Chapter 2

Autism Spectrum Disorder, Fear Response, and Environmental Exposures

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ABSTRACT

Autism spectrum disorder (ASD) is a developmental condition characterized by impaired social interactions and communication, as well as by stereotypic movements, that affects 1 in 59 children. ASD is expected to reach 1 in about 40 children by 2020, yet it remains without distinct pathogenesis and effective treatment. Children with ASD respond with high anxiety to almost any unknown stimulus and appear to misread danger/threat signals, and may not experience anxiety in situations where normotypic children do. The authors propose that environmental stimuli stimulate the unique immune cells, known as mast cells (MC), which then trigger microglia, leading to dysfunctional neuronal connectivity in the amygdala. This process lowers or disrupts the "fear response" and leads to an exaggerated "fight-or-flight" reaction. corticotropin-releasing hormone (CRH) could have a synergistic effect with environmental stimuli, especially mycotoxins. Recognizing this association and preventing stimulation of mast cells/microglia could lead to effective treatment of ASD.

INTRODUCTION

Autism Spectrum Disorder (ASD) is a developmental condition characterized by impaired social interactions and communication, as well as by stereotypic movements. It affects 1 in 59 children (Centers for Disease Control and Prevention, 2018; Fombonne, 2009; Lai et al., 2014; McPartland & Volkmar,
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2012), but is projected to reach 1 in 40 children by 2020. In spite of the discovery of numerous gene mutations in patients with ASD, no direct link has so far been uncovered (Abrahams & Geschwind, 2008; Geschwind & State, 2015; Willsey & State, 2015). The lack of reliable biomarkers (Ruggeri et al., 2014) and a specific pathogenesis (Theoharides et al., 2008), as well as the existence of subgroups and comorbidities (Bauman, 2010), complicates the diagnosis and treatment of ASD. Increasing evidence indicates that microglia, responsible for innate immunity of the brain (Aguuzzi et al., 2013; Ransohoff & Brown, 2012), are activated in ASD (Gupta et al., 2014; Koyama & Ikegaya, 2015; Rodriguez & Kern, 2011; Takano, 2015), but the triggers are not known.

Neuroinflammation (Theoharides et al., 2016) may result from stimulation of unique tissue immune cells called mast cells (MC) (Theoharides et al., 2015c), which are located around blood vessels and nerves in the brain (Edvinsson et al., 1977; Goldschmidt et al., 1984; Marathias et al., 1991; Matsumoto et al., 2001; Taiwo et al., 2005), especially at the amygdala, the thalamus and the hypothalamus (Pang et al., 1996). Mediators derived from MC (Mukai et al., 2018; Theoharides et al., 2012, 2015c) could then activate microglia (Patel et al., 2016; Zhang et al., 2016), causing localized inflammation (Girolamo et al., 2017; Skaper et al., 2014; Theoharides et al., 2015a, 2015b) and leading to symptoms of ASD (Theoharides et al., 2016). Mast cells act as sensors of environmental and psychological stress (Theoharides, 2017), secreting danger signals (Theoharides, 2016) such as mitochondrial DNA (mtDNA) (Zhang et al., 2012), which acts as an “innate pathogen” (Theoharides et al., 2013) that causes auto-inflammatory responses (Collins et al., 2004; Marques et al., 2012; Sun et al., 2013). In fact, we reported that mtDNA is increased in the serum of children with ASD (Zhang et al., 2010).

Indirect evidence of the role of MC in ASD stems from the recognition that ASD has been significantly associated with atopic diseases (Theoharides et al., 2016) such as allergies (Liao et al., 2016; Lyall et al., 2015), asthma (Kotey et al., 2014) and eczema (Billeci et al., 2015), all of which involve MC. In addition, we reported that the incidence of ASD is 10 times higher in children with mastocytosis than in the general population (Theoharides, 2009). Moreover, most patients with mastocytosis complain of a variety of neuropsychological symptoms, including fatigue (Georgin-Lavialle et al., 2016a), cognitive impairment (Moura et al., 2012) and depression (Georgin-Lavialle et al., 2016b).

Immune-neural connections regulate responses to environmental and infectious agents, leading to altered behavior (McCusker & Kelley, 2013). We propose that stimulation of brain MC by environmental, neural, immune, pathogenic or stress triggers disrupt the normal “fear threshold” in the amygdala and the hypothalamic-pituitary-adrenal axis (HPA) (Chrousos, 1995). Mast cells act as sensors of environmental and psychological health (Theoharides et al., 2004) via corticotrophin-releasing hormone (CRH) together with the peptide neurotensin (NT) (Donelan et al., 2006). Triggers of MC can reach the hypothalamus from the nasal cavity through the cribriform plexus (Kalogeromitros et al., 2007), or may reach the brain through the lymphatics (Louveau et al., 2015). In addition, mast cell-derived mediators, especially cytokines (Abbott, 2000; Pan et al., 2011), increase the permeability of the gut-blood and blood-brain barriers (BBB) (Esposito et al., 2002; Fiorentino et al., 2016; Theoharides & Doyle, 2008). As a result, circulating and environmental toxins are allowed to pass into the brain, trigger microglia (Patel et al., 2016; Zhang et al., 2016), and disrupt neuronal connectivity, especially in the amygdala (Cowan et al., 2018; Rozniecki et al., 2009; Theoharides et al., 2016).
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