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A NOVEL TREATMENT OPTION FOR AUTISM SPECTRUM DISORDER: VASOPRESSIN RECEPTOR ANTAGONISTS

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Abstract

Autism spectrum disorder is a developmental disability affecting 1 in every 59 newborns and causes significant morbidity while exact pathophysiology is unclear. Recent hypothesis includes vasopressin in patients with ASD while vasopressin receptor antagonists including balovaptan appears to be promising option for treatment especially in ASD patients with high functionality. In this study, our aim is to describe recent developments in vasopressin receptor antagonists involving ASD treatment which have potential for future clinical implementation.

Keywords: Autism spectrum disorder, vasopressin, vasopressin receptor antagonists

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Dear Editor,

Autism spectrum disorder (ASD) is a developmental disability characterized by social deficits, social communication defects, and repetitive restricted behaviors affecting 1 in 59 newborns (Lord et al., 2020). Multiple genetic factors including fragile X syndrome, mutations at certain chromosomal locations (2q, 7q, 15q, and 16p), tuberous sclerosis, neurofibromatosis, and environmental factors such as exposure to valproic acid and toxins have been proposed as etiological risk factors, though the exact underlying pathophysiological mechanism remains unknown (Lord et al., 2020; Park et al., 2016). The potential role of vasopressin in the pathophysiology of ASD has recently been hypothesized (Forgeot et al., 2019; Hendaus et al., 2019). Vasopressin, a nonapeptide primarily affecting collecting tubules of nephrons for water reabsorption, is implicated in the regulation of social and aggressive behavior through V1a receptor, while primary production sites are supraoptic and paraventricular cells of the hypothalamus (Engelmann et al., 2004; Insel et al., 2010). Polymorphisms at V1a gene located on chromosome 12 have been linked to autistic behaviors in animal models and humans in large-scale studies (Kim et al., 2002; Yang et al., 2017). Two regions located at 5′ promoter region of AVP receptor gene, namely RS1 and RS3, have gained significant research interest following the studies demonstrating an association with social behaviors and autistic behaviors (Kim et al., 2002; Francis et al., 2016). V1a gene has been associated with prepulse inhibition, social integration, empathy, processing of facial expressions, and altruism all of which are defective features in patients with ASD (Israel et al., 2008; Wang et al., 2016). Intranasal administration of vasopressin daily for 30 days has shown to improve social deficits in 30 children with ASD in a randomized placebo-controlled trial (Mulholland et al., 2020). In addition, analysis of peripheral mononuclear cell receptors demonstrates a negative correlation between V1a receptor expression and Aberrant Behavior Checklist scores in children with ASD (Voinsky et al., 2019). Similarly, the administration of vasopressin to healthy subjects results in left temporoparietal junction activation which is related to social recognition assessed via functional magnetic resonance imaging (Zink et al., 2011).

The effectiveness of V1a antagonists in the treatment of ASD has only been studied in few clinical trials. Single dose of 20 mg RG7713, a newly developed V1a antagonist, has been demonstrated as an efficient option that leads to improvement in eye tracking, affective speech recognition, and olfactory identification in a double-blind placebo-controlled randomized controlled trial conducted with 19 high functioning adults aged between 18 and 45 with ASD (full intelligence score >70) diagnosed in accordance with the criteria of Diagnostic and Statistical Manual-IV (Umbricht et al., 2017). Balovaptan, another oral V1a antagonist, has similarly been shown to be effective in improving social and communicative skills, assessed via the Vineland-II Adaptive Behavior Scales, when administered daily for 12 weeks in a phase 2 placebo-controlled clinical trial involving 223 male patients with ASD (Intelligence score >70) (Bolognani et al., 2019). Adverse effect profiles of such drugs are relatively safe such as dizziness, inattention, rash at the infusion site, and anxiety, while none of those are considered as significant (Umbricht et al., 2017; Bolognani et al., 2019).

Even though large-scale comprehensive RCTs investigating the efficiency of V1a antagonists in ASD are needed before the inclusion of vasopressin antagonists' inclusion in the treatment guidelines, they appear as a promising therapeutic option with mild side effect profile, especially in high functional ASD patients.

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Author contribution subject and rate:

Sidar Çöpür: Literature search, Study design and Manuscript preparation.

Mazlum Çöpür: Study design and Manuscript preparation.

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