Vasopressin-Related Possible Therapies in Autism

Subjects: Neurosciences

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Autism spectrum disorder (ASD) is rather common, presenting with prevalent early problems in social communication and accompanied by repetitive behavior. There is no cure for ASD, and there is currently no medication to treat it. The medications are prescribed mainly to treat self-injury, inability to focus, anxiety and depression (SSRIs), aggression (alpha-2 adrenergic agonist, Clonidine) and hyperactivity (dopamine and noradrenaline stimulant methylphenidate, Ritalin). Strategies to treat the core symptoms of ASD are directed to correct synaptic dysfunctions, abnormalities in central VP, OT and serotonin neurotransmission, and neuroinflammation.

autism spectrum disorder vasopressin social behavior stereotype behavior

1. Available Therapies with Possible Vasopressinergic Contribution

Among the most prescribed medications for autism [1], the following VP interactions can be supposed:

From the second-generation antipsychotics used for the treatment of irritability, cariprazine is promising and their serotoninergic effect suggest a possible VPergic contribution [2].

For the improvement of mood, as well as to reduce the frequency and intensity of repetitive behaviors and improve eye contact, SSRIs are often used. In this regard, VP–serotonin interaction might contribute to the possible effectiveness of aggression treatment using SSRIs [3].

As regards methylphenidate (Ritalin), a dopamine (DA) reuptake inhibitor, it is used as a stimulant for the treatment of hyperactivity (paradoxically) and lack of attention in ASD. It was shown that it may influence the VP system [4] and it acts—at least partly—via the V_{1a} receptor [5].

Alpha2-agonist (e.g., Clonidine) may be used for ASD-related hyperactivity, attention deficit, and aggression, and may interact with VP on the cardiovascular function. Indeed, i.c.v. Clonidine administration-induced pressor response was prevented by i.c.v. V_1 antagonist administration in rats [6]. Interestingly, in humans, Clonidine administration decreased plasma VP levels [7]. In horses, no interaction was found between Clonidine and VP on

HPA axis [8]; however, in rats, Clonidine reduced the firing of SON VPergic cells, further supporting an interaction at the level of water balance [9].

As for applied behavior analysis (ABA), in a backtranslation study using ASD model mice, this intervention normalized VP and V_{1a} expression in several brain areas, including MeA [10].

Even transcutaneous electrical acupoint stimulation elevated VP levels in connection with an improvement of ASD symptoms [11].

Although experts do not recommend any specific diets for children (not even gluten- or casein-free), some probiotics might improve gastrointestinal symptoms [12]. As a possible link to VP, in prairie voles, *Limosilactobacillus reuteri* administration resulted in lower anxiety, but also lower social affiliation in female but not male individuals, with a decrease in PVN V_{1a} expression [13].

For a summary, see **Figure 1**.

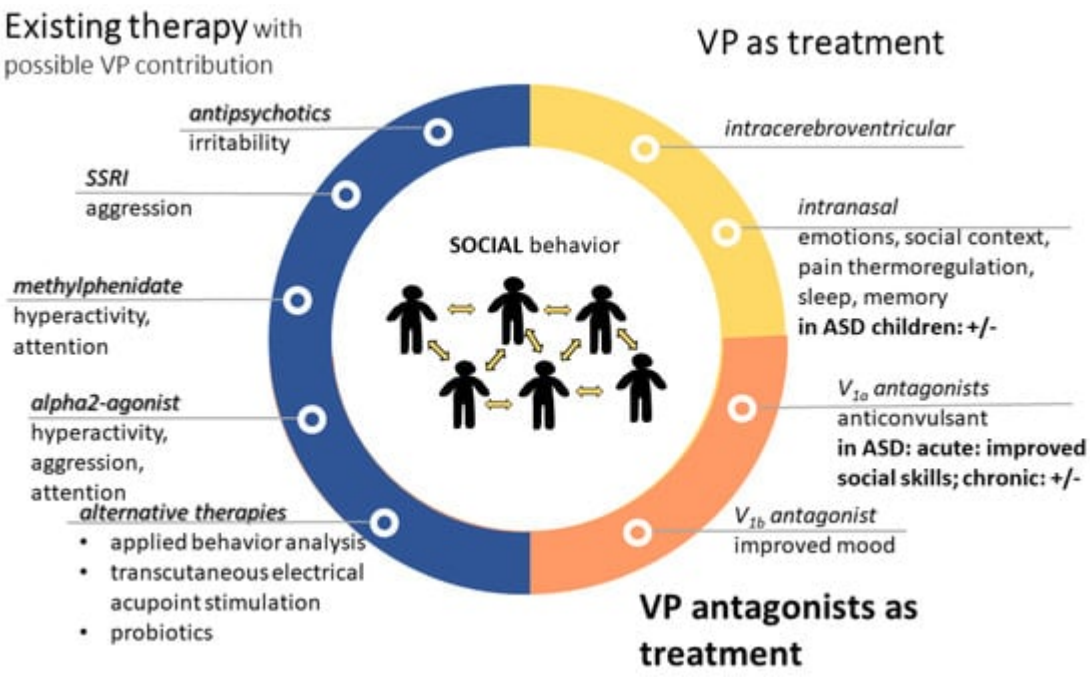

Figure 1. Treatment options in autism with contribution of vasopressin. VP might contribute to the effectiveness of presently available therapies (blue). However, VP alone (yellow) or its antagonists (orange) can be used for therapy. Most of the treatments aim to improve social skills; however, sometimes the results are questionable (+/−). Abbreviations: ASD: autism spectrum disorder; SSRI: selective serotonin reuptake inhibitor; V_{1a}: vasopressin 1a receptor; VP: vasopressin.

2. Influencing the Vasopressinergic System in Autism-Related Problems

Besides the aforementioned indirect effects, the direct influence on the VP pathway might have therapeutic potential on its own.

As VP does not cross the blood–brain barrier [14], for influencing the central VPergic system, i.c.v. or i.n. application is preferable.

In a rat VPA model, acute i.c.v. VP administration prevented social-interaction-induced brain activation based on blood oxygenation level (BOLD) signal in fMRI [15].

2.1. Intranasal Vasopressin Application

In rats, i.n. VP treatment (from PND 21 for 3 weeks) improved maternal VPA injection-induced (E12.5) social deficit, elevated the serum VP level and corrected expression changes related to synaptic and axon dysplasia and oligodendrocyte development in the PFC [16] and amygdala [17].

In male, but not female, marmosets, i.n. VP administration reduced food sharing with increased aggressive vocalization [18]. Accordingly, in monogamous male prairie voles [19], as well as in the coppery titi monkey (*Callicebus cupreus*) [20], a similar treatment reduced partner preference. These preclinical results did not suggest a possible positive effect on ASD symptoms.

However, when VP was administered i.n. for 4 weeks in ASD children aged 6–13 years in a phase 2 randomized clinical trial, improved social responsiveness and social abilities with decreased anxiety and limited repetitive behavior were reported [21]. The response was the strongest in high-plasma VP patients, and depended on the expression pattern of the V_{1a} and OTR receptors. The latter might explain the controversially decreased anxiety, as V_{1b} receptors were more involved in this stress-related disorder. In contrast, a randomized, double-blind, placebo controlled, between-subjects design on 125 undergraduate students (with 41 placebo, 30 females in each), using i.n. VP administration, did not find any effect on social outcomes [22]. In support, i.n. VP administration in rats failed to influence social recognition [23], despite previous effectiveness of the direct olfactory bulb manipulation [24]. Moreover, in healthy male volunteers, i.n. VP administration decreased goal-directed top-down attention control to social salient stimuli with an increase in bottom-up social attentional processing [25]. This effect was similar to OT administration and accompanied by an anxiolytic effect as well. In another study on face processing, a single low-dose i.n. VP (20 IU) administration to men decreased social assessments with a most pronounced effect in V_{1a} risk allele carrier subjects [26]. This suggest that via i.n. application, significant amounts of VP might not reach behaviorally relevant areas in the brain described previously as targets for the central administration of the peptide [23].

For other ASD-related alterations, where possible VP contribution was suggested (**Figure 2**), the following treatment effects were found:

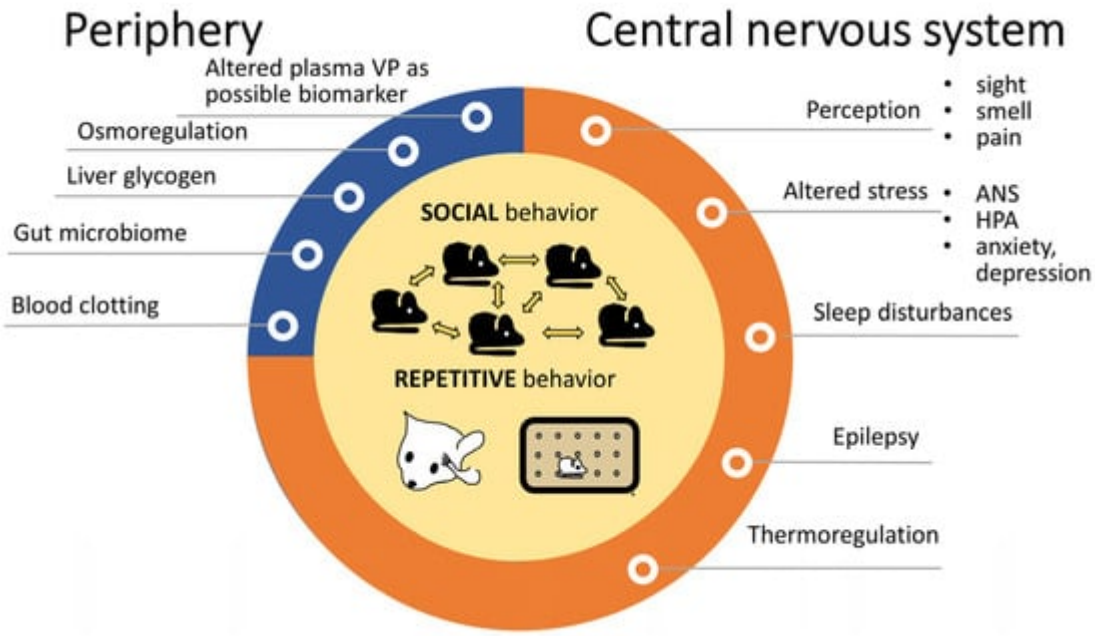

Figure 2. Alterations in autism spectrum disorders with possible contribution of vasopressin. The observations were mainly in animals. Both social problems and repetitive behaviors—depicted in the middle—are core features of autism spectrum disorders and VP is obviously implicated in them. Peripheral VP functions (blue) might be only indirectly linked to autism, while other central VP effects (orange) might have a more important, although not yet fully clarified role. Abbreviations: ANS: autonomous nervous system; HPA: hypothalamic pituitary adrenocortical axis, VP: vasopressin.

The activity of brain regions implicated in emotion processing was altered by i.n. VP treatment [27]. In this regard, in humans, i.n. VP regulated the processing of infant cry sounds with emotional contextual information in fathers [28]. In male volunteers, i.n. VP administration increased approaching ratings to some faces, together with increased processing suggested by higher N1 amplitude on the electroencephalograph; however, this effect was highly context-dependent [29]. Another study using fMRI in healthy male subjects reported reduced amygdalar activation to emotional faces after i.n. VP administration [30]. In contrast, another study reported enhanced neural pattern in the right amygdala to social–emotional stimuli observed via MRI [31].

As mentioned before, i.n. VP administration was also able to reduce pain in relation to postoperative orthopedic surgery [32].

Regarding its thermoregulatory role, i.n. VP (more specifically desmopressin, a V_2 receptor-selective agonist) reduced persisting coldness after brain injury in six patients [33].

In contrast, i.n. VP administration exacerbated physiological ANS parameters in combat veterans [34].

In healthy, elderly subjects, i.n. VP promoted sleep time and improved sleep architecture [35], reinforcing the potential beneficial effect of VP in ASD treatment. However, it was ineffective as regards verbal memory function [36].

2.2. Vasopressin Antagonist Treatment

In recent years, vasopressin receptor antagonists have been in the spotlight of drug discovery, especially V_{1a} selective molecules [37]. Publishing Balovaptan as a possible treatment for ASD greatly increased the interest in CNS-acting vasopressin antagonists. Although clinical trials were unsuccessful in many cases, there is still potential in the VP antagonists as shown by several currently ongoing clinical studies.

The main focus is on V_{1a} receptor antagonists. In this context, SRX246, a V_{1a} receptor antagonist, blocked the effect of i.n. VP administration-induced reduced amygdalar activation to angry faces [30]. Moreover, in 2017, a multicenter double-blinded crossover study found that single-dose intravenous (i.v.) infusion of RG7713, a highly selective V_{1a} antagonist in adult males with high-functioning ASD, resulted in a subtle but statistically significant improvement in social communications and social sensitivity [38]. As a follow up, the VP Antagonist to Improve Social Communication in Autism (VANILLA), a double-blinded placebo controlled clinical trial, examined 223 adult men with high-functioning ASD using another selective V_{1a} receptor antagonist, RG7714 (commercially known as Balovaptan) for 3 months [39]. The treatment was well tolerated and resulted in improvement in communication and socialization scores, though not in all aspects of the ASD spectrum (e.g., social responsiveness was not improved). Despite effectiveness during the phase 2 trial [40], in subsequent phase 3 trials in high-functioning children (5–17-year) [41] and adults (above 18-year) [42], the 6-month Balovaptan treatment was ineffective as regards social communication.

Other selective V_{1a} receptor antagonists (like the orally active Relcovaptan) might be effective as regards comorbid epilepsy [14]. On the other hand, for many years, V_{1b} receptor antagonists were developed to treat mood disorders. Despite previous ineffectiveness in major depression [43], V_{1b} receptor antagonists might be effective in subpopulations [44][45] and are therefore still under development (e.g., THY1773 [46], TS-121 [47], ABT-436 [48]). We cannot ignore V_2 receptors either, as Tolvaptan, a V_2 antagonist was implicated in the treatment of tuberous sclerosis, a genetic ASD, in a case report [49] (**Table 1**).

Table 1. Animal models of autism with possible contribution of vasopressin.

Type	Model Name/Implicated Molecule		Major Problems	References
Genetic models		OTR	soc.	[50]
		CNTNAP2	soc., com.	[51]
	KO	MAGEL2	soc.	[52]
		OPRM1	soc.	[53][54]
		Klf7	soc., rep.	[55]
	Fragile X	FMR1	soc., rep., motor problem, mood	[56]

Type	Model Name/Implicated Molecule		Major Problems	References
Environmental models	Rett syndrome	MECP2	soc., com.	[57]
	Tuberous sclerosis	TSC1, TSC2	soc., rep.; cerebellum; V2 antagonist	[49]
	Indirect evidence	NLGN mutations	soc., rest., com.	[58][59]
		TSHZ3 KO	soc., rep., narrowness of the field of interest	[60][61]
		GLUT3 KO	soc., rep., com., memory problems	[62][63]
		parvalbumin KO	soc., rep., com.	[64][65]
		GAP43	soc., resistance to change	[66][67]
		SERT variants	soc., rep.	[68][69][70][71]
	Drugs	VPA	soc., rep., com.	[17][72]
	Maternal infection and inflammation	poly I:C	soc., rep.	[73][74]
		LPS	soc.	[75][76]
		MIA	soc.	[74]

Abbreviations: CNTNAP2: Contactin Associated Protein 2; Com: communication problems; Fragile Mental Retardation 1 locus (FMR1); GAP43: synaptic growth-associated protein-43; GLUT3: neuronal glucose transporter isoform 3; klf7: Kruppel-like factor 7; KO: knockout; LPS: lipopolysaccharide; MAGEL2: Melanoma Antigen Gene Family Member L2; MIA: maternal immune activation; methyl-CpG binding protein 2 (MECP2), NLGN: neuroligin; rep: repetitive behavior; poly I:C: polyriboinosinic: polyribocytidylic acid; OPRM1: μ opioid receptor; soc: social problems; TSC: tuberous sclerosis complex; TSHZ3: a zinc-finger transcription factor; VPA: valproate [77].

2.3. Oxytocin Treatment

As VP might bind to OTRs (see earlier), it is important to note that several animal trials of OT treatment suggested beneficial effects. In children, even a single intranasal OT administration increased the nonverbal information-based judgments [78]. Despite mixed results, a recent meta-analysis found moderate evidence that a 6-week OT treatment might improve the reduced interest and repetitive behavior of ASD children and the effect lasted for at least 6 months [79].

2.4. Contradiction

There is an apparent contradiction between the effectiveness of VP as well as its antagonist. A possible explanation can be the age of the participants as well as the method used for drug administration (i.n. for children, other peripheral routes for adults), thereby targeting central or peripheral receptors. Moreover, although VP may stimulate all receptors including OTRs, its effectiveness can be different on them, while antagonists are highly selective, which might shift balance between the VP receptor actions.

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