

## REVIEW

# Vasopressin $V_{1B}$ Receptor Antagonists as Potential Antidepressants

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## Abstract

Accumulating evidence shows that certain populations of depressed patients have impaired hypothalamus-pituitary-adrenal (HPA) axis function. Arginine-vasopressin (AVP) is one of the primary factors in HPA axis regulation under stress situations, and AVP and its receptor subtype ( $V_{1B}$  receptor) play a pivotal role in HPA axis abnormalities observed in depression. Based on this hypothesis, several non-peptide  $V_{1B}$  receptor antagonists have been synthesized, and the efficacies of some  $V_{1B}$  receptor antagonists have been investigated in both animals and humans.  $V_{1B}$  receptor antagonists exert antidepressant-like effects in several animal models at doses that attenuate the hyperactivity of the HPA axis, and some of their detailed mechanisms have been delineated. These results obtained in animal models were, at least partly, reproduced in clinical trials. At least 2  $V_{1B}$  receptor antagonists (TS-121 and ABT-436) showed tendencies to reduce the depression scores of patients with major depressive disorder at doses that attenuate HPA axis hyperactivity or block the pituitary  $V_{1B}$  receptor. Importantly, TS-121 showed a clearer efficacy for patients with higher basal cortisol levels than for those with lower basal cortisol levels, which was consistent with the hypothesis that  $V_{1B}$  receptor antagonists may be more effective for patients with HPA axis hyperactivity. Therefore,  $V_{1B}$  receptor antagonists are promising approaches for the treatment of depression involving HPA axis impairment such as depression.

**Keywords:** ABT-436, hypothalamus-pituitary-adrenal axis, SSR149415, TS-121,  $V_{1B}$  receptor antagonist

## Introduction

Major depressive disorder (MDD) is among the most disabling medical conditions, with a lifetime prevalence of approximately 20% of the US population (Hasin et al., 2018). All current antidepressant medications have stemmed from the study of mechanisms of serendipitously discovered agents that act on monoamine neurotransmissions. While the large majority of individuals (approximately 70%) with depression exhibit at least some improvement with antidepressant medication, approximately 30% of patients remain resistant to series of treatments (Rush et al., 2006; Trivedi et al., 2006). Moreover, for currently available antidepressants, about 3–6 weeks is required before the manifestation of a significant therapeutic effect. Therefore, the focus of drug discovery research has recently shifted from the

currently prescribed monoamine-based antidepressants to non-monoamine-based agents. In March 2019, the US Food and Drug Administration approved 2 novel antidepressants (esketamine for treatment-resistant depression and brexanolone for postpartum depression) with mechanisms that differ from monoamine systems (Cristea and Naudet, 2019). Although these drugs represent breakthroughs for depression therapy, activities to find newer antidepressants with improved safety and compliance are ongoing (Chaki et al., 2006; Chaki, 2017).

Depression is a clinically heterogeneous condition defined by several subtypes, the features of which may change over time within the same individual. These different symptom clusters can respond selectively to different treatments. Therefore, different

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## Significance Statement

Given that dysfunction of the hypothalamus-pituitary-adrenal (HPA) axis is observed in certain populations of depressed patients, the  $V_{1B}$  receptor, a receptor subtype of arginine-vasopressin (AVP) that is deeply involved in the regulation of HPA axis, has gained attention as a promising target for the development of novel antidepressants. However, despite encouraging results for  $V_{1B}$  receptor antagonists in rodents, the outcomes of clinical studies for the first  $V_{1B}$  receptor antagonist, SSR149415, were not necessarily encouraging. However, 2 recent trials with new  $V_{1B}$  receptor antagonists (ABT-436 and TS-121) have suggested that these antagonists are effective for the treatment of depressed patients with a highly active HPA axis at dose(s) that block the pituitary  $V_{1B}$  receptor or attenuate HPA axis activity. Therefore, revisiting the HPA hypothesis of depression and reconsidering the utility of  $V_{1B}$  receptor antagonists as a novel treatment for depression, particularly in patients with impaired HPA axis function, are appropriate.

pathophysiological processes are required to be operating in the different subtypes of depression. Based on this nature of depression, it is important to focus on pathophysiological events that differ from the ones targeted by current pharmacotherapies to discover and develop novel antidepressants.

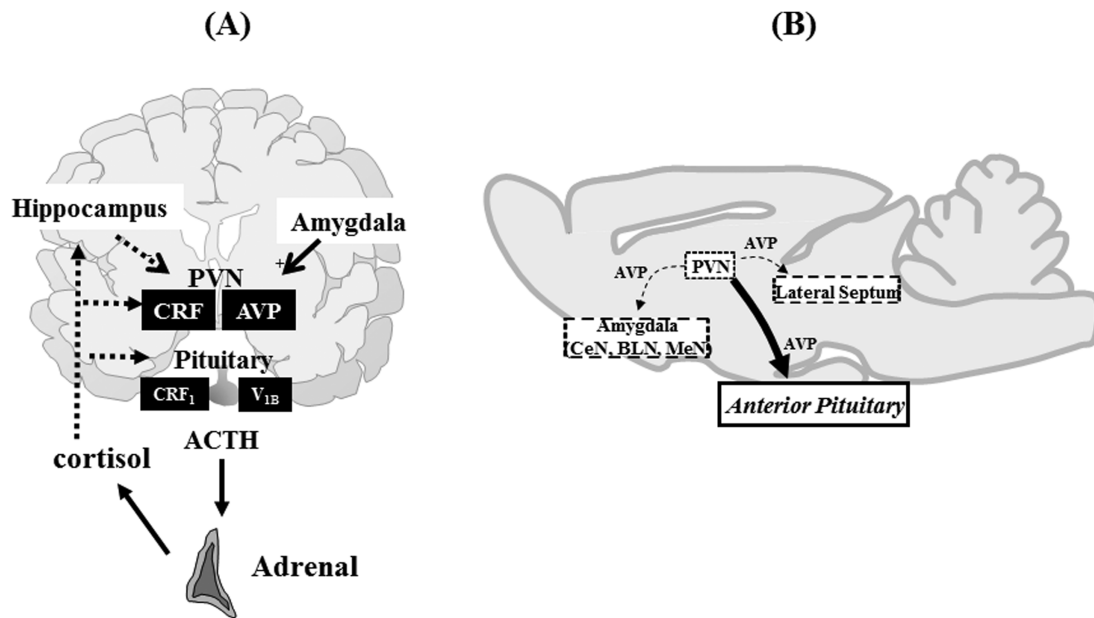
Chronic dysfunction of the hypothalamus-pituitary-adrenal (HPA) axis is generally acknowledged to occur in a subset of MDD patients (Dinan and Scott, 2005; Stetler and Miller, 2011), and patients with treatment-resistant depression or severe depression tend to show HPA axis dysfunction (Jurruena et al., 2009; Rosenblat et al., 2015; Nikkheslat et al., 2020). A sustained elevation of HPA activity is considered to be a causal factor in human affective disorders (Dinan, 1994), and irregularities include elevated serum and 24-hour urinary free cortisol, dexamethasone non-suppression (Carroll et al., 1981), a blunted release of adrenocorticotrophic hormone (ACTH) to corticotropin-releasing hormone (CRH) challenge (von Bardeleben et al., 1988), and exaggerated ACTH and cortisol responses in a dexamethasone/CRH test (Ising et al., 2007). Moreover, successful pharmacological therapy has been linked to the normalization of HPA activity (Ising et al., 2005; Schüle, 2007). Therefore, dampening HPA axis hyperactivity has been hypothesized to be a potential avenue for the treatment of depression. However, clinical studies with compounds regulating the HPA axis have not been successful to date (Griebel and Holsboer, 2012; Menke, 2019). Among the components that regulate the HPA axis, arginine-vasopressin (AVP) and its receptor subtype have attracted attention. In this review, the role of the AVP system in the HPA axis dysfunction observed in depressed patients will first be summarized, followed by a summary of representative preclinical studies of antagonists of the  $V_{1B}$  receptor, an AVP receptor subtype that is deeply involved in the regulation of the HPA axis by AVP. Finally, the potential of  $V_{1B}$  receptor antagonists for the treatment of patients with MDD will be presented through a discussion of the clinical studies on  $V_{1B}$  receptor antagonists conducted to date. In addition, the potential of  $V_{1B}$  receptor antagonists for the treatment of anxiety disorders, which are commonly encountered in patients with MDD, will be briefly mentioned.

## Role of AVP and $V_{1B}$ Receptor in the Regulation of the HPA Axis

HPA activity is driven by the secretion of CRH from the hypothalamic paraventricular nucleus (PVN), which in turn stimulates the secretion of ACTH. AVP, in conjunction with CRH, is also a primary factor in the regulation of HPA axis activity (Aguilera and Rabadan-Diehl, 2000). AVP is a cyclic nonapeptide produced in the PVN and supraoptic nucleus of the hypothalamus and is released from the median eminence into the pituitary portal circulation, where it strongly potentiates the effects of CRH on

ACTH release. AVP exerts its effects through 3 receptor subtypes ( $V_{1A}$ ,  $V_{1B}$ , and  $V_2$  receptors), all of which are G-protein coupled receptors (Peter et al., 1995). Of these receptor subtypes,  $V_{1B}$  receptor mRNA is expressed in the majority of anterior pituitary corticotrophs that secrete ACTH; therefore, it mediates the regulation of HPA axis activity by AVP. The  $V_{1B}$  receptor is also expressed within the brain, particularly within the hypothalamus and limbic brain regions, which have been implicated in stress and emotions (Lolait et al., 1995; Vaccari et al., 1998; Hernando et al., 2001; Corbani et al., 2018). The regulation of the HPA axis by AVP and the extrahypothalamic  $V_{1B}$  receptor are illustrated in Figure 1.

There is a hypothesis that AVP may play a more important role in the regulation of the HPA axis than CRH in chronic stress situations. Repeated stress markedly increases the proportion of AVP-containing neurons among the CRH neurons in the PVN (de Goeij et al., 1992) and increases  $V_{1B}$  receptor expression in the pituitary (Rabadan-Diehl et al., 1995). The sensitivity of CRH and AVP to glucocorticoid feedback is markedly different; the mRNA expression of CRH and its receptor (CRHR<sub>1</sub>) is reduced by elevated glucocorticoid levels (Zhou et al., 1996), whereas the mRNA levels of the  $V_{1B}$  receptor and the coupling of the receptor to phospholipase C are stimulated by glucocorticoids (Aguilera and Rabadan-Diehl, 2000). These effects may contribute to the refractoriness of AVP-stimulated ACTH secretion to glucocorticoid feedback. Therefore, vasopressinergic regulation of the HPA axis is presumed to be critical for sustaining corticotroph responsiveness in the presence of high levels of circulating glucocorticoids during chronic stress. The predominant roles of the AVP- $V_{1B}$  receptor system in the regulation of the HPA axis in chronic stress are supported by the finding that the correlation between AVP and ACTH is stronger than between CRH and ACTH (Scott and Dinan, 1998). All these findings indicate a switch from a CRH system to an AVP system in the regulation of ACTH release during chronic stress, and  $V_{1B}$  receptor antagonists might be an adequate approach for the treatment of psychiatric disorders involving chronically stressful conditions. On the other hand, it should be noted that more recent reports contradict the hypothesis that the AVP- $V_{1B}$  receptor system has a more important role in the regulation of HPA axis under chronic stress. For example, lower ACTH and corticosterone responses to noise stress were noted after repeated restrained stress in rats while vasopressinergic activity was increased, and a  $V_1$  receptor antagonist did not block increased ACTH and corticosterone induced by hypertonic saline in repeated chronic stress conditions (Chen et al., 2008). Moreover, AVP-deficient Brattleboro rats show normal HPA axis responses to stress (Makara et al., 2012). Although differences in experimental conditions need to be taken into account, role of the AVP- $V_{1B}$  receptor system in chronic stress remains to be thoroughly investigated.



**Figure 1.** Regulation of hypothalamus-pituitary-adrenal (HPA) axis by arginine-vasopressin (AVP) (A) and extrahypothalamic AVP system (B). (A) Both AVP and corticotropin-releasing factor (CRF) produced in the paraventricular nucleus (PVN) of the hypothalamus act on  $V_{1B}$  and  $CRF_1$  receptors in the pituitary, respectively, to stimulate adrenocorticotropic hormone (ACTH) release from the anterior pituitary. In response to ACTH, the cortex of the adrenal glands produces cortisol (corticosterone in rodents), which penetrates the blood-brain barrier and exerts its actions in the brain through the high-affinity mineralocorticoid receptors and the low-affinity glucocorticoid receptors. Cortisol provides negative feedback at the limbic, hypothalamic, and pituitary level. In contrast, the amygdala enhances CRF production in the PVN. The AVP and  $V_{1B}$  receptor systems are rather resistant to feedback mechanisms via cortisol. Under chronic stress, the proportion of AVP-containing neurons among the CRF neurons in the PVN increases. In addition, the pituitary  $V_{1B}$  receptor is upregulated, while the pituitary  $CRF_1$  receptor is downregulated by chronic stress. (B) The  $V_{1B}$  receptor is expressed in the brain, including the lateral septum and amygdaloid nuclei, and  $V_{1B}$  receptors in these nuclei are postulated to play some roles in the regulation of emotion. BLN, basolateral nucleus; CeN, central nucleus; MeN, medial nucleus.

### Role of the AVP- $V_{1B}$ Receptor System in MDD

Several lines of evidence have implicated the AVP- $V_{1B}$  receptor system in depression. First, AVP levels are increased not only in plasma but also in brain nuclei (the PVN and supraoptic nucleus of the hypothalamus and the suprachiasmatic nucleus) in MDD patients (Purba et al., 1996; van Londen et al., 1997; Zhou et al., 2001; Meynen et al., 2006), indicating that AVP is overly activated in depressed patients, although a previous report showed no change in AVP levels in cerebrospinal fluid (CSF) (Heuser et al., 1998). Importantly, the increase in AVP is more pronounced in patients with melancholic-type depression or anxious-retarded depression (van Londen et al., 1997; De Winter et al., 2003; Meynen et al., 2006), which is in line with the reported HPA axis dysfunctions in these patients. In addition, treatment with fluoxetine decreases the AVP levels in the CSF of depressed patients, which is accompanied by a decrease in the depression scores (De Bellis et al., 1993). Moreover, the plasma AVP level is reportedly correlated with cortisol levels during depression in a positive manner, particularly in suicide victims (Inder et al., 1997). There are reports indicating the hyperactivity of the  $V_{1B}$  receptor in MDD patients. In patients with MDD, HPA responsiveness to AVP is increased while responsiveness to CRH is decreased (O'Keane et al., 2012), and the administration of the AVP analog desmopressin to patients with MDD induces an augmented ACTH and cortisol secretion compared with that in non-depressed patients (Dinan et al., 2004). These findings suggest that the anterior vasopressin receptors ( $V_{1B}$  receptors) are more sensitive to AVP in depressed patients than in healthy individuals. Moreover, a single nucleotide polymorphism of the  $V_{1B}$  receptor has been found to protect against major

depression (van West et al., 2004). These above-mentioned lines of evidence indicate that hyperactivity of the AVP- $V_{1B}$  receptor system is mainly responsible for the dysfunction of the HPA axis observed in patients with MDD.

In addition to patients with MDD, increased AVP levels have been observed in patients with several other psychiatric disorders. The plasma AVP levels of patients with post-traumatic stress disorder (PTSD) are reportedly higher than those in both healthy controls and traumatic controls (de Kloet et al., 2008); therefore, elevated plasma AVP levels are specifically related to PTSD and not to exposure to traumatic stress. Moreover, the AVP levels in the CSF are increased in patients with either obsessive-compulsive disorder (Altemus et al., 1992) or bulimia nervosa (Demitrack et al., 1992). Although AVP release is reportedly correlated with anxiety symptom responses in healthy individuals challenged with an anxiogenic CCK-B agonist (Abelson et al., 2001), the role of AVP in panic symptoms remains to be clarified, since increased AVP levels were observed by inducers of panic symptoms in both patients with panic disorder and healthy volunteers who did not experience panic symptoms (Peskind et al., 1998).

In addition to clinical studies, animal studies have also shown a correlation between depressive- and anxiety-like behaviors and elevated AVP levels. The Brattleboro rat strain, which displays a spontaneous AVP deficiency stemming from a single nucleotide deletion in the AVP gene, exhibits reduced depressive- and anxiety-like behaviors (Mlynarik et al., 2007; Varga et al., 2015). In contrast, among Wistar rats that have been selectively bred for high or low anxiety-like behavior, the high anxiety-like behavior lines exhibit higher AVP expressions in the PVN of the hypothalamus than the low anxiety-like behavior lines, accompanied by elevated HPA activations in response to

stress and a dexamethasone/CRH challenge (Keck et al., 2002). Therefore, the relationship between increased AVP levels and depressive- and anxiety-like behaviors is underpinned by the behaviors of genetic animal models.

## Pharmacology of $V_{1B}$ Receptor Antagonists

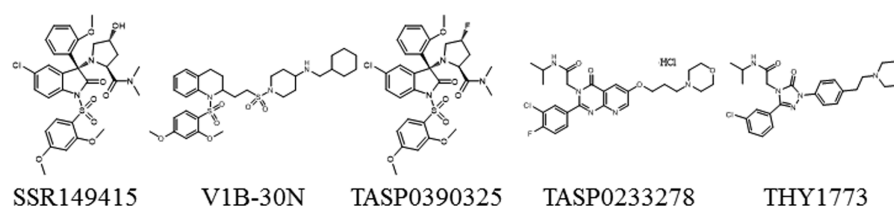
To date, several selective and potent non-peptide  $V_{1B}$  receptor antagonists have been synthesized, and their antidepressant potential has been tested in animal models. The chemical structures and some of their profiles of representative  $V_{1B}$  receptor antagonists are illustrated in Figure 2.

SSR149415 was the first  $V_{1B}$  receptor antagonist that could be administered systemically and was used for pharmacological studies in animals (Serradeil-Le Gal et al., 2002). However, SSR149415 had some drawbacks, including receptor selectivity (active against  $V_{1A}$  and oxytocin receptors as well; Griffante et al., 2005) and a suboptimal pharmacokinetic profile in rats (extensive first-pass metabolism and low brain penetration [brain/plasma ratio=0.03], etc.) (Oost et al., 2011). To overcome the drawbacks of SSR149415, 2 approaches were taken: further optimization of the scaffold of SSR149415 and searches for a different scaffold. Using the former approach, compounds with improved pharmacokinetic profiles (oral bioavailability, half-life, and brain penetration) have been successfully synthesized, representatives of which exerted antidepressant-like effects in the forced swimming test (Oost et al., 2011; Geneste et al., 2018). The other approach was to identify a novel scaffold using a high-throughput screening and hit-to-lead (Letourneau et al., 2010), followed by optimization of the lead. These efforts successfully produced several compounds with improved pharmacokinetic profiles, including a lack of CYP enzymes inhibition (Napier et al., 2011a, 2011b). In addition, the compounds produced using this approach had improved selectivity with negligible activity at  $V_{1A}$ ,  $V_2$ , and oxytocin receptors as well as a broad panel of unrelated

targets (Napier et al., 2011a, 2011b). Moreover, the representative compounds were demonstrated to attenuate increases in ACTH secretion induced by CRH/desmopressin.

## Antidepressant-like Effects and underlying Mechanisms of $V_{1B}$ Receptor Antagonists in Rodents

The antidepressant-like effects of representative  $V_{1B}$  receptor antagonists are summarized in Table 1. The antidepressant-like effects of  $V_{1B}$  receptor antagonists in animal models were first demonstrated using SSR149415, a prototype  $V_{1B}$  receptor antagonist (Serradeil-Le Gal et al., 2002). SSR149415 exerted antidepressant-like effects in several animal models, and these studies have been replicated using other  $V_{1B}$  receptor antagonists (Table 1). Importantly, the antidepressant-like effects of  $V_{1B}$  receptor antagonists occurred at doses capable of attenuating the increase in plasma ACTH induced by stress or CRH/desmopressin, suggesting that  $V_{1B}$  receptor antagonists exerted their antidepressant-like effects by inhibiting HPA axis activated by acute stress.  $V_{1B}$  receptor antagonists exerted antidepressant-like effects not only in animal models used to evaluate conventional antidepressants but also in an animal model resistant to conventional antidepressants (Iijima et al., 2014; Kamiya et al., 2020), as has been observed for ketamine treatment (Koike et al., 2013). On the other hand,  $V_{1B}$  receptor antagonists might not have a rapid onset of action. In an olfactory bulbectomy model, SSR149415 exerted antidepressant-like effects after repeated administrations (7, 14, or 28 days), but not after acute administration (Iijima and Chaki, 2007; Breuer et al., 2009; Poretti et al., 2016). In addition, in a chronic mild stress model, SSR149415 exerted antidepressant-like effects after 7 or 14 days of treatment, similar to conventional antidepressants (Griebel et al., 2002; Alonso et al., 2004; Surget et al., 2008; Bessa et al., 2009). The time course for the antidepressant-like effects is consistent with



Receptor binding affinity ( $K_i$ ; nM)					
human $V_{1B}$	1.7	64.5	4.85*	2.72*	unpublished
Receptor binding affinity ( $K_i$ ; nM)					
human $V_{1A}$	94	218.3	286*	>10,000*	unpublished
human Oxytocin	25	>1,000	45.8*	>10,000*	unpublished
Pharmacokinetic profiles					
	B/P ratio = 0.03 (rat) t1/2 = 0.5 h (rat) F(oral %)=12 (rat)	unpublished	unpublished	unpublished	B/P ratio = 0.2 (rat)
References					
	Oost et al., 2011	Hodgson et al., 2014	Iijima et al., 2014	Iijima et al., 2014	Kamiya et al., 2020

\*: IC<sub>50</sub> (nM)

Figure 2. Chemical structures and profiles of representative  $V_{1B}$  receptor antagonists.

Table 1. Effect of V<sub>1B</sub> receptor antagonists in animals (antidepressant-like effects)

Compound	Model	Test	Species/strain	Dose (route)	Results	Reference
SSR149415	- UCMS	FST Physical state, EPM, FST, etc.	Wistar rat CD-1 mouse	3, 10, 30 mg/kg (PO) 10, 30 mg/kg (IP)	Decrease immobility Reverse decreased physical state scale after 2 wk dosing (reverse anxiety- and depressive-like behaviors) Reverse increased immobility	Griebel et al., 2002
-	-	FST	Flinders Sensitive Line rat	3, 10, 30 mg/kg (IP, dosing for 14 d)	Increase percentage of lever presses emitted in the IRT bin (inter-response time)	Overstreet and Griebel, 2005
-	-	DRL-72s	Wistar rat	3, 10, 30 mg/kg (IP)	Reverse increased hyperemotionality (no effect after a single dosing)	Louis et al., 2006
-	Olfactory bulbectomy	Hyperemotionality	Wistar rat	10, 30 mg/kg (PO, dosing for 14 d)	Reverse increased hyperactivity (no effect after a single dosing)	Iijima and Chaki, 2007
-	Olfactory bulbectomy	Hyperemotionality	Sprague-Dawley rat	10, 30 mg/kg (IP, dosing for 7 or 14 d)	Reverse increased immobility	Breuer et al., 2009
-	Olfactory bulbectomy	TST	N:NIH mouse	30 mg/kg (PO, dosing for 28 d)	No effect	Poretti et al., 2016
-	-	FST	CD rat	3, 10, 30 mg/kg (IP)	No effect	Hodgson et al., 2007
-	-	FST	CD-1 mouse	3, 10, 30 mg/kg (IP)	Increase immobility	
-	-	TST	CD-1 mouse	3, 10, 30 mg/kg (IP)	Reverse decreased physical state scale after 1 week dosing	Alonso et al., 2004
-	UCMS	Physical state	BALB/c mouse	30 mg/kg (IP, dosing for 4 wk)	Reverse decreased physical state scale after 2 wk dosing (reverse decreased grooming frequency and increased latency to feed)	Surget et al., 2008
-	UCMS	Physical state, splash test, NSFT	BALB/c mouse	30 mg/kg (IP, dosing for 3 wk)	Reverse increased immobility, reduced sucrose preference, and increased latency to feed	Bessa et al., 2009
-	UCMS	FST, SPT, NSFT	Wistar rat	30 mg/kg (IP, dosing for 14 d)	Decrease immobility	Stemmelin et al., 2005
-	-	FST	Sprague-Dawley rat	1, 10, 100 ng (intra-septum)	Decrease immobility	Salomé et al., 2006
-	-	FST	Sprague-Dawley rat	0.1, 1, 10 ng (intra-BIA) 0.1, 1, 10, 100 ng (intra-CeA) 10, 100 ng (intra-MeA)	Decrease immobility	
TASP0233278	-	FST	Sprague-Dawley rat	0.3, 1, 3 mg/kg (PO)	Reverse increased immobility	Iijima et al., 2014
-	Corticosterone treated	FST	Sprague-Dawley rat	3 mg/kg (PO)	Reverse increased immobility	
TASP0390325	-	FST	Sprague-Dawley rat	0.1, 0.3, 1 mg/kg (PO)	Reverse increased hyperemotionality (no effect after a single dosing)	
-	Olfactory bulbectomy	Hyperemotionality	Wistar rat	0.1, 0.3 mg/kg (PO, dosing for 14 days)	No effect	Hodgson et al., 2014
V1B-30N	-	FST	CD rat	1, 3, 10, 30 mg/kg (IP)	No effect	
-	-	FST	CD-1 mouse	3, 10, 30 mg/kg (IP)	No effect	
THY1773	-	FST	Sprague-Dawley rat	0.1, 0.3, 1 mg/kg (PO)	Reverse increased immobility	Kamiya et al., 2020

Abbreviations: -, naïve; BLA, basolateral nucleus of amygdala; CeA, central nucleus of amygdala; DRL-72s, differential reinforcement of low-rate 72s; FST, forced swimming test; IP, intraperitoneal; MeA, medial nucleus of amygdala; NSFT, novelty-suppressed feeding test; PO, per os; SPT, sucrose preference test; TST, tail suspension test; UCMS, unpredictable chronic mild stress. Blue: effective dose(s); black: ineffective dose(s).

another  $V_{1B}$  receptor antagonist, TASP039025, which required 2 weeks of treatment before noticeable effects in an olfactory bulbectomy model (Iijima et al., 2014). Nonetheless, it is important to note that the antidepressant-like effects of SSR149415 lasted for at least a week after the cessation of treatment (Breuer et al., 2009), suggesting that changes in neuroplasticity may play a role in the actions of  $V_{1B}$  receptor antagonists.

Nonetheless, opposing reports on  $V_{1B}$  receptor antagonists should be mentioned. Hodgson et al. (2007) reported that  $V_{1B}$  receptor antagonists, including SSR149415, did not exert antidepressant-like effects in rodents in the rat forced swimming test, while CP-154 526 (a  $CRH_1$  receptor antagonist) exerted effects in the same paradigm. They additionally reported that a newly synthesized  $V_{1B}$  receptor antagonist  $V_{1B}$ -30N did not have antidepressant-like effects in rodents (Hodgson et al., 2014). Although the reason for this discrepancy is not known, the majority of studies conducted to date have favored antidepressant-like effects of  $V_{1B}$  receptor antagonists in several animal models.

The site of action for  $V_{1B}$  receptor antagonists remains controversial. Although the  $V_{1B}$  receptor in the pituitary has been postulated to play a critical role, a role of central  $V_{1B}$  receptors in exerting the antidepressant effects has also been proposed based on the following evidence. SSR149415 reportedly exerted the antidepressant-like effects in hypophysectomized rats, although the effects were weaker than those in normal rats (Griebel et al., 2002). Moreover, the injection of SSR149415 into certain brain nuclei, such as the lateral septum and amygdaloid nuclei (central nucleus, basolateral nucleus, medial nucleus), exerted antidepressant-like effects (Stemmelin et al., 2005; Salomé et al., 2006). In contrast,  $V_{1B}$  receptor antagonists such as TASP0390325 and THY1773 exerted antidepressant-like effects at doses resulting in a pituitary  $V_{1B}$  receptor occupancy of nearly 50% (Iijima et al., 2014; Koga et al., 2016; Kamiya et al., 2020). Given the rather low brain penetration of these compounds in rodents, it is unlikely that these  $V_{1B}$  receptor antagonists exert their effects by directly acting on  $V_{1B}$  receptors in the brain. Moreover, studies using central injections were performed using only SSR149415. Because SSR149415 has some activity against the  $V_{1A}$  receptor, which is highly expressed in the brain (Allaman-Exertier et al., 2007), the role of the  $V_{1A}$  receptor cannot be ruled out. Therefore, further investigation is needed to clarify the roles of central  $V_{1B}$  receptors in the antidepressant-like effects of  $V_{1B}$  receptor antagonists. For reference, as described in clinical studies, TS-121 (in which the active ingredient is THY1773) tended to reduce the depressive scores at doses resulting in a pituitary  $V_{1B}$  receptor occupancy of nearly 50% in a Phase 2a study (Kamiya et al., 2020), providing further evidence that the pituitary  $V_{1B}$  receptor plays a critical role in the effects of  $V_{1B}$  receptor antagonists.

Hippocampal neurogenesis has been presumed to play an important role in the actions of antidepressants (Duman et al., 2001), and it has been reported that AVP is involved in neuroplasticity (Yang et al., 2017; Sipos et al., 2020). In addition, SSR149415 reversed a decrease in the hippocampal neurogenesis induced by chronic mild stress, which coincided with a reversal of depressive-like behavior (Alonso et al., 2004). Interestingly, the loss of hippocampal neurogenesis as a result of focal hippocampal irradiation did not affect the antidepressant-like effects of SSR149415, while the same manipulation completely blocked the effects of conventional antidepressants (imipramine and fluoxetine) (Surget et al., 2008). Moreover, the antidepressant-like effects of SSR149415 were still observed

when neurogenesis was arrested by simultaneous treatment with methylazoxymethanol (Bessa et al., 2009). Therefore, more works need to clarify role of hippocampal neurogenesis in the antidepressant-like effects of  $V_{1B}$  receptor antagonists.

## Anxiolytic-like effects of $V_{1B}$ Receptor Antagonists in Rodents

Although clinical evidence linking the AVP- $V_{1B}$  receptor system and anxiety disorders is not as plentiful as that for depressive disorders, anxiolytic-like effects of  $V_{1B}$  receptor antagonists have been reported in numerous rodent models, the representative results of which are summarized in Table 2.  $V_{1B}$  receptor antagonists including SSR149415, TASP0233287, TASP0390325, and V1B-30N exerted anxiolytic-like effects in classical animal models in which benzodiazepine anxiolytics have been shown to be effective. Notably, Hodgson et al. (2007) reported that SSR149425 was more effective in anxiety models than in depression models. In addition, TASP0233287 attenuated sodium lactate-induced panic-like responses in panic-prone rats (Iijima et al., 2014). Interestingly, a  $CRH_1$  receptor antagonist also blocked lactate-induced behavior and cardiovascular responses (Shekhar et al., 2011), suggesting that compounds that act on the HPA axis may be useful for the treatment of panic disorder. In contrast, SSR149415 was not effective in a marble burying test in which both selective serotonin reuptake inhibitors and benzodiazepine anxiolytics have been shown to be effective (Hodgson et al., 2007).

There is some debate about the primary site of action for the anxiolytic-like effects of  $V_{1B}$  receptor antagonists (central vs pituitary). The injection of SSR149415 into certain brain nuclei (lateral septum, amygdaloid nuclei [central nucleus, medial nucleus], PVN of the hypothalamus) did not exert anxiolytic-like effects, unlike the results for antidepressant-like effects (Stemmelin et al., 2005; Salomé et al., 2006; Bayerl et al., 2016), indicating that central  $V_{1B}$  receptors have a minimal role in exerting the anxiolytic-like effects of  $V_{1B}$  receptor antagonists. This finding is consistent with our previous report that the anxiolytic-like effect of SSR149415 in a social interaction test was no longer observed in hypophysectomized rats, while the anxiolytic-like effect of chlordiazepoxide was preserved (Shimazaki et al., 2006). Therefore, the pituitary  $V_{1B}$  receptor is the premier site in the exertion of anxiolytic-like effects. However, the role of the  $V_{1B}$  receptor in certain brain nuclei cannot be fully ruled out, because the injection of SSR149415 into the basolateral nucleus of the amygdala has been reported (Stemmelin et al., 2005), and SSR149415 also attenuated AVP-induced anxiety-like behavior when injected into the central nucleus of amygdala (Hernández-Pérez et al., 2018). Moreover, chronic social defeat increased  $V_{1B}$  receptor expression in the medial nucleus of the amygdala and lateral septum (Litvin et al., 2011). However, as described above, SSR149415 has some affinity for the  $V_{1A}$  receptor, and  $V_{1A}$  receptor antagonists have been shown to exert anxiolytic-like effects (Bleickardt et al., 2009), raising the possibility that the effects of SSR149415 in the brain nuclei may be mediated through the blockade of the  $V_{1A}$  receptor. Moreover, an earlier study suggested that the central role of the AVP system on anxiety-like behavior is anxiolytic rather than anxiogenic (Appenrodt et al., 1998). Therefore, not enough evidence exists to support the role of the  $V_{1B}$  receptor in the brain in the anxiolytic-like effects of  $V_{1B}$  receptor antagonists and anxiety-like behavior.

Table 2. Effect of V<sub>1B</sub> receptor antagonists in animals (anxiolytic-like effects)

Compound	Model	Test	Species/strain	Dose (route)	Results	Reference
SSR149415	-	Four-plate	NMRI mouse	1, 3, 10 mg/kg (PO, IP)	Increase number of punished crossing	Serradeil-Le Gal et al., 2002 Griebel et al., 2002
	-	Vogel	Sprague-Dawley rat	1, 3, 10 mg/kg (IP)	Increase number of shocks	
	-	Light/dark	BALB/c mouse	1, 3, 10, 30 mg/kg (IP)	Increase time in lit box	Overstreet and Griebel, 2005
	-	EPM	Sprague-Dawley rat	3, 10, 30 mg/kg (PO)	Increase % open arm entries	
	-	EPM	Swiss mouse	3 mg/kg (PO)	Reverse decreased % time open arms	
	-	Social interaction	Flinders Sensitive Line rat	3, 10, 30 mg/kg (IP, dosing for 14 days)	Increase social interaction	
	-	Social interaction	Sprague-Dawley rat	0.1, 0.3 mg/kg (PO)	Increase social interaction	Shimazaki et al., 2006 Iijima and Chaki, 2005
	-	Separation-induced ultrasonic vocalization	Sprague-Dawley rat pup	3, 10, 30 mg/kg (IP)	Tendency to decrease number of calls	
	-	Separation-induced ultrasonic vocalization	Brattleboro rat pup	10 mg/kg (IP)	Decrease USV duration/frequency	Varga et al., 2015
	-	EPM	CD rat	3, 10, 30 mg/kg (IP)	Increase % open arm entries	Hodgson et al., 2007
-	Conditioned lick suppression	CD rat	3, 10, 30 mg/kg (IP)	Increase number of punished licks		
-	Separation-induced ultrasonic vocalization	CD rat pup	3, 10, 30 mg/kg (IP)	Decrease number of calls		
-	Separation-induced vocalization	Hartley guinea pig pup	3, 10, 30 mg/kg (IP)	Decrease number of calls	Litvin et al., 2011	
-	Marble burying	CD-1 mouse	3, 10, 30 mg/kg (IP)	No effect		
-	Anxiety-like behaviors	Swiss-Webster mouse	30 mg/kg (IP)	Reverse anxiety-like behaviors	Stemmelin et al., 2005	
-	Vogel	Sprague-Dawley rat	1, 10, 100 ng (intra-septal)	No effect	Salomé et al., 2006	
-	EPM	Sprague-Dawley rat	1, 10, 100 ng (intra-septal)	No effect		
-	EPM	Sprague-Dawley rat	0.1, 1, 10 ng (intra-BIA) 1, 10, 100 ng (intra-CeA) 10, 100 ng (intra-MeA)	Increase % time spent in open arms no effect no effect		
-	EPM	Wistar rat (female)	100 ng/side (intra-PVN)	No effect	Bayerl et al., 2016	
-	Shock-probe burying	Wistar rat	1, 10 ng/side (intra-CeA)	Attenuate AVP-increased burying behavior (no effect by itself)	Hernández-Pérez et al., 2018	
TASP023287	-	Social interaction	Sprague-Dawley rat	0.1, 0.3, 1, 3 mg/kg (PO)	Increase social interaction	Iijima et al., 2014
	-	Stress-induced hyperthermia	ICR mouse	3, 10, 30 mg/kg (PO)	Decrease stress-induced hyperthermia	
	-	Separation-induced ultrasonic vocalization	Sprague-Dawley rat pup	3, 10, 30 mg/kg (IP)	Tendency to decrease number of calls	
-	Forced swim stress	EPM	Sprague-Dawley rat	0.3, 1, 3 mg/kg (PO)	Reverse decreased time in open arms	Hodgson et al., 2014
-	Panic model	Sprague-Dawley rat	1, 3 mg/kg (PO)	Reverse decreased social interaction		
TASP0390325	-	Stress-induced hyperthermia	ICR mouse	3, 10, 30 mg/kg (PO)	Decrease stress-induced hyperthermia	Hodgson et al., 2014
	-	Vogel	CD rat	3, 10, 30 mg/kg (IP)	Increase number of punished licks	
V1B-30N	-	Separation-induced ultrasonic vocalization	CD rat pup	1, 3, 10, 30 mg/kg (IP)	Decrease number of calls	
-	Separation-induced vocalization	Hartley guinea pig pup	3, 10, 30 mg/kg (IP)	Decrease number of calls		

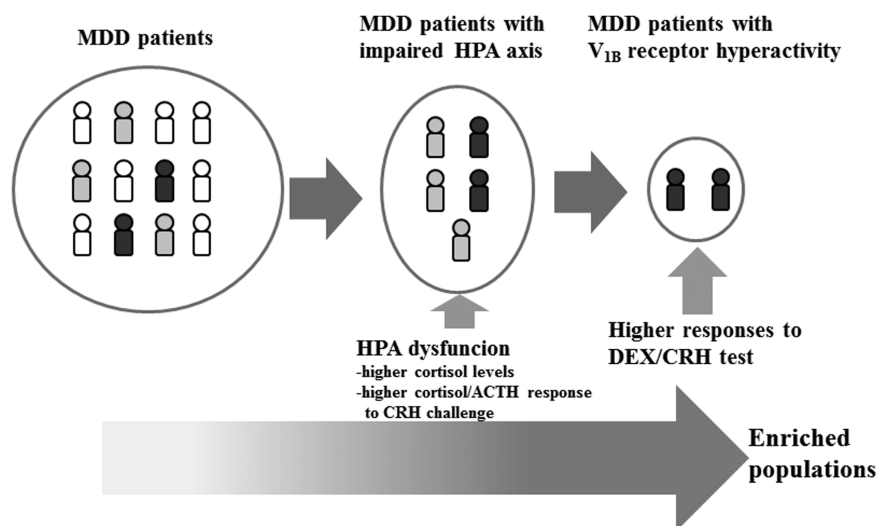
Abbreviations: -, naive; BIA, basolateral nucleus of amygdala; CeA, central nucleus of amygdala; EPM, elevated plus maze; IP, intraperitoneal; MeA, medial nucleus of amygdala; PO, per os; PVN, paraventricular nucleus. Blue: effective dose(s); Black: ineffective dose(s).

Table 3. Effect of V<sub>1B</sub> receptor antagonists in clinical trials (depression)

Compound	Trial	Dose regimen	Patients	Primary endpoint	Results	ClinicalTrial.gov identifier	Reference
SSR149415	Randomized, double-blinded, placebo-controlled study (DFI5878)	SSR149415 (100 mg, 250 mg) or placebo, BID for 8 wk (active control: escitalopram, 10 mg QD)	MDD patients SSR149415 100 mg (n = 80) SSR149415 250 mg (n = 79) placebo n = 75 escitalopram n = 84	Changes from baseline HDRS total score at wk 8	<ul style="list-style-type: none"> <li>SSR149415 (250 but not 100 mg) had significantly greater reductions in HDRS changes from baseline compared with placebo, while escitalopram had nonsignificant reduction in HDRS</li> <li>Similar trends of greater improvements in SSR149415 observed in secondary endpoints (CGI-S, MADRS), while these effects did not reach statistical significance</li> <li>Differences between placebo and each SSR149415 dose on HDRS score not statistically significant, while paroxetine significantly reduced HDRS score</li> <li>No statistical difference between placebo and each SSR149414 dose on secondary endpoints (CGI-S, MADRS).</li> </ul>	NCT00358631	Griebel et al., 2012
	Randomized, double-blinded, placebo-controlled study (DFI5879)	SSR149415 (100 mg, 250 mg) or placebo, BID for 8 wk (active control: paroxetine, 20 mg QD)	MDD patients SSR149415 100 mg (n = 82) SSR149415 250 mg (n = 81) placebo n = 77 escitalopram n = 80	Changes from baseline HDRS total score at wk 8	<ul style="list-style-type: none"> <li>Differences between placebo and each SSR149415 dose on primary endpoint not statistically significant</li> <li>SSR149415 group showed greater mean improvements from baseline HDRS score and CGI-S than placebo group, although differences not statistically significant</li> </ul>	NCT00361491	
	Randomized, double-blinded, placebo-controlled study (PDY5467)	SSR149415 (100 mg, 250 mg) or placebo, BID for 4 wk	MDD patients SSR149415 100 mg (n = 25) SSR149415 250 mg (n = 24) placebo n = 24	Plasma cortisol concentration response to CRF administration before and after 27 d dosing	<ul style="list-style-type: none"> <li>Differences between placebo and each SSR149415 dose on primary endpoint not statistically significant</li> </ul>	NCT01606384	
ABT-436	Randomized, double-blinded, placebo-controlled study	ABT-436 (800 mg) or placebo, QD for 7 d	MDD patients ABT-436 800 mg (n = 31) placebo n = 20	Basal HPA parameters at d 7	<ul style="list-style-type: none"> <li>Basal HPA parameters (urine total glucocorticoids, plasma ACTH, urine/serum/saliva cortisol, etc.) lower in ABT-436 group than in placebo group</li> <li>Dynamic HPA parameters (plasma ACTH and serum cortisol response to CRF) lower in ABT-436 group than in placebo group</li> <li>ABT-436 had favorable symptom responses on 2 of 5 MASQ subscale compared with placebo but no differences on HDRS score</li> </ul>	NCT01380704	Katz et al., 2017
TS-121	Randomized, double-blinded, placebo-controlled study	TS-121 (10 mg, 50 mg) or placebo, QD for 6 wk (adjunctive treatment)	MDD patients with inadequate response to current antidepressant treatment TS-121 10 mg (n = 16) TS-121 50 mg (n = 17) placebo n = 18	Changes from baseline MADRS score at wk 6	<ul style="list-style-type: none"> <li>TS-121 had greater reductions in MADRS change from baseline compared with placebo but changes not statistically significant</li> <li>Similar trends of non-significantly greater improvements in TS-121 observed in secondary endpoints (CGI-S, HAM-A, SDQ, etc.), but effects not statistically significant</li> <li>Higher baseline urinary and hair cortisol associated with greater separation between TS-121 and placebo in MADRS score</li> </ul>	NCT03093025	Kamiya et al., 2020

Abbreviations: ACTH, adrenocorticotropic hormone; CGI-S, Clinical Global Impressions-Severity of Illness Score; CRF, corticotropin-releasing factor; HAM-A, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; HPA, hypothalamus-pituitary-adrenal; MADRS, Montgomery-Åsberg Depression Rating Scale; MASQ, Mood and Anxiety Symptom Questionnaire; MDD, major depressive disorder; SDQ, Symptoms of Depression Questionnaire.





**Figure 3.** Conceptualized scheme for patient segmentation for  $V_{1B}$  receptor antagonists treatment. Among patients with major depressive disorder (MDD), there are certain populations with impaired hypothalamus-pituitary-adrenal (HPA) axis who might show higher cortisol levels in blood, urine, or saliva. Moreover, even among MDD patients with impaired HPA activity, there are certain populations of patients with  $V_{1B}$  receptor hyperactivation. It is important to appropriately stratify patients who could respond better to  $V_{1B}$  receptor antagonists.

### Clinical Studies of $V_{1B}$ Receptor Antagonists for Patients with MDD

To date, clinical trials of 3  $V_{1B}$  receptor antagonists for the treatment of patients with MDD have been conducted, as summarized in Table 3. SSR149415 was the first  $V_{1B}$  receptor antagonist to be tested in clinical studies. In 2 trials, SSR149415 failed to clearly demonstrate efficacy in the treatment of depressive symptoms (Griebel et al., 2012). In 1 of the 2 trials, a high dose of SSR149415 (250 mg, BID) resulted in a greater improvement in the Hamilton Depression Rating Scale (HDRS) score relative to the baseline score compared with a placebo at 8 weeks after the start of administration; however, the administration of escitalopram, which was used as a positive control, did not produce a significant reduction in the HDRS score, causing the trial to fail. Moreover, SSR149415 was not superior in efficacy to the placebo for the treatment of MDD in another trial in which a robust signal detection was obtained with paroxetine. Of note, 2 different doses (100 mg and 250 mg) of SSR149415 did not reduce the cortisol response to CRH challenge, while doses higher than 250 mg of SSR149415 were shown to attenuate this response significantly in a Phase I study. Therefore, the doses used in these trials might have been insufficient to block HPA activity and achieve therapeutic effects. ABT-436, another  $V_{1B}$  receptor antagonist, has been demonstrated to reduce HPA parameters (urine total glucocorticoids, plasma ACTH, and serum/urine cortisol) at a dose of 800 mg QD after 7 days of treatment in both healthy adults (Katz et al., 2016) and patients with MDD (Katz et al., 2017). ABT-436 not only reduced the basal HPA parameters but also attenuated the plasma ACTH and serum cortisol responses to a CRH challenge in patients with MDD (Katz et al., 2017), indicating that a dose of 800 mg of ABT-436 attenuated the increased HPA activity in patients with MDD. Importantly, ABT-436 showed favorable symptom responses on 2 (General Distress-Depressive Symptoms and General Distress-Mixed Symptoms) of the 5 subscales of the Mood and Anxiety Symptom Questionnaire (MASQ) compared with the results for a placebo, although favorable symptom changes in the HDRS score were not observed. Given that a cross-sectional analysis of symptom severity measured using

MASQ showed a correlation with cortisol levels (Veen et al., 2011) and that a difference in symptom change using the HDRS at 7 days is not typically observed for most antidepressants, the favorable symptom changes obtained using ABT-436 at a dose that attenuates HPA activation supports the potential of  $V_{1B}$  receptor antagonists as effective antidepressants. The potential of  $V_{1B}$  receptor antagonists for the treatment of depression is underpinned by a trial examining TS-121 (Kamiya et al., 2020). In this trial, the doses that were used were determined based on  $V_{1B}$  receptor occupancy in the pituitary as observed using a positron emission tomography (PET) study (ClinicalTrials.gov Identifier: NCT02448212) and a PET tracer that we developed (Koga et al., 2017). Thus, 2 doses (10 mg and 50 mg), which were expected to occupy the  $V_{1B}$  receptor by 55.3% (10 mg) and 75.1% (50 mg), were selected. Of note, to our knowledge, this is the first and only clinical study of a  $V_{1B}$  receptor antagonist in which the optimal doses were determined based on receptor occupancy. In our previous non-clinical studies, doses producing more than 50% occupancy of the pituitary  $V_{1B}$  receptor were shown to exert antidepressant-like effects and to attenuate HPA activation in animal models (Iijima et al., 2014; Koga et al., 2016; Kamiya et al., 2020). TS-121 produced a greater reduction in not only the Montgomery-Åsberg Depression Rating Scale (MADRS) score but also across secondary measures (Clinical Global Impression-Severity, Hamilton Anxiety Rating Scale, Symptoms of Depression Questionnaire) compared with a placebo, although these changes were not statistically significant because of the small sample size. Importantly, higher baseline urinary and hair cortisol levels were associated with a greater separation between the TS-121 and placebo results, indicating that MDD patients with higher HPA activity may respond better to TS-121. This assumption is supported by the results of another trial in which the magnitude of the attenuation in basal HPA activity produced by ABT-436 was larger in MDD patients with higher HPA activity levels than in those with lower HPA activity levels (Katz et al., 2017). These clinical trials support the concept that  $V_{1B}$  receptor antagonists are effective at doses that attenuate HPA axis activity and are most efficacious in MDD patients who exhibit HPA axis hyperactivity (Figure 3). Therefore, further clinical studies of  $V_{1B}$  receptor antagonists should take

**Table 4.** Effect of  $V_{1B}$  Receptor Antagonists in Clinical Trials (Other Stress-related Disorders)

Compound	Trial	Dose regimen	Patients	Primary endpoint	Results	Clinical/Trial.gov identifier	Reference
SSR149415	Randomized, double-blinded, placebo-controlled study (DFI5880)	SSR149415 (100 mg, 250 mg) or placebo, BID for 8 wk (active control: paroxetine, 20 mg QD)	GAD patients SSR149415 100 mg (n = 79) SSR149415 250 mg (n = 82) placebo n = 81 paroxetine n = 82	Changes from baseline in HAM-A total score at wk 8	<ul style="list-style-type: none"> <li>Differences between placebo and each SSR149415 dose on HAM-A score were not statistically significant, while paroxetine significantly reduced HAM-A score</li> <li>No statistical difference between placebo and each SSR149415 dose on secondary endpoints (CGI-S, MADRS)</li> </ul>	NCT00374166	Griebel et al., 2012
ABT-436	Randomized, double-blinded, placebo-controlled study	ABT-436 (titrated from 200 to 800 mg) or placebo for 12 wk (wk 2–12, 400 mg BID used; 400 mg BID selected to reduce risk of drop-outs due to gastrointestinal effects)	Alcohol dependence ABT-436 n = 73 placebo n = 71	Weekly percentage of heavy drinking days	<ul style="list-style-type: none"> <li>ABT-436 group showed lower adjusted levels of percentage of heavy drinking days than placebo group, although effect was not statistically significant</li> <li>ABT-436 group had significantly greater percentage of days abstinent than placebo group</li> <li>No statistical difference between placebo and ABT-436 on alcohol-related craving and consequences</li> </ul>	NCT01613014	Ryan et al., 2017

Abbreviations: CGI-S, Clinical Global Impressions-Severity of Illness Score; GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale.

these factors into consideration to clarify their potential as antidepressants fully.

## Clinical Studies of $V_{1B}$ Receptor Antagonists for other Psychiatric Disorders

Given that  $V_{1B}$  receptor antagonists show anxiolytic-like effects (see Table 2) and reduce alcohol intake in animal models (Zhou et al., 2011; Edwards et al., 2012), clinical studies of  $V_{1B}$  receptor antagonists for generalized anxiety disorder (GAD) and alcohol use disorder have been conducted, as summarized in Table 4. Contrary to the convincing results in animal models, SSR149415 (100 or 250 mg, BID for 8 weeks) did not produce statistically significant improvements in both primary and secondary measures of anxiety symptoms (Griebel et al., 2012). However, concluding that  $V_{1B}$  receptor antagonists are not efficacious for GAD might be premature because the doses might not have been sufficient to exert the desired effects. In addition, other disorders for which increased AVP levels have been reported, such as PTSD or obsessive-compulsive disorder, are worth considering (Altemus et al., 1992; de Kloet et al., 2008), since there is no evidence of changes in AVP in patients with GAD to date. Notably, TS-121 reduced Hamilton Anxiety Rating Scale of depressed patients compared with placebo (Kamiya et al., 2020). On the other hand, ABT-436 reduced the percentage of heavy drinking days compared with a placebo, although this effect was not statistically significant (Ryan et al., 2017). Therefore, the potential of  $V_{1B}$  receptor antagonists for the treatment of alcohol dependence has not been fully determined. Interestingly, patients with relatively greater baseline stress levels responded better to ABT-436 in terms of a reduction in both the frequency of drinking and the number of heavy drinking days, which is consistent with the concept that  $V_{1B}$  receptor antagonists may reduce alcohol drinking by ameliorating HPA axis abnormalities. Future trials should be conducted under conditions that maximize the treatment effect of ABT-436 by enriching the treatment population with participants who have clinically elevated anxiety levels (and/or hyper-reactivity to stress).

## Conclusions

Accumulating evidence suggests that certain populations of depressed patients have impaired HPA axis function, and agents ameliorating HPA axis dysfunction have gained attention. Nonetheless, the outcomes of several agents acting on the HPA axis, such as a cortisol synthesis inhibitor and a glucocorticoid receptor antagonist, were inconsistent in clinical trials (Schüle et al., 2009), raising skepticism about the role of HPA axis in the pathophysiology of depression. Although precise reasons for these inconsistent results have not been clarified yet, several factors including differences in clinical designs (dose regimens and patient populations) should be considered.

Given that the HPA axis is regulated by numerous factors and processes and that  $V_{1B}$  receptor signaling is overly activated in certain populations of depressed patients, blockade of the  $V_{1B}$  receptor may be a more appropriate approach to normalize HPA axis dysfunction in depression among regulators of HPA axis. The results that both ABT-436 and TS-121 tended to improve depressive symptoms when administered at doses that attenuated HPA axis hyperactivity or occupied the pituitary  $V_{1B}$  receptor may underpin this hypothesis. Importantly, the efficacy of TS-121 was more apparent in patients with higher basal cortisol levels.

These results suggest that  $V_{1b}$  receptor antagonists are more effective in patients with impaired HPA axis activities when they are administered at doses that suppress the over-activation of HPA axis activity.

Given that depression is a clinically heterogeneous condition defined by several subtypes and that different symptom clusters may respond selectively to different treatments, the development of novel antidepressants that focus on HPA axis dysfunction, which is a pathophysiological event in depression, is important.  $V_{1b}$  receptor antagonists could be the best candidate in this domain. Still, several issues, including (1) evaluation of the full potential of  $V_{1b}$  receptor antagonists in an adequately powered study, (2) precise mechanisms underlying the antidepressant effects of  $V_{1b}$  receptor antagonists, and (3) comparisons with other mechanisms relating HPA axis regulation remain to be investigated.

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