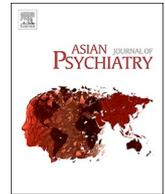




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Letter to the Editor

The growth factors/neuropeptides axis in the pathogenesis of autism spectrum disorder and schizophrenia



Dear Sir,

To the editor

There has been a massive growth in prevalence, public awareness and research funding around autism spectrum disorders (ASD) over the past decades. ASD is one of the groups of neurodevelopmental disorders characterized by three core deficits: impaired communication, impaired reciprocal social interaction and restricted, repetitive and stereotyped patterns of behaviors or interests. To date, there is no curative psychopharmacologic treatment for the core symptoms of autism.

ASD and schizophrenia are both severely impairing mental disorders that share several clinical features such as the theory of mind deficit. Most importantly, ASD and schizophrenia have in common several neurobiological commonalities such as a dysfunction in the mirror neuron system, abnormalities in functional connectivity in brain key networks and genetic deletions especially in the 22q11-13 region (King and Lord, 2011).

Brain growth and development seem to be altered at some stage of development of children with ASD (Donovan and Basson, 2017). Some growth factors' deficiencies such as that of brain derived neurotrophic factor (BDNF), a neurotrophic factor exponentially implicated in the development of severe mental disorders and suicide, has been considered to be at the center of ASD pathogenesis (Das, 2013; Sonal and Raghavan, 2018). BDNF has been found to be involved in various biological processes such as neurogenesis, neural plasticity and regeneration that are essential contributors for an adequate social integration and adjustment to psychosocial stress (Sonal and Raghavan, 2018).

Other growth factors such as insulin growth factor-1 (IGF-1) may offer some promising usefulness for ASD-affected children. IGF-1 administration to children at early stages of ASD and/or for patients at their first psychotic episode might present several potential neurobiological benefits. First, IGF-1 can reduce neuronal excitability via decreasing the ratio between NKCC1 and KCC2 cation/chloride transporters on the neuronal membranes favoring an intraneuronal chloride ion input. Second, IGF-1 can improve oligodendrocytes function which targets myelination defects. Third, IGF-1 may enhance the TRPV2 channel function which is known to improve oxytocin secretion. Fourth, IGF-1 may compensate the defect in SHANK3 by reactivating the phosphatidylinositol 3-AKT pathway (which is an important signal transduction pathway that promotes cellular survival and growth) or inhibiting the dual specificity protein kinase CLK2 (which regulates several cellular processes such as apoptosis) (Bou Khalil, 2017).

Most recently, balovaptan, an orally administered selective vasopressin V1a receptor antagonist has been found to be effective in improving socialization and communication behaviors in men suffering from ASD at the dose of 4 to 10 mg per day (Bolognani et al., 2019). The inhibition of vasopressin receptor V1a has been considered in this study

as the major factor contributing to the improvement in social behavior of patients with ASD. However, evidence supports the fact that IGF-1 may play a role in suppressing vasopressin secretion promoting a diuretic effect (Moreau et al., 2010; Ster et al., 2005). This is in line with the rationale supporting the administration of IGF-1 for the treatment of patients suffering from ASD (Riikonen, 2016).

An important proof in favor of the existence of a growth factors /neuropeptides axis is incarnated in the Williams-Beuren syndrome (WBS). Patients with WBS have growth retardation along with social interaction difficulties in parallel with a hypersociability. The origin of these disturbances is related to the 28 genes deletion that characterizes WBS. Most recently, a myelination defect has been incriminated in the dysfunctional social behavior of patients with WBS (Procyshyn et al., 2017). The deletion in the general transcription factor Ili (Gtf2i) may be incriminated in myelination defects as well as in the sensitivity to social cues that is known to be mediated by neuropeptides that are found to be high in patients with WS. Accordingly, a growth factors / neuropeptides axis can be related to social trust and adequate interaction, two of the core pathological dimensions of ASD and schizophrenia patients.

Due to the similarity between ASD and schizophrenia regarding the pathogenesis, clinical manifestation and response to psychotropic treatments in both disorders, it would be important to start considering - after having better understood the implication of growth factors / neuropeptides axis in social behavior - the presence of a growth factors / neuropeptides axis that is involved in brain anatomic and functional maturation. It seems likely that patients with ASD or schizophrenia present dysfunctions in IGF-1 brain related growth that enhance vasopressin secretion and increase water retention in neurons. This may affect social behaviors and communication skills early during brain development resulting in ASD phenotype but may also lead to brain disconnectivity later in life leading to schizophrenia phenotype. Accordingly, the administration of IGF-1 (or any other myelinating drug) or vasopressin receptors antagonists should not only be tried in patients with ASD but also in patients with schizophrenia.

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Declaration of Competing Interest

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