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Review

Serotonin mediated immunoregulation and neural functions: Complicity in the aetiology of autism spectrum disorders

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ABSTRACT

Serotonergic system has long been implicated in the aetiology of autism spectrum disorders (ASD), since platelet hyperserotonemia is consistently observed in a subset of autistic patients, who respond well to selective serotonin reuptake inhibitors. Apart from being a neurotransmitter, serotonin functions as a neurotrophic factor directing brain development and as an immunoregulator modulating immune responses. Serotonin transporter (SERT) regulates serotonin level in lymphoid tissues to ensure its proper functioning in innate and adaptive responses. Immunological molecules such as cytokines in turn regulate the transcription and activity of SERT. Dysregulation of serotonergic system could trigger signalling cascades that affect normal neural-immune interactions culminating in neurodevelopmental and neural connectivity defects precipitating behavioural abnormalities, or the disease phenotypes. Therefore, we suggest that a better understanding of the cross talk between serotonergic genes, immune systems and serotonergic neurotransmission will open wider avenues to develop pharmacological leads for addressing the core ASD behavioural deficits.

Contents

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1. Overview on autism spectrum disorders

Autism spectrum disorders (ASD) are a group of highly heritable complex neurodevelopmental disorders, having an onset before the age of three years, varying from mild to severe phenotypes. Clinical features that characterize ASD include impairments in social interaction and communication skills with the presence of stereotypic behaviour and interests (American Psychiatric Association, 2000) (Box 1). ASD is a broad term that covers three subgroups of pervasive developmental disorders such as; autistic disorder, Asperger syndrome and pervasive developmental disorder-not otherwise specified (PDD-NOS). The recent fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V) includes only a single diagnosis as ASD covering disorders with symptoms of social communication dysfunction and repetitive behaviour (American Psychiatric Association, 2013).

Behavioural features being the major phenotype of ASD, its relevance to the functions of central and peripheral serotonergic system is equated not only to neurological defects but also to immunological malfunction; since this biogenic amine is now known to actively regulate brain development, signal transduction as well as immune responses. With these in mind, a certain involvement of serotonin (5-hydroxytrypamine; 5-HT) in the central nervous system (CNS) functioning in relation to immune mechanisms is brought out to suggest a neuro-immune cooperation as a basis of ASD manifestation in the present study.

Box 1: Behavioural deficits that characterize autism.
Impairment of Social Interaction: Deficits in non-verbal behaviours such as eye contact, facial expression, gestures to regulate social interaction, lack of social reciprocity, failure to develop peer relationships.
Impairment of Communication: Delay or total lack of conversational use of language, with no compensation by gesture, preservative questioning, inability to initiate a conversion despite having adequate speech.
Repetitive and Restrictive Interest and Behaviour: Intense preoccupation showing stereotyped interests, distress over change, repetitive motor mannerisms such as hand flapping, twisting.

1.1. History

Autism research has picked up momentum during the last two decades, despite its first description as “infantile autism” by the American Psychiatrist, Kanner (1943), to represent a group of socially isolated children showing severe behavioural impairments. Asperger (1944) independently identified children with similar behaviours in milder form with adequate speech capability and described as ‘Asperger syndrome’. The current concept of ASD was proposed by Wing and Gould (1979) to stress upon the symptom heterogeneity that exists with these disorders.

1.2. Prevalence

Prevalence rate of ASD is estimated to be more than 1% with a gender bias, where more males are affected than females (ratio is 4.5:1) (CDC, 2014). Apparently the prevalence rate of ASD is alarmingly increasing world-wide with a South Korean community showing 2–3% affected amongst children aged 7–12 years from main stream and special education schools in 2006 (Kim et al., 2011b), and the latest estimate of US Centres for Disease Control and Prevention revealing 1 in 68 children aged 8 years (CDC, 2014). The reason for the disturbing rate of increase in incidence could be a reflection of the wider public awareness of the disease, broadened diagnostic criteria of ASD, diagnostic substitution and better understanding of the concepts through improved educational policies (Fombonne, 2009).

1.3. Genetic factors

Epidemiological, family based twin and sibling studies have unequivocally established the genetic basis behind autism. Large differences in concordance rates between monozygotic and dizygotic twins were exposed at the initial stages of twin studies (Bailey et al., 1995; Folstein and Rutter, 1977; Ritvo et al., 1985; Steffenburg et al., 1989). Recent studies estimated high ASD concordance of 88–95% in monozygotic and 31% in dizygotic twins for broadly defined category (Rosenberg et al., 2009; Taniai et al., 2008), and the current estimate backs a high heritability of 70–90% for ASD (Ronald and Hoekstra, 2011). In recent times, whole-genome linkage, genetic association, copy number variation (CNV) screening and