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# The role of vasopressin (VP) and oxytocin (OT) in autism: A potential treatment targets for the disease. (A review)

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**Abstract**
Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by challenges in social interaction, communication, and repetitive behaviors. The potential therapeutic uses of neuropeptides, especially oxytocin and vasopressin, in treating some of the primary symptoms linked to ASD have drawn more attention in recent years. The brain produces the peptides oxytocin (OT) and arginine-vasopressin (AVP), which are then released into the peripheral bloodstream via the pituitary gland. These peptides serve a variety of physiological purposes. It has become evident in recent years that these peptides also have a major impact on how the brain regulates social behavior in mammals. Numerous lines of evidence point to their role in autism spectrum disorder (ASD), which is linked to social cognition and behavior impairments. As a result, recent clinical trials on both animal and human models of AVP administration have reported promising results in improving social cognition and behavior, and communication which are impaired in autistic patients, therefore, Male susceptibility to ASD may be exacerbated by excessive VP or disturbances in the VP system. Alternatively, the comparatively rare incidence of ASD in females may be explained by protective mechanisms mediated by OT or the OT receptor. These findings imply that AVP is a potentially useful therapeutic target to improve social cognition in individuals with autism.

**Keywords:** Autism spectrum disorder, oxytocin, vasopressin, neuropeptides, gene expression

## Introduction
Autism is a neurodevelopmental disorder that is typified by limited and repetitive behavior, as well as poor verbal and nonverbal communication and social interaction (Hodges *et al.*, 2020) [27]. According to Myers and Johnson (2007) [33], the name "autism" is etymologically derived from the Greek word "autos," which means "self." It is used to describe pathological self-admiration, which is the autistic patient's withdrawal into his delusions, against which any outside influence becomes an intolerable disturbance. In 1910, while characterizing the symptoms of schizophrenia, Swiss psychiatrist Eugen Bleuler came up with the term "autism." Johnson and Myers (2007) [33]. Though it wasn't commonly accepted as a distinct diagnosis until 1981 for a variety of reasons, Hans Asperger of the Vienna University Hospital coined the contemporary meaning of the term autism in 1938 while conducting research on the condition that is now known as Asperger Syndrome.
According to research, this disorder affects up to 40% of people with learning disabilities and up to 1% of children and adults in the general population. It is typified by repetitive behaviors, limited interest, and problems with verbal and nonverbal communication, language, and social interaction and relatedness (e.g., eye contacts, effective expression) (Hodges *et al.*, 2020) [27]. It is one of the three recognized illnesses that make up autism spectrum disorders (ASD). The other two are Pervasive Developmental Disorder, sometimes known as PDD-NOS, and Asperger syndrome, which is linked to a lack of language and cognitive development as reported by Johnson and colleagues (2007) [33]. As per the 2013 Global Burden of Disease study, autism is thought to impact approximately 21.7 million individuals worldwide and affects boys four to five times more frequently than girls. As of 2014, one in 68 children in the US has been diagnosed with autism, representing a 30% rise from the disease's prevalence of one in 88 children in 2012 (Blumberg *et al.*, 2014) [8].

The prevalence of autism in adults in the UK who are 18 years of age or older is 1.1% (Brugha *et al.*, 2012) [10], and the number of people receiving a diagnosis has been sharply rising since the 1980s, in part because of improvements in diagnostic procedures and government-funded financial incentives for a named diagnosis (Blumberg *et al.*, 2013) [8]. However, it is unclear whether actual rates of the condition have increased.

The diagnosis of this disease usually happens between 24 and 36 months after birth, though symptoms may appear earlier in infants less than 6 months; in most cases, the diagnosis may not be made until adulthood (Okoye *et al.*, 2023) [48]. However, autism can be said to be a multifactorial disorder that is caused by the combination of neurologic, environmental, and genetic variables (Karimi *et al.*, 2017; Almandil *et al.*, 2019; Zhuang *et al.*, 2024) [1, 34, 68]. As a result, there is no known explanation for autism disorder, and in most cases when the etiology is unclear, the condition is labeled as non-syndromic autism or idiopathic autism (Hodges *et al.*, 2020) [27]. Over the years, several drugs have been developed to manage and treat this condition; these are typically psychoactive or anti-convulsant medications, with the majority being anti-depressants, stimulants, and antipsychotic medications like Risperidone and Aripiprazole (Maniram *et al.*, 2024; Zhuang *et al.*, 2024) [42, 68]. These drugs have been found to be very effective in treating autism-related irritability, repetitive behavior, and insomnia (Alsayouf*et al.*, 2021; Yang *et al.*, 2025) [2, 66].

In order to pinpoint a specific target for treatment, researchers have attempted to ascertain the true origins of this illness as well as any potential hormonal deficiencies that may be involved. Over the years, studies have shown that children with autism disorder have poorer levels of the neuropeptide hormones oxytocin and vasopressin (arginine vasopressin), which are synthesized in the brain's hypothalamus, compared to children without autism (Cid-Jofré *et al.*, 2021; John & Jaeggi, 2021) [15, 32]. This affects the social behavior, cognitive skills, and communication abilities of these children because variations in vasopressin levels or defects in its receptor can affect the characteristics of individuals with autism (De Luca, 2020; László *et al.*, 2023) [16, 39].

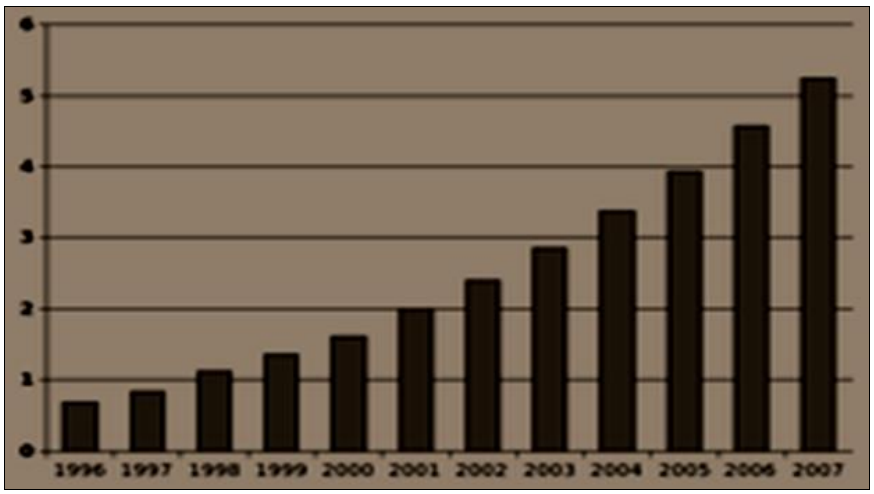


**Fig 1:** Reports of autism cases per 1,000 children grew dramatically in the US from 1996 to 2007. It is unknown how much, if any, growth came from changes in rates of autism. (Wing and Potter, 2002) [65]

**Vasopressin and Oxytocin**

Oxytocin and vasopressin have been linked to important functions in animal social behavior. Two (2) locations within the nine amino acid sequence of these two nanopeptides' structures differ from one another. The majority of male autistic behaviors are caused by higher amounts of arginine vasopressin, whereas female autistic patients have higher levels of oxytocin (Harony and Wagner, 2010) [24].

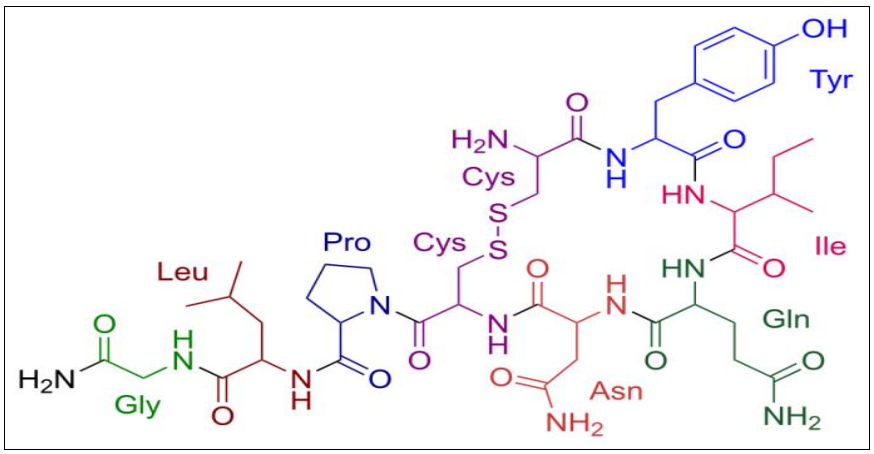


**Fig 2:** Structure of Oxytocin (Holmes *et al.*, 2003) [29]

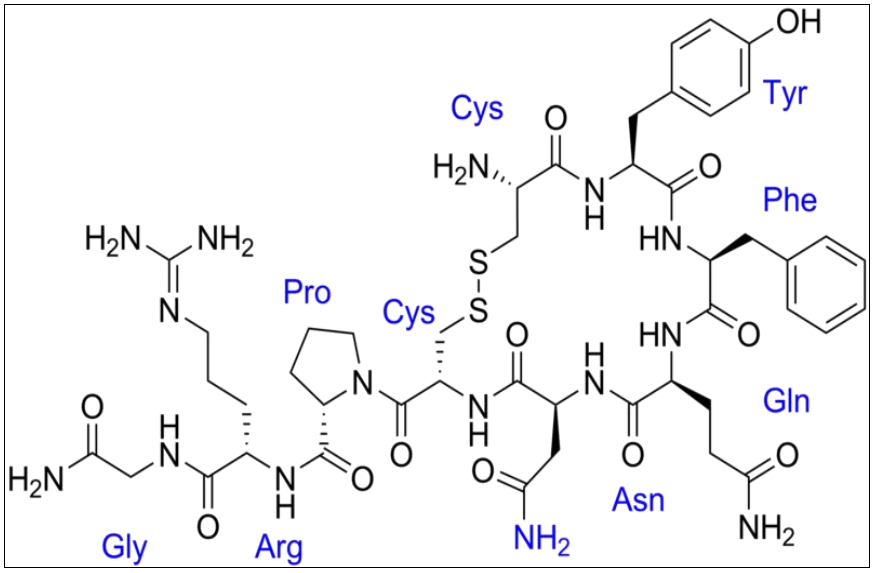


**Fig 3:** Structure of Arginine Vasopressin (Holmes *et al.*, 2003) [29]

Since the homologous genes encoding these two nanopeptides are believed to have arisen from gene duplication events before vertebrate divergence, nearly all invertebrates have one homolog of oxytocin/arginine vasopressin, whereas vertebrates have two (Oztan *et al.*, 2022; Ocampo Daza *et al.*, 2022) [47, 51]. But in mammals, the genes for oxytocin and (arginine) vasopressin are situated close to one another in the genome (Paré *et al.*, 2016) [52]. The mRNAs of both peptides, for example are translated into a precursor preprohormone that contains the signal peptide, the nanopeptide, and a common polypeptide known as neurophysin (Sparapani *et al.*, 2021). This polypeptide is processed and cleared in a dense-core vessel during its transport to the release site (Sparapani *et al.*, 2021). In the mouse genome, they are located on chromosome 2 and are only separated by an intergenic region of 3.6 kb that contains several regulatory elements crucial to the proper expression of both genes (Harmony and Wagner, 2010) [24].

These compounds' dynamic production and degradation determine their functional availability. For instance, the synthesis and breakdown of OT and VP are controlled by peptidases and proteases (Carte, 2017; Glavaš *et al.*, 2022) [21]. Males and females have different levels of these genetically controlled enzymes, but they can also be impacted by dietary factors, salt consumption, and stress-related changes in anxiety or trauma over the course of a lifetime (Dumais & Veenema, 2016; Lu & Hu, 2021) [17]. Prolyl endopeptidases (PEP), which control the metabolism of several peptides, including OT and VP, are of special importance. Changes in PEPs may have regionally specific effects; for example, inhibition of PEP produces an increase VP in the septal nucleus. Because VP in the septal area is sexually dimorphic, individual or sex differences in the effects of enzymes such as PEP, especially in this region, offer a possible substrate for individual differences in behavioral reactivity (Carter, 2007) [13].

According to research on animals, OT and VP may have overlapping roles and have the capacity to affect one another's receptors or activities (Carter, 2007) [13]. Continuing, Carter (2007) [13] posited that although the behavioral actions of OT and VP can occasionally be comparable, there are also distinctions between the functions linked to OT and VP, which may be due to receptor affinities. According to Carter (2007) [13], there may be significant cross-communication between the functional effects of OT and VP, based on both behavioral and tissue binding investigations.

It is not very typical to compare VP and OT directly *in vivo*. The hormonal state at the time of testing or during development, as well as differential receptor binding, can affect these comparisons, making them challenging to evaluate. Comparing the effects of OT and VP in human uterine tissue, it was shown that OT only affected the OTR, but VP affected both the OTR and V1aR. Furthermore, the effects of VP on uterine tissue were four times stronger than those of OT, however, there is sexual dimorphism in the interactions between OT and VP (Carter, 2007) [13]. Therefore, the exogenous delivery of these peptides can encourage the establishment of pair bonds and pleasant social interaction.

**Role of vasopressin in social behavior**

Vasopressin's function is determined by how it interacts with its V1a, V1b, and V2 receptors. It has been discovered that these receptors, particularly the V1a and V1b receptors, mediate the central endocrine and behavioral processes in the brain as well as the peripheral fluid-regulating effects of vasopressin (Carter, 2007) [13]. Continuing, Carter (2007) [13] stated that the infusion of (arginine) vasopressin in the central nervous system was found to enhance mate preference, particularly in males, in a survey using animal models like prairie voles, which are monozygous and known to exhibit a strong preference for a familiar mate over a stranger. Functional studies have also revealed that the action of arginine vasopressin in specific brain areas, such as the ventral pallidum, is responsible for certain aspects of voles' social behavior, including sharing a nest, displaying extensive parental behavior, and increased pair bonding (Holmes, 2003) [29].

Research on social recognition memory using animal models, such as rats and mice, showed that arginine vasopressin plays a critical role in the social recognition memory of Brattleboro rats (Harony and Wagner, 2010) [24]. These rats have a spontaneous null mutation in the AVP gene, which causes them to have a similar impaired social

recognition memory to AVPR1a knockout mice. However, it was found that both viral-mediated delivery of a functional AVPR1a gene into the lateral septum (LS) of the Brattleboro rats' brains restored social recognition memory (Harony and Wagner, 2010) [24]. Arginine vasopressin appears to have anxiogenic properties in humans. This is because, in contrast to oxytocin, which promotes relaxation and lowers anxiety levels, an increased expression of this hormone in the hypothalamic paraventricullar nuclei is linked to an increased degree of anxiety and arousal (Harony and Wagner, 2010) [24]. Because autistic patients lack these traits, vasopressin has been mainly linked to male-typical social behaviors like aggression, pair-bond formation, and stress reactivity (Nephew, 2012) [46]. According to a survey conducted by a team of researchers who looked at the relationship between indices of aggression in subjects with personality disorders and cerebrospinal fluid (arginine) vasopressin, they discovered a positive correlation between the levels of CSF arginine vasopressin and life histories of aggression against other people and general aggression, which suggests that central AVP has an enhancing effect on people who exhibit impulsive aggressive behavior (Heinrichs *et al.*, 2009) [26].

In a survey conducted by some researchers that examined the effect of intranasal AVP administration on human facial response related to social communication, the result showed that 201u intranasal AVP did not affect attention towards autonomic arousal in response to emotional facial expressions with different valence (neutral, happy, and angry) (Heinrichs and Domes, 2008) [25]. However, the subjects group yielded magnitude in response to neutral facial expression that were similar to the magnitude of placebo subjects in response to angry facial expressions, thus suggesting that AVP may influence aggression by biasing individuals to respond to emotionally ambiguous social stimuli as if they were threatening or aggressive (Heinrichs and Domes, 2008) [25]. In light of this, new studies have discovered that a vasopressin receptor subtype (AVPr-1a) has a role in social behavior (Heinrichs and Domes, 2008) [25]. In an experiment employing the monetary/dictator game paradigm to ascertain how this receptor acts in human trust, the length of the AVPr-1a RS3 promoter region has been linked to altruistic conduct (Harony and Wagner, 2010) [24]. This experiment revealed that people with long AVPr-1a RS3 were more willing to take on risks that came up in social interactions, which prevented them from losing faith in people who had betrayed their trust (Harony and Wagner, 2010) [24]. As a result, multiple studies have linked the AVPr-1a receptor gene to autism as reported by Harony and Wagner (2010). [24] Although it has been demonstrated to have a greater influence on male behaviors, particularly those pertaining to reproductive functions, the effect of (arginine) vasopressin appears to be sex-specific, encouraging agonistic and affliative types of responses in men and women, respectively, towards same-sex faces (Heinrichs *et al.*, 2009) [26].

**Social Cognition and Social Approach**

OT and AVP have been linked in numerous animal studies to adult-infant attachment, pair-bonding, and mating (Harony and Wagner 2010) [24]. For instance, it is widely known that AVP controls pair-bonding in prairie voles. AVP regulates social approach behavior, social connection, and attachment in addition to its regulating function in psychosocial stress (Carter, 2007, Grigor'eva and Golubeva 2010) [13, 23]. An increasing amount of experimental research has started to provide light on how AVP affects human social approach behavior, attachment, and related cognitive processes (Heinrichs and Domes, 2008) [25]. These researches as reported by Carter (2007) [13] have so far employed paradigms that look at memory for socially significant knowledge, facial emotion processing, and trusting behavior. Continuing, Carter (2007) [13] asserts that human social attachment and social approach are predicated on trust in others. A behavioral study demonstrated that 24 IU intranasal AVP significantly enhanced human trust using a trust game. Specifically, just 21% of participants in the placebo group exhibited a maximal trust level, whereas 45% of people in the AVP group did. Crucially, AVP and OT particularly raised the person's willingness to take social hazards in social interactions rather than increasing their general preparedness to tolerate risks (Carter, 2007) [13]. A study carried out by researchers found that a post-learning dose of intranasal AVP improved immediate recognition of face identity as reported by (Carter, 2007) [13]. In another memory study, intranasal AVP selectively modulated implicit memory based on the social relevance (neutral vs. reproduction-related) of semantic word stimuli (Cater, 2007) [13].

**Repetitive Behavior**

Repetitive behaviors in people with obsessive-compulsive disorders and other disorders that include repetitive tendencies as a hallmark, including ASD, have been linked to vasopressin (O'Loghlen *et al.*, 2025) [49]. AVP has been shown to decrease repetitive behaviors when administered intravenously, which is consistent with its effects (Carter, 2007) [13].

**Vasopressin in Autism**

Both (Arginine) vasopressin and oxytocin have been implicated to be associated with most social behavior of humans which are also seen as symptoms of autistic disorder, thereby suggesting that autism occurs as a result of dysfunctional regulation of these two nanopeptides in the amygdala (Cataldo *et al.*,2018; László *et al.*, 2023) [14, 39]. The role of vasopressin in autism is potentially more complex than oxytocin. This is in part because there are three vasopressin receptors, plus the interactions that can occur among oxytocin, vasopressin, and their receptors as reported by Heinrichs *et al.*, (2009) [26]. The effects of vasopressin on behavior and physiology might vary based on the amount and length of peptide produced, the time course of release or exposure to vasopressin, and the presence or absence of oxytocin, which can sometimes function as an antagonist to vasopressin and vice versa (Carter, 2017) [13]. Although there have been no reports of vasopressin peptide measures as a function of autism, linkage and linkage disequilibrium for the vasopressin V1a receptor gene have been identified in a subset of families that include individuals with autism (Heinrichs *et al.*, 2009) [26].

Repetitive and fast-mutating microsatellites can change the expression of the vasopressin V1a receptor gene and its behavioral effects, which were particularly noticeable in males (Rigney *et al.*, 2023) [56]. Autism has also been linked to abnormalities in a number of other neurotransmitters,

including serotonin, and serotonin-based treatments are used in autistic disorders (Heinrichs *et al.*, 2009) [26]. It is important to note that serotonin plays a role in the regulation of Vasopressin and Oxytocin, most likely down-regulating the vasopressin system and up-regulating Oxytocin (Raznahan and Pugliese, 2009; Rigney, *et al.*, 2023) [55, 56]. In hamsters (Arginine), vasopressin acting at the vasopressin V1aR can cause aggressive behaviors; this effect of vasopressin was blocked by the concurrent use of a serotonin (5HT-1a) agonist (Ferris *et al.*, 1997) [19]. Serotonin agonists also have the ability to boost oxytocin release; these effects may vary depending on the receptor subtype and age (Baribeau & Anagnostou, 2015; Petersson & Uvnäs-Moberg, 2024) [5, 53]. The indirect effects of selective serotonin reuptake inhibitors (SSRIs) on the vasopressin systems may account for at least some of their actions (Edinoff, *et al.*, 2021; Ruiz-Santiago *et al.*, 2024) [18, 57]. It has also been shown that SSRI responsiveness varies by sex (Edinoff, *et al.*, 2021; Ruiz-Santiago *et al.*, 2024) [18, 57]. The effects of SSRIs on autism may differ in males and females, and their widespread use may also have an impact on vasopressin's functions (Heinrichs *et al.*, 2009, (Edinoff, *et al.*, 2021; Ruiz-Santiago *et al.*, 2024) [18, 26, 57].

Dysfunction of the amygdala has been hypothesized to play a role in the development of autistic disorder (Heinrichs *et al.*, 2009). Continuing, Heinrichs *et al.*, (2009) [26], asserts that this brain area shows a particularly strong expression of AVP receptors. Moreover, vasopressin administration and polymorphisms in the AVPR1a gene were found to affect amygdala responses in humans. Secondly, individuals with autism show a specific deficit in face recognition, which may be related to the specific deficits of OT -OT-knockout and OTR-knockout mice in social recognition memory. Thirdly, vasopressin administration to humans was found to enhance the ability to infer the mental states of others, an ability that is specifically impaired in autism patients (Heinrichs *et al.*, 2009) [26]. Thus, autism is well known to be sexually biased, with a rate of occurrence that is 3-5 times higher in males. It is also known that OT and AVP have a gender biased effect on animal behavior, with OT having a greater effect on females and AVP having a stronger effect on males (Carter, 2007) [13]. Moreover, according to Harony and Wagner (2010) [24], sexual dimorphism is known to exist in the mammalian brain's oxytocinergic and vasopressinergic systems. In particular, men have much higher levels of AVP expression in the MeA and BNST, two brain areas that have been demonstrated to be crucial for social and reproductive mammalian behavior. Therefore, the sex-biased occurrence of autism may be linked to the sex-biased brain activity of oxytocin and AVP (Harony and Wagner, 2010) [24].

As autism appears to be a genetic disorder, mutations in peptide receptors or linkage-specific developmental genes could lead to altered oxytocin or vasopressin neurotransmission (Harony and Wagner, 2010) [24]. Vasopressin receptor knockout mice have demonstrated a significant impairment in social recognition, suggesting a significant role for this peptide in social and affective disorders, such as anxiety disorders and autism (Laila, 2005) [38]. However, oxytocin and vasopressin levels in autistic children are much lower than those in normal children, according to a survey done by researchers. This could be related to the atypical social behavior that autistic children exhibit (Laila, 2005) [38].

Increases in central vasopressin, which are experimentally produced by intranasal infusion of this peptide, may have behavioral effects on humans by making them more reactive to social stimuli that are not ordinarily harmful or irrelevant. Because as reported by Laila (2005) [38] exogenous Vasopressin also had sexually dimorphic behavioral effects, males who received more of the hormone exhibited more corrugator muscle activity, which is a component of frowning, and assessed neutral facial expressions as more "unfriendly." Conversely, women who received Vasopressin reported more pleasant, affiliative reactions to new neutral faces and smiled more (Carter, 2007) [13].

According to a survey, blood AVP concentrations can be used as a biomarker of Theory of Mind ability in children with autism and as a surrogate for brain AVP activity in humans (Carson *et al.*, 2015) [11]. Furthermore, according to Carson *et al.*, (2015) [11], this is because blood measures of (arginine) vasopressin, which are much easier to obtain than brain measures, are most meaningful if they are related to brain AVP activity. Since invasive measures of brain activity, such as lumbar punctures, are unlikely to be employed in typical clinical settings, finding a reliable blood-based biomarker of social competence in autism is especially crucial.

The main findings in human research regarding the role of vasopressin as reported by Heinrichs *et al.*, (2009) [26] can be summarized as follows; (i) AVP is associated with the regulation of the behavioral and endocrine stress response, i.e., AVP is released in response to socially relevant challenges and attenuates endocrine and autonomic responses to stress. (ii) AVP is released in response to positive social interactions, such as social support or social proximity, thus possibly representing a mediator for the well-known stress-protective effects of social support. (iii) The neural substrate for the anxiolytic effects of vasopressin has been suspected in limbic areas of the brain, particularly in the amygdala. Specifically, VP has been found to attenuate amygdala reactivity to social stimuli and to reduce brainstem activity, which is associated with autonomic arousal. (iv) AVP has been found to promote social cognition and the interpretation of social signals, possibly representing an enhanced readiness to show social approach behavior and empathy. (v) There is initial evidence that the central AVP system is altered in several mental disorders that are characterized by severe social disturbances, such as ASD, OCD, personality disorders, and early trauma. There is preliminary evidence suggesting that genetic alterations of neuropeptide receptors and developmental challenges (e.g., early adverse experience) interact in the etiology and development of these disorders. Continuing, Heinrichs *et al.*, (2009) [26] demonstrated that central AVP specifically affects social communication in a sex-specific way, encouraging affiliative facial reactions in women but agonistic facial responses in men when they encounter same-sex faces. Given that research on both humans and animals have demonstrated that AVP improves social skills, the neuropeptide may be a promising target for innovative treatment strategies in a number of mental illnesses that are marked by dysfunction related to social interactions.

Although single doses of intranasal OXT help individuals with autism on laboratory-based social tests, longer-term clinical trials for autism disorder have not shown that OXT is more effective than a placebo. Nonetheless, there is strong evidence that suggests the biology of AVP may be more

significant in social functioning than previously thought as reported by Carson *et al.*, (2015) [11]. In rodents with normal brain OXT signaling, central injection of selective AVP v1a receptor (AVPRv1a) antagonists reduces social functioning (Carson *et al.*, 2015) [11]. Given the male-biased frequency of autism, these pharmacological effects are particularly noticeable in males, and abnormalities in brain AVP peptide signaling may be especially pertinent to understanding autism risk. On a laboratory-based cooperative test, however, single doses of intranasal AVP given to neurotypical people improve detection of favorably and negatively balanced social terms, improve memory for joyful and angry faces, and increase neuronal activity in known AVP brain circuitry. However, the findings of the Carson *et al.*, (2015) [11] survey offered important guidance for future AVP medication in autistic patients. A study by Carson *et al.*, (2015) [11] reported the first neuropeptide receptor mapping investigation of postmortem monkey brain tissue highlighting the potential for therapeutically increasing brain AVP signaling in individuals with autism. According to this study, AVPRv1a is extensively dispersed across the extended neuronal amygdala, indicating that AVP given exogenously may directly target neural circuits that are known to govern social functioning. Continuing, Carson *et al.*, (2015) [11] posited that remarkably, OXT receptors were found only in a few hindbrain regions that were primarily involved in early visual and auditory processing, rather than in typical "social" brain regions. The effectiveness of single doses of vasopressin in improving eye gazing to social signals in people with autism and associated disorders, as well as the conflicting results of longer-term OXT treatment trials intended to improve sophisticated social cognition, may also be explained by these receptor distribution data. Even though AVP and OXT can bind to each other's receptors at high enough concentrations, these neuropeptide receptor mapping and pharmacological data still raise the intriguing question of whether AVP pharmacotherapy, rather than OXT, holds the most promise for successfully improving social functioning in patients with autism. As a result, it is possible to identify which patients are most likely to benefit from AVP treatment (Carson *et al.*, 2015) [11].

## Conclusion

Even though autism is one of the most debilitating childhood diseases, nothing is known about its underlying causes, and there are currently no treatments for its primary social characteristics. Finding biomarkers and treatment targets for autism is crucial, and the brain systems that are essential for normative social functioning are perhaps the most promising options. The neuropeptides arginine vasopressin (AVP) and oxytocin (OXT) are two examples of such candidates. The brain (arginine) vasopressin (AVP) critically regulates normative social behavior in mammals, and experimental disruption of the AVP signaling pathway produces social impairments in rodent and human models. As a result, we postulated that deficiencies in AVP signaling could be a factor in the social impairment observed in kids with autism. Consequently, deficiencies in AVP signaling could be a factor in the social impairment observed in kids with autism. Therefore, blood AVP and OXT concentrations can be used as biomarkers of Theory of Mind ability in children with autism and as a surrogate for brain AVP and OXT activities in human. These also imply that AVP and OXT signaling deficiencies may be a viable target for medication development, especially in a subgroup of people with autism disorder who have the lowest Theory of the Mind scores.

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