COMMENT

Vasopressin deficiency: a hypothesized driver of both social impairment and fluid imbalance in autism spectrum disorder

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OVERVIEW

Scientific naming conventions are often idiosyncratic. For example, biological processes have acquired names after a physician who described a syndrome (Alois Alzheimer), the resemblance of a structure to a common item (sella turcica or Turkish saddle), or a function a molecule is observed to mediate (growth hormone). Although these names may be useful for initial characterization, they can also create confusion (e.g., when a biological entity receives multiple names) or be misleading (e.g., when critical aspects of a molecule's function are overlooked because it is named after a different, unrelated action).

We believe that arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is one such "casualty." Its dual scientific names – suggesting important effects on blood pressure maintenance and renal water regulation – have made integrating knowledge of AVP's diverse functions across disciplines challenging. Moreover, because this molecule was named for its peripheral actions – twice! – its function in the central nervous system as a key regulator of mammalian social behavior was insufficiently studied for decades.

The goals of this perspective are four-fold: 1) to advance the novel hypothesis that brain AVP deficiency drives both social interaction impairments and fluid imbalance in at least some individuals with autism spectrum disorder (ASD); 2) to synthesize emerging evidence consistent with this hypothesis; 3) to outline a strategy for testing and confirming this hypothesis; and 4) to propose a laboratory-based method for detecting AVP deficiency, in order to identify autistic individuals who may be most likely to benefit from AVP therapy.

A BRIEF HISTORY OF AVP'S PERIPHERAL AND CENTRAL FUNCTIONS

AVP is a nonapeptide initially studied as a classic hormone due to its release from the hypothalamic-pituitary-portal into peripheral circulation. The name AVP refers to the hormone's role in increasing vascular resistance and regulating blood pressure (via AVP receptor 1A [AVPR1A]), whereas the name ADH refers to its role in regulating osmolality and renal water handling (via AVPR2). Although hypothalamic and extra-hypothalamic AVP neurons were known to project throughout the brain [1], AVP's names hindered the elucidation of its role in brain-related behavioral processes. Decades would pass before neuroscientists identified AVP as a key regulator of mammalian social behavior (e.g., social recognition memory, pair-bond formation, paternal care) [2], acting primarily through brain AVPR1A.

A role for the central AVP pathway in ASD was later hypothesized [3], as persistent social interaction difficulties are a core feature of ASD. Empirical research subsequently showed that both children with ASD and infants who later receive an ASD diagnosis have significantly lower cerebrospinal fluid (CSF) AVP concentrations compared to controls [4–6]. (Notably, these studies found no group differences in CSF concentrations of oxytocin (OXT), a nearly structurally identical neuropeptide also involved in social functioning [1], demonstrating the specificity of these AVP findings.) Finally, consistent with brain AVP deficiency, a pilot placebo-controlled trial recently reported that intranasal AVP treatment improves social abilities in children with ASD [7].

AVP-RELATED MEDICAL COMORBIDITIES IN ASD

Given the emerging evidence for central AVP signaling abnormalities in ASD, we would expect individuals with ASD, or a subgroup of them, to be at increased risk of AVP-related medical conditions and symptoms. For example, substantially decreased brain AVP production and/or release into systemic circulation can lead to the development of full or partial central diabetes insipidus (CDI), a condition characterized by polydipsia (excessive thirst) and polyuria (excessive urine production). However, there has been limited effort to link the presence of medical symptoms associated with AVP deficiency to social function impairment observed in individuals with ASD. We believe that initial evidence of central AVP deficiency in patients with ASD exists, but has been overlooked, not only because these patients are cared for by clinicians from different specialties, but also because clinicians may attribute these behaviors to a patient's diagnosis of ASD, rather than to an underlying physiological process. Below we review published findings supporting the association of ASD with functions in which AVP is unequivocally a key regulator (i.e., CDI, polydipsia, polyuria).

CDI

No published information is available on the rate of CDI in individuals with ASD, making it difficult to ascertain whether the two conditions co-occur at a higher rate than would be expected based on current population prevalence rates. The only available literature on CDI in ASD comes from two intriguing case reports.

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The first report described a 33-year-old man diagnosed with Asperger disorder (now considered ASD), CDI, and empty sella syndrome [8]. A more recent case report described an infant boy with a family history of CDI who developed polydipsia and polyuria during his first year of life. The child was eventually diagnosed with CDI, and genetic testing confirmed both autosomal dominant familial neurohypophyseal diabetes insipidus and Gitelman syndrome (a defect of renal tubular electrolyte wasting). While the case report did not mention the child receiving a formal diagnosis of ASD, follow-up evaluation "confirmed a developmental disorder characterized by impairment in social interaction and in communication abilities" [9] – a description consistent with ASD's phenotypic presentation. These findings are also consistent with those from a naturally occurring AVP gene null mutant model – the Brattleboro rat – which shows robust social behavior impairment in addition to developing CDI, polydipsia, and polyuria [10].

Polydipsia

There is also emerging evidence to suggest that people with ASD, even when compared to people with other neurodevelopmental diagnoses, are at an increased risk of experiencing polydipsia. Results from a survey of 674 people with ASD found that 74% experienced excessive drinking and that this behavior was not correlated with their level of intellectual disability [11]. (Unfortunately, the relationship between polydipsia and social symptom severity was not assessed in this report.) Similarly, among 138 children with either ASD or intellectual disability, children with ASD were more than twice as likely to experience polydipsia (16.3% vs 6.7%) and had significantly more severe symptoms. These findings were not readily associated with psychotropic medication use [12]. Finally, a study of 110 individuals revealed that rates of polydipsia were higher in people with ASD compared to those with other neurodevelopmental disorders [13]. These collective findings suggest that the increased rate of polydipsia among individuals with ASD is not attributable to intellectual or neurodevelopmental disability, but instead, may be driven by a physiological process unique to ASD, consistent with our hypothesis of an underlying AVP deficiency.

Polyuria

While we were unable to find reports that directly quantified rates of polyuria in individuals with ASD, there are several studies of urinary incontinence, one potential sign of polyuria [14], in this population. In a sample of 83 participants, children with ASD had significantly higher rates of daytime urinary incontinence (25% vs 4.7%) and nocturnal enuresis (30% vs 0%) compared to neurotypical children [15]. In a separate sample of 785 participants, 29% of children with ASD experienced more bedwetting: a percentage significantly ($p < 0.03$) greater than children with attention deficit hyperactivity disorder (ADHD)-combined type (21%), ADHD-inattentive type (10%), and anxiety/depression (7%), as well as healthy controls (10%) [16]. The increased incidence of polyuria in children with ASD compared to children with other neurologic and psychiatric disorders points toward a process enriched in ASD, which is again consistent with an underlying AVP deficiency.

IMPLICATIONS AND DIRECTIONS FOR FUTURE RESEARCH

The emerging evidence reviewed above is consistent with decreased brain AVP production in at least some individuals with ASD. If AVP signaling was globally deficient in individuals with ASD, we would expect a much higher CDI prevalence (currently 0.004%) [17], given ASD impacts greater than 1% of the world's population [18]. We would also expect to observe a clear bimodal distribution of CSF AVP concentration in those with ASD compared to controls. Neither is the case. Indeed, given that AVP is not a high-confidence ASD susceptibility gene, central AVP signaling may be a downstream pathway critical for the expression of ASD symptoms and a point of convergence for multiple and diverse ASD susceptibility genes [19]. This would explain why CSF AVP concentration is closely linked to quantitative variation in autistic-like traits in socially impaired monkeys [19] and social symptom severity in children with ASD [6]. We would then also expect to observe a gradient of co-occurring AVP-related medical symptoms in people with ASD. However, given a lack of awareness of AVP's diverse functions, these symptoms may be subtle enough to go unnoticed or, if prominent, may be misattributed to other causes (e.g., polydipsia being psychogenic rather than neurogenic; enuresis being due to intellectual disability). In addition, although a synthetic analog of AVP (i.e., desmopressin, a compound which targets AVPRV2), has been widely prescribed for over 40 years to treat nocturnal enuresis in ASD, serendipitous observation of social symptom improvement would be unlikely to occur, as discussed in detail elsewhere [7].

Rigorous epidemiological research is now needed to evaluate whether there is an increased prevalence of AVP-related medical conditions (e.g., CDI, polydipsia, polyuria) in ASD. Laboratory research is likewise needed to carefully characterize the relationship between social symptom severity and severity of AVP-related medical symptoms among individuals with ASD. It will be particularly important to confirm that these medical symptoms arise from an endogenous AVP deficiency rather than from medications that alter water consumption or AVP production [20]. Should these clinical investigations bear fruit, copeptin (a molecule co-synthesized and secreted with endogenous AVP) [21] could be used as a complementary or companion precision diagnostic tool to detect AVP deficiency in this clinically heterogeneous patient population. This information, in turn, could guide targeted utilization of AVP therapy, both for the psychiatric management of core social symptoms and medical management of fluid imbalance, thereby significantly improving quality of life for individuals with ASD.

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All authors contributed to the conceptualization of this manuscript. LC and KJP performed the literature review and wrote the first draft of the manuscript. NG, EHS, and AYH reviewed the manuscript and provided critical editorial feedback on it. All authors read and approved the final manuscript.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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