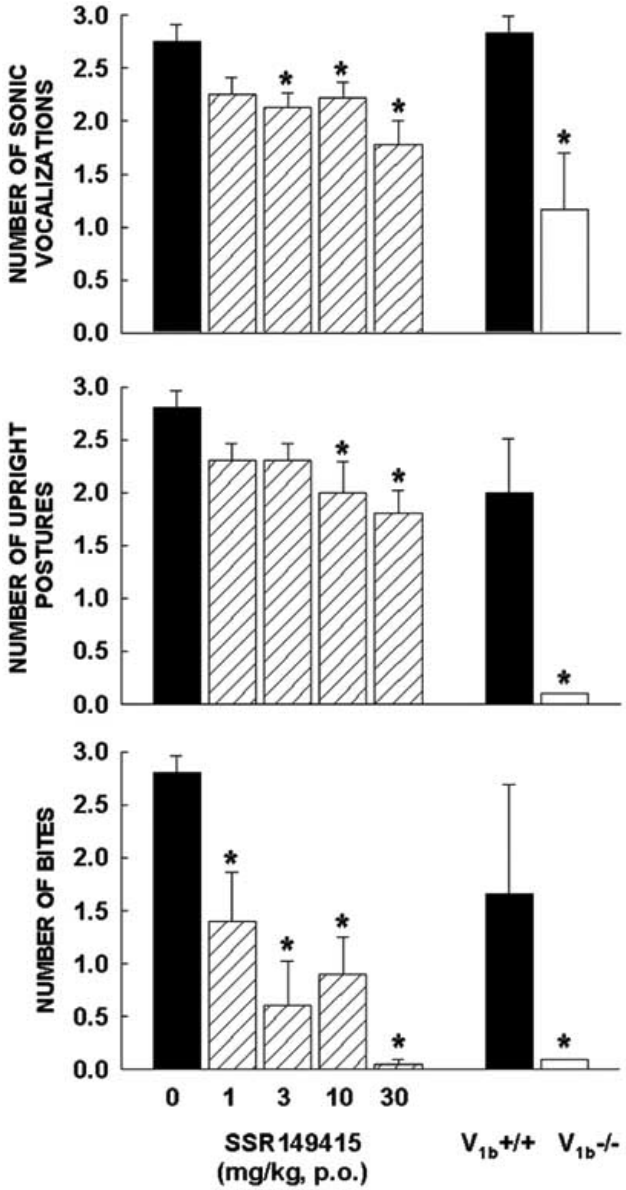

Fig. (5). Comparison of the behavioral profile displayed by mice treated with the V_{1b} receptor antagonist, SSR149415, and V_{1b} receptor knockout mice on defensive aggression upon forced contact with a Long Evans rat in the mouse defense test battery. Adapted from [49, 53].

A few of the well-characterized brain circuits that participate in the regulation of the neuroendocrine responses to stressors a summarized in Figure 3. Multiple brain structures are involved in the organization of responses to aversive or stressful stimuli. Among these is the hypothalamus. The hypothalamic paraventricular nucleus plays a pivotal role in the adaptive response to stressors. CRF, the releasing factor for ACTH, is synthesized by the parvocellular neurons of the hypothalamic paraventricular nucleus and its action is essential in the neuroendocrine control of ACTH release from the pituitary gland [56]. 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 [57, 58]. We therefore tested the ability of SSR149415 to prevent restraint stress-induced elevation of ACTH levels and the synergistic action between vasopressin and CRF on ACTH release in corticotroph cells in rats. Results showed that the V_{1b} receptor antagonist inhibited both stress-induced ACTH secretion and the release of the stress hormone following combined vasopressin and CRF challenge [5].

Studies in animals have shown a relationship between alterations in noradrenergic (NA) brain system function and behaviors associated with stress and anxiety [59-61]. The majority of NA cell bodies in the brain are located in the locus coeruleus, with projections throughout the cerebral cortex and multiple subcortical areas, including hippocampus, amygdala, thalamus, and hypothalamus. The neuroanatomy of the afferent and efferent inputs to the locus coeruleus is suggestive of the role it may play in the stress response. 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 [62], an effect that could be prevented by prior administration of potential anti-stress drugs, such as the CRF_1 receptor antagonist, SSR125543A, and the NK_2 receptor antagonist, SR48968 [63, 64]. When SSR149415 was tested in this model, it reduced similarly the evoked NA release following tail pinch stress [48]. Tail pinch was also used to investigate the effects of SSR149415 on certain aspects of the autonomic stress response, namely the increase in body temperature. Results showed that SSR149415 reduced significantly stress-induced hyperthermia as did the tricyclic antidepressant, imipramine, but not the BZ anxiolytic, diazepam, and the selective 5-HT reuptake inhibitor, fluoxetine (Fig. (**6**)). 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.

3.2. Profile of SSR149415 in Animal Models of Depression

The antidepressant-like efficacy of SSR149415 has been evaluated in several procedures, including the forced-swimming test in rats [65], the stress-induced tonic immobility paradigm in gerbils [66], the tail-suspension test in mice [67], the chronic mild stress model in mice [68, 69]

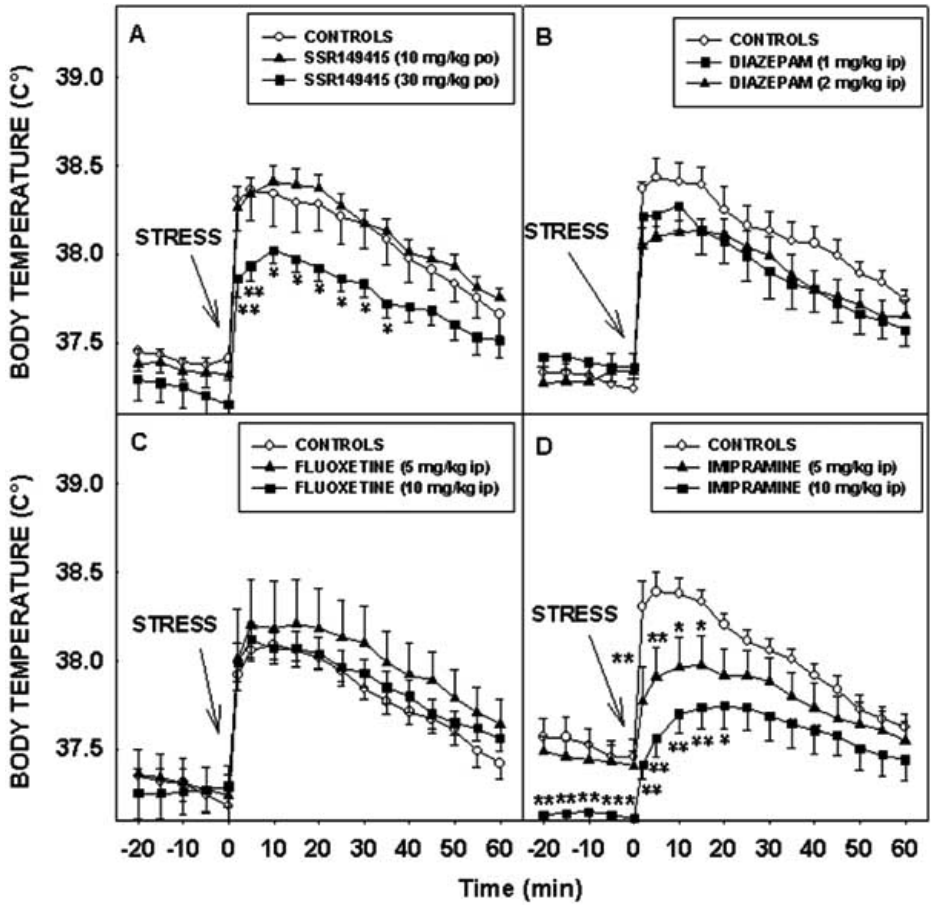

Fig. (6). Effects of the V_{1b} receptor antagonist, SSR149415, on an autonomic index of the stress response produced by tail pinch.

Table 2. The Effects of the V_{1b} Receptor Antagonist SSR149415 in Animal Models of Depression

Models	Species	Dosing	Activity	Positive control	Reference
Forced-swimming	Wistar rats (255-315g)	3-30 mg/kg, p.o., for 2 days	Active at 10 and 30	Imipramine, fluoxetine	[49]
Tail-suspension	NMRI mice (22-27g)	3-30 mg/kg, i.p., 30 min	Active at 3 and 30	Imipramine at 20	Unpublished
Tonic immobility	Mongolian gerbils (51-60g)	3-30 mg/kg, p.o., 60 min	Active at 10 and 30	Imipramine, fluoxetine	[66]
Chronic mild stress	BALB/c mice (17-32g)	10 and 30 mg/kg, i.p., for 39 days	Active at 10 and 30	Fluoxetine at 10	[49]
Chronic mild stress	BALB/c mice (24-32g)	30 mg/kg, i.p., for 4 weeks	Active at 30	Fluoxetine at 10	[51]
Subordination stress	Long Evans rats (>90-day old)	10 and 30 mg/kg, p.o., for 14 days (b.i.d.)	Active at 10 and 30	Fluoxetine at 10	[74]

and the chronic subordination stress paradigm in rats [70] (Table **2**).

In the forced-swimming test, one of the most widely used tool for assessing antidepressant activity preclinically, SSR149415 reduced immobility time of rats placed in an inescapable cylinder of water [49]. The immobility is thought to reflect a failure of persistence in escape-directed behavior, leading to behavioral despair. Similarly, in the tonic immobility paradigm in gerbils, SSR149415 prevented the development of passive behavior that disengages the animal from active forms of coping with stressful stimuli such as the sudden grasping of their back [66]. In both test situations, the effects of SSR149415 were comparable to those observed with reference antidepressants, such as imipramine or fluoxetine. Importantly, the finding that the antidepressant-like effects of SSR149415 in the forced-swimming test were still present in hypophysectomized rats [49], 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. To support this idea is a recent finding, which demonstrated that infusion of SSR149415 into the lateral septum, or the central nucleus of the amygdala in rats yielded antidepressant-like activity, suggesting that these structures participate in the anti-stress action of SSR149415 [71].

The antidepressant potential of SSR149415 was confirmed in two models of depression based on repeated unavoidable exposures to stressors, the chronic mild stress (CMS) test in mice and the chronic subordination stress model in rats. The CMS procedure, originally designed by Willner *et al*. [72], is generated by sequential applications of different unpredictable stressful conditions such as restraint, forced swimming, water deprivation, pairing with another stressed animal, each for a period of between 2 and 24h, in a schedule that lasts for three weeks, and is repeated thereafter. It leads to a degradation of the physical state, increased emotionality and a reduced ability to cope with aversive situations. These behavioral effects are accompanied by a severe reduction in the rate of newborn cell proliferation in the hippocampus leading to a suppression of neurogenesis. When SSR149415 was given repeatedly to chronically stressed mice it reversed the degradation of the physical state two weeks after the beginning of the treatment. It also prevented anxiety, despair and the loss of coping behavior produced by stress [49, 51]. Moreover, SSR149415 significantly reversed the suppression of cell proliferation produced by chronic stress, and prevented the dramatic reduction of granule cell neurogenesis 30 days after the end of the stress period [73] (Fig. (**7**)).

Subordination stress, as opposed to other experimental procedures has the advantage of face validity, in that most human stressors appear to be much more closely related to social factors than the unusual and physically painful experiences [70]. 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 non-agonistic behaviors, wound patterns and weight changes. Their behavior changes suggest chronic defensiveness and are also broadly isomorphic to many of the symptoms of depression [70]. When SSR149415 was administered for two weeks to subordinate rats, it reduced defensiveness in the presence of the dominant rat and behavioral inhibition such as mounting of females in the presence of the dominant [74]. Plasma ACTH levels were reduced in vehicle subordinates compared to dominants, but SSR149415-treated rats showed much higher plasma ACTH levels relative to vehicle subordinates, suggesting normalization of this HPA axis parameter change [75].

3.3. Profile of SSR149415 in Animal Models of Aggression

Vasopressin plays a facilitatory role in aggressive behavior in a variety of species, including humans. In these latter, a relationship between cerebrospinal fluid vasopressin and indices of aggression has been established [76]. In rodents, vasopressin infusions into the hypothalamus or amygdala enhance aggression in hamsters and rats, while vasopressin receptor antagonist infusions reduce aggression

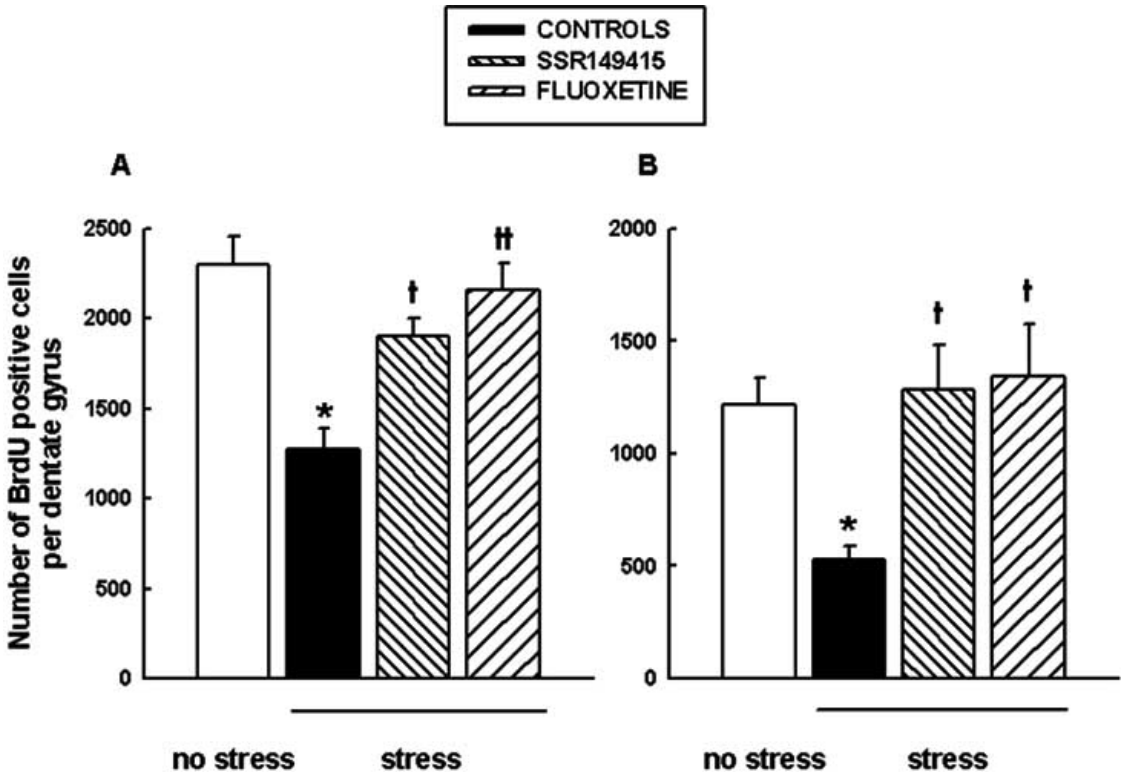

Fig. (7). Effects of 4-week treatment with SSR149415 (30 mg/kg) and fluoxetine (10 mg/kg) on chronic mild stress-induced reduction of cell proliferation (A) and suppression of neurogenesis (B) in the dentate gyrus of mice. Adapted from [73].

[77-80]. These findings, along with the above-mentioned results that SSR149415 reduced markedly defensive aggression upon forced encounter with a threatening predator, prompted us to assess the potential antiaggressive properties of SSR149415. In the resident-intruder aggression paradigm, the V_{1b} receptor antagonist significantly reduced the duration of fighting between isolated and intruder mice [48]. Golden hamsters communicate dominance status by flank marking. Administration of SSR149415 to dominant hamsters blocked flank marking in the presence of their subordinate partners. Moreover, the drug reduced chase and lateral attack behaviors (Fig. (**8A-C**)). All these effects are consistent with an anti-aggression action of SSR149415. It is noteworthy that mice lacking the V_{1b} receptor have been reported to show reduced aggressive behavior, thereby pointing to an important role of the V_{1b} receptor in the modulation of aggression [53, 81] (Fig. (**8D**)).

3.4. Evaluation of the Effects of SSR149415 in Behavioral Models not Related to Emotionality

A major point of concern when developing new anxiolytic and antidepressant drugs is the propensity to induce various side effects. 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 tested SSR149415 in a variety of standard procedures to evaluate possible unwanted effects. Results showed that the drug was devoid of central depressant effects (ataxia, myorelaxation and sedation) as evidenced by a lack of activity in the rotarod, the traction test and in activity cages up to 100 mg/kg [49] (Table **3**). Moreover, SSR149415 did not modify sleep patterns following electroencephalographic analysis. The precise role of vasopressin in cognitive processes remains unclear, but the peptide has frequently been implicated in learning and memory (for reviews, see [29, 82]). Although a facilitatory role in cognitive functions has been suggested with vasopressin, evidence for disruption of cognitive processes by SSR149415 has not been demonstrated as evidenced by the lack of effect of the drug on spatial memory in the Morris water maze task in mice and rats [50]. Instead, it is possible that a V_{1b} receptor antagonist may actually improve cognitive processes in highly stressful situations. Overall, the findings of a lack of activity of

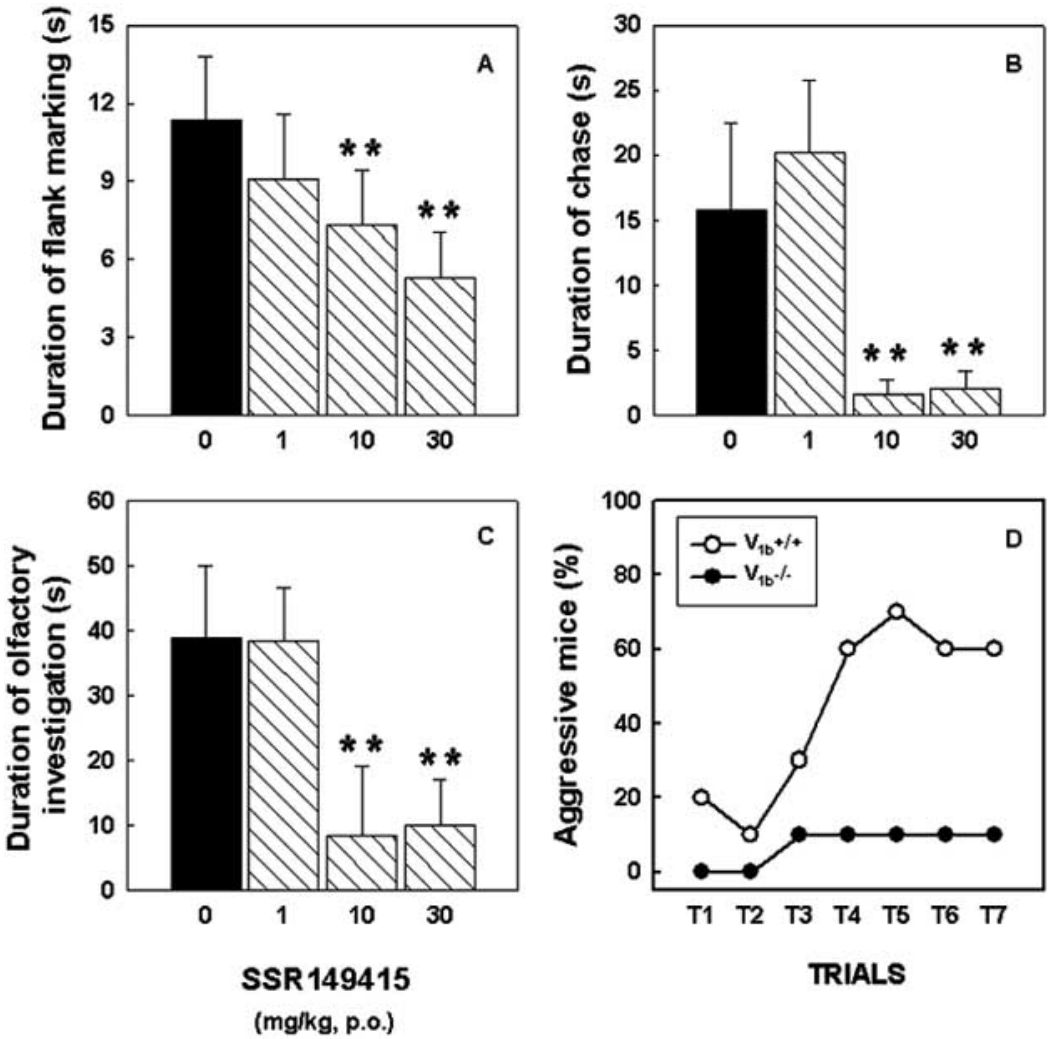

Fig. (8). Comparison of the behavioral profile displayed by hamsters treated with the V_{1b} receptor antagonist, SSR149415 (A-C), and V_{1b} receptor knockout mice in the resident-intruder model of offensive aggression (D). Adapted from [53].

SSR149415 in these models 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.

Table 3. Summary of the Side Effect Profile of the V_{1b} Receptor Antagonist, SSR149415, in Animal Models

Tests	SSR149415 (MED, mg/kg p.o.)
EEG in rats	>30
Locomotor activity	>100
Traction test in mice	>100
Rotarod in mice	>100
Morris water maze in mice	>30
Morris water maze in rats	>30

MED = minimal effective dose

CONCLUSION

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 that attempting to short-circuit the stress response. Increasingly, the HPA is seen as a target site for anxiolytic and antidepressant development, with CRF receptor antagonists at the forefront of current research. However, there is an accumulating body of evidence suggesting that the vasopressinergic system may play an equal role in the HPA hyperactivity observed in stress-related disorders, and that V_{1b} receptor antagonists may be of potential therapeutic benefit. From the data presented in this review, the V_{1b} receptor antagonist SSR149415 may find utility in a number of therapeutic areas, including anxiety, depressive and aggressive disorders. Notably, SSR149415 produced antidepressant-like activity qualitatively and quantitatively similar to those of established antidepressants. Although the anxiolytic potential of SSR149415 appears to be somewhat weaker than that of BZs, unlike these latter, it did not produce depressant effects or cognitive deficits, suggesting a large therapeutic window. In conclusion, the development of non-peptide V_{1b} receptor antagonists, such as SSR149415, opened a new era for examining the role of vasopressin in animal models of stress, and may provide a novel avenue for the treatment of affective disorders.

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