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REVIEW

BRAIN IL-6 AND AUTISM

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Abstract—Autism is a severe neurodevelopmental disorder characterized by impairments in social interaction, deficits in verbal and non-verbal communication, and repetitive behavior and restricted interests. Emerging evidence suggests that aberrant neuroimmune responses may contribute to phenotypic deficits and could be appropriate targets for pharmacologic intervention. Interleukin (IL)-6, one of the most important neuroimmune factors, has been shown to be involved in physiological brain development and in several neurological disorders. For instance, findings from postmortem and animal studies suggest that brain IL-6 is an important mediator of autism-like behaviors. In this review, a possible pathological mechanism behind autism is proposed, which suggests that IL-6 elevation in the brain, caused by the activated glia and/or maternal immune activation, could be an important inflammatory cytokine response involved in the mediation of autism-like behaviors through impairments of neuroanatomical structures and neuronal plasticity. Further studies to investigate whether IL-6 could be used for therapeutic interventions in autism would be of great significance.

Key words: autism, brain, Interleukin-6, neuroimmune response, behavior.

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Abbreviations: CSF, cerebrospinal fluid; GM-CSF, Granulocyte–macrophage colony-stimulating factor; IFN-γ, Interferon-γ; IL, Interleukin; MCP, macrophage chemoattractant protein; MIA, maternal immune activation; MRI, magnetic resonance imaging; TNF-α, tumor necrosis factor alpha.

INTRODUCTION

Autism is a severe neurodevelopmental disorder with a large population prevalence, characterized by impairments in social interaction, deficits in verbal and non-verbal communication, repetitive behavior and restricted interests. Although a few pharmacological treatments appear to reduce some of the associated symptoms, there are no therapeutic options that target the core symptoms of autism. Susceptibility to autism has been suggested to be attributable to genetic factors and environmental risk factors (Abrahams and Geschwind, 2008; Weiss, 2009; Buxbaum et al., 2010; Devlin et al., 2011; Hallmayer et al., 2011), however the etiology of the disorder is poorly understood. Emerging evidence suggests that aberrant neuroimmune responses may contribute to phenotypic deficits and could be appropriate targets for pharmacologic intervention (Theoharides et al., 2009; Hagberg et al., 2012; Onore et al., 2012). The neuroimmune network includes astrocytes and microglia, immune mediators as well as other classical immune pathways. The function of neuroimmune factors plays an important role in brain development and is critical for the processes of neuronal migration, axonal growth, neuronal positioning, cortical lamination, as well as dendritic and synaptic formation (Boulanger, 2009; Pardo-Villamizar and Zimmerman, 2009). Defects in neuroimmune factors could lead to neuropsychiatric disorders (McAllister and Patterson, 2012; Onore et al., 2012).

A number of studies have reported cytokine abnormalities in the peripheral blood of autistic patients (Molloy et al., 2006; Ashwood et al., 2011a,b), as well as in the gastrointestinal tract (DeFelice et al., 2003; Ashwood et al., 2004). However, different research groups showed different findings on the cytokines profile in autism. We reckon these differences could be resulted from different autistic samples used and the differences in phenotype severity. In addition, the immune findings in the peripheral blood of autistic patients may not correlate with the immune-mediated pathology within the central

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nervous system (CNS). So far, relatively few studies concerning the expression of cytokines in the autistic brain have been conducted. Using postmortem brain specimens from autistic individuals, a study demonstrated that transforming growth factor (TGF)-β1 was significantly increased in the middle frontal gyrus of autistic patients, while macrophage chemoattractant protein (MCP)-1, Interleukin (IL)-6 and IL-10 were increased in the anterior cingulated gyrus. In addition, MCP-1, IL-6, IL-8 and Interferon (IFN)-γ were shown to be significantly increased in the cerebrospinal fluid (CSF) of autistic subjects (Vargas et al., 2005). Chez et al. has also reported the elevation of tumor necrosis factor (TNF)-α in the cerebrospinal fluid of autistic subjects (Chez et al., 2007). Most recently, Li et al. determined the activities of a set of cytokines including the pro-inflammatory cytokines [IL-6, IL-1β, TNF-α, Granulocyte–macrophage colony-stimulating factor (GM-CSF)], Th1 cytokines [IL-2, IFN-γ], Th2 cytokines (IL-4, IL-5, IL-10) and chemokine (IL-8) in the brain of autistic individuals using multiplex bead immunoassays. In this study, IL-6, TNF-α, GM-CSF, IFN-γ and IL-8 were reported to be significantly increased in the brains of autistic subjects as compared with the controls (Li et al., 2009). However, immune therapy applied to human children or adults with autism is mainly limited to a number of case reports, unpublished information, and rare case series (Chez and Guido-Estrada, 2010). Further examination of the action of drugs on cytokine profiles and how it affects autistic behaviors are of great significance.

BRAIN IL-6 AND AUTISM

The role of IL-6 in CNS

IL-6, one of the most important neuroimmune factors, was shown to be involved in physiological brain development and in several neurological disorders such as schizophrenia, major depression and Alzheimer's disease (Garay and McAllister, 2010; Spooren et al., 2011). In the CNS, the cellular sources of IL-6 include astrocytes, microglia, neurons and endothelial cells of the brain microvasculature (Juillerat-Jeanneret et al., 1995; Benveniste, 1998; Juttler et al., 2002). IL-6 is normally expressed at relatively low levels and increases under pathological conditions (Gadient and Otten, 1997; Juttler et al., 2002). Experimental evidence suggests IL-6 has many different roles within the CNS. IL-6 has been shown to stimulate the differentiation of astrocytes, primary dorsal root ganglion neurons, hippocampal neurons and Schwann cells (Zhang et al., 2004, 2007; Nakanishi et al., 2007; Oh et al., 2010). IL-6 can be neurotoxic and may mediate associations between maternal infection and neurodevelopmental damage (Benveniste, 1998). Samuelsson et al. (Samuelsson et al., 2006) demonstrated that prenatal exposure to IL-6 results in inflammatory neurodegeneration in the hippocampus and impaired spatial learning during adulthood. Depending on the concentration, brain region and cell type, IL-6 has been shown to promote neural growth as well as to cause neuronal death (Conroy et al., 2004), to protect against excitotoxicity in cortical and cerebellar neurons, as well as to enhance N-methyl-D-aspartate (NMDA)-induced excitotoxicity in cerebellar granule neurons (Conroy et al., 2004; Peng et al., 2005; Wang et al., 2007, 2009). IL-6 has also been demonstrated to promote neuronal differentiation of neural progenitor cells in the adult hippocampus (Oh et al., 2010). In addition, another study reported a critical finding that supports the role of IL-6 in the pathophysiology of schizophrenia and autism in the context of maternal immune activation (MIA) (Smith et al., 2007). IL-6 signaling has also been suggested as a key mechanistic pathway in the MIA that may be associated with autism (Parker-Athill and Tan, 2010).

Elevated IL-6 in the autistic brain

Many studies show IL-6 dysregulation in individuals with autism in plasma (Emanuele et al., 2010; Ashwood et al., 2011a,b), peripheral blood cells (Jyonouchi et al., 2001; Enstrom et al., 2010) and lymphoblasts (Malik et al., 2011). Of the brain cytokines in autism, IL-6 elevation in the autistic brain has been a repeated finding and may be worth noting (Vargas et al., 2005; Li et al., 2009; Wei et al., 2011). Vargas et al. have demonstrated that IL-6 was increased in the anterior cingulated gyrus of autistic brains and also in the cerebrospinal fluid of autistic children (Vargas et al., 2005). Consistent with these findings, the evidence from Li's group showed that IL-6 was significantly increased in the frontal cortices and cerebellum of autistic subjects as compared with the age-matched control subjects (Li et al., 2009; Wei et al., 2011). It should be noted that the IL-6 expression was not significantly changed in the subjects with high-functioning autism (Suzuki et al., 2011). BTBR *T+tf*/J mice have been reported to exhibit autistic-like behaviors including impairments in social interactions and restricted repetitive behavior. One study that examined the expression of various cytokines in the whole brain of BTBR mice also showed a trend toward a significantly increased production of IL-6 (Heo et al., 2011). Any evidence of IL-6 alteration in other autism genetic models, such as FMR1 knockout mice and SHANK3 mutant mice, would be helpful in a more cause and outcome manner.

There are several ways in which IL-6 can be elevated in the brain of autistic subjects. First, MIA during pregnancy may be a source of brain IL-6 (Smith et al., 2007). Pro-inflammatory cytokines arising from MIA could pass through the placenta; enter the fetal circulation; cross the fetal blood–brain barrier; and cause aberrant neuronal growth and plasticity within the fetal brain (Buehler, 2011). It was also reported that IL-6 induced MIA-associated autism probably by activating the JAK2/STAT3 signaling (Parker-Athill et al., 2009). However, in a case-control study, a profile of elevated serum IFN-γ, IL-4 and IL-5, but not IL-6, was more common in women who gave birth to a child subsequently diagnosed with autism (Goines et al., 2011). Secondly, it has been suggested that microglia and astrocyte stimulation could lead to an IL-6 elevation in the brain. Expression profiling of postmortem brain

tissue from autistic individuals revealed increased messenger RNA transcript levels of several immune system-associated genes, implicating neuroimmune processes in autism (Garbett et al., 2008). Vargas et al. demonstrated an active neuroimmune process in the cerebral cortex, white matter, and notably in the cerebellum of autistic subjects. The results of this study showed marked activation of microglia and astrocytes and suggested that reactive astrocytes could be the main source of MCP-1 and IL-6 in the brains of autistic subjects (Vargas et al., 2005). Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex of the autistic brain have also been reported in another independent study (Morgan et al., 2010).

All these evidences suggest that brain IL-6 may play an important role in the development of autism. However, the exact mechanism in which IL-6 alteration contributes to the pathophysiology of autism remains undefined. A maternal injection of IL-6 on mouse pregnancy causes prepulse inhibition and latent inhibition deficits in the adult offspring. Moreover, an anti-IL-6 antibody that inactivates IL-6 improves autism-like behaviors and normalizes the associated changes in gene expression in the brains of adult offspring mice (Smith et al., 2007). Wei et al. developed a mouse model of over-expressing IL-6 in the brain with an adenoviral gene delivery approach and confirmed that IL-6 is an important mediator of autism-like behaviors. This study found that mice with an elevated IL-6 level in the brain developed autism-like behaviors (Wei et al., 2012a). These findings suggest that IL-6 elevation in the brain could modulate certain pathological alterations and contribute to the development of autism. On the other hand, we cannot exclude the possibility that IL-6 may not be the cause but resume from some abnormal environmental or genetic predisposition.

Earlier studies have shown that structural abnormalities occur in many areas of the autistic brain (Bauman and Kemper, 1985; Ritvo et al., 1986). Prenatal exposure of pregnant mice to an influenza virus was found to affect the developing brain structure as evident by pyramidal cell atrophy and macrocephaly in adulthood (Fatemi et al., 2002). A number of structural neuroimaging studies have shown that individuals with autism exhibit neuroanatomical abnormalities. The clinical onset of autism appears to be related to a reduced head size at birth and a sudden and excessive increase in head size between 1 to 2 months and 6 to 14 months (Courchesne et al., 2003). In a larger autism study, magnetic resonance imaging (MRI) data demonstrated that early brain overgrowth during infancy and the toddler years in autistic boys and girls, followed by an accelerated rate of decline in size and perhaps degeneration from adolescence to late middle age tends to occur in this disorder (Courchesne et al., 2011). Using high-resolution MRI, Wei et al. found that mice with elevated IL-6 in the brain display an increase in total brain volume. In addition, the lateral ventricle is also enlarged in mice that overexpress IL-6. The brain structure surrounding the lateral ventricle was squeezed and deformed from the normal location (Wei et al., 2012b). These results indicate that IL-6 elevation in the brain could mediate neuroanatomical abnormalities.

A possible mechanism through which brain IL-6 elevation contributes to the development of autism

Inhibitory and excitatory synapses play fundamental roles in information processing in the brain. Inappropriate loss of synaptic stability could lead to the disruption of neuronal circuits and to brain dysfunction. A key role for excitatory/inhibitory alterations in autism is supported by the observation that 10–30% of autistic individuals have epilepsy (Canitano, 2007). The synaptic abnormality hypothesis is further supported by the identification of mutations affecting synaptic cell adhesion molecules, including NRXN1, NLGN3/4, SHANK3, as well as mutations in synaptic proteins, including CNTNAP2, CACNA1C, CNTN3/4 and PCDH9/10, in autistic subjects (Durand et al., 2007; Abrahams and Geschwind, 2008; Alarcon et al., 2008; Arking et al., 2008; Bakkaloglu et al., 2008; Kim et al., 2008; Marshall et al., 2008; Morrow et al., 2008). Several animal studies also indicate that the imbalance between excitatory and inhibitory synapses is involved in the pathology of autism (Tabuchi et al., 2007; Peca et al., 2011).

Many studies have demonstrated a detrimental effect of elevated IL-6 levels on long-term synaptic plasticity and that IL-6 has physiological and pathological effects on learning and memory (Yirmiya and Goshen, 2011). At a certain concentration, IL-6 significantly reduced the number of primary dendrites, nodes, total dendritic length and neuron survival was also reduced (Gilmore et al., 2004). Chronic IL-6 altered the level of synaptic proteins in the hippocampus in cultured cells and *in vivo* (Vereyken et al., 2007). Elevated IL-6 levels in cultured cerebellar granule cells led to alterations in neural cell adhesion and migration and also caused an imbalance of excitatory and inhibitory circuits (Wei et al., 2011). In the aforementioned IL-6 autistic mice, IL-6 elevation in the brain has also been shown to result in an alteration in excitatory and inhibitory synaptic formations and imbalance of excitatory/inhibitory synaptic transmissions (Wei et al., 2012a). IL-6 elevation stimulated excitatory synapse formation, while it impaired the development of inhibitory synapses and reduced the paired-pulse inhibition, a form of short-term synaptic plasticity.

Dendritic spines are small membranous protrusions from the neuronal surface, each of which receives input typically from one excitatory synapse (Nimchinsky et al., 2002). It is becoming evident that spine morphology is intimately linked to synapse function, which is the basis of learning and memory (Yuste and Bonhoeffer, 2001). Several studies have shown reduced dendritic spine density in specific brain regions of subjects with schizophrenia (Glantz and Lewis, 2000; Sweet et al., 2009). Dendritic spine loss has also been described in mouse models of Alzheimer's disease (Knobloch and Mansuy, 2008; Bittner et al., 2010). This is relevant as there are both clinical and biological links between autism and schizophrenia (Meyer et al., 2011). For

instance, it has been shown that serum and CSF IL-6 levels are abnormally altered in schizophrenia patients (Ganguli et al., 1994; van Kammen et al., 1999) in a manner similar to autistic patients. The accumulating evidence supports the hypothesis that the pathogenesis of autism and schizophrenia is linked via exposure to inflammation at early stages of development of the respective disease (Meyer et al., 2011; Patterson, 2011). However, unlike in schizophrenia and Alzheimer's disease, Golgi-impregnated postmortem autistic brain tissue revealed an increase in spine density on apical dendrites of pyramidal neurons from cortical layer 2 in the frontal, temporal and parietal lobes and layer 5 in the temporal lobe only (Hutsler and Zhang, 2010). Elevated spine density has also been reported in the brain of fragile X syndrome patients, in which one third of the subjects exhibit autistic symptoms (Irwin et al., 2001). Peça et al. (Peca et al., 2011) reported that Shank3 mutant mice display autistic-like behaviors, but these mice display a significant reduction in spine density. Up to now, the evidence of IL-6 and dendritic spine pathology is limited. Wei et al. found that IL-6 elevation stimulated the formation of mushroom-shaped dendritic spines and resulted in a significant increase in the length of dendritic spines (Wei et al., 2012a). The stimulatory effect of IL-6 on the mushroom-shaped spines further supports the possibility that IL-6 elevation may stimulate the formation of excitatory synapses and result in enhanced excitatory synaptic transmission in the autistic brain.

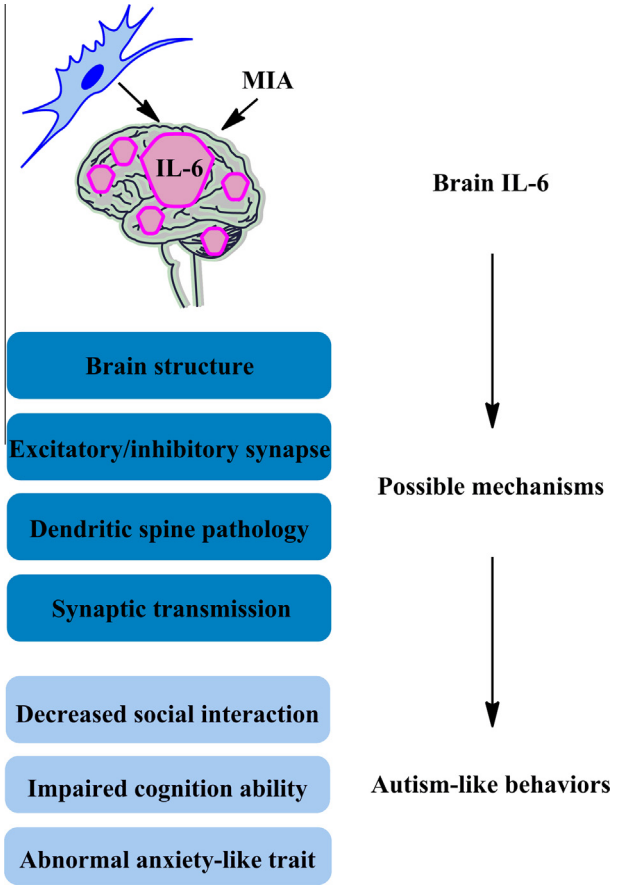

Fig. 1. A possible pathological mechanism by which IL-6 may be involved in autism.

CONCLUSION

In conclusion, a possible pathological mechanism behind autism is speculated. IL-6 elevation in the brain, caused by the activated glia and/or MIA could mediate autism-like behaviors, through impairments of neuroanatomical structures and neuronal plasticity (Fig. 1). It is of great importance to further investigate whether therapeutic interventions in autism can be achieved through the manipulation of IL-6. For example, the blockade of IL-6 signaling in animal models of autism could be examined to analyze whether autism-like behaviors are modulated. However, it is conceivable that other cytokines in the autistic brain, except IL-6, could also have a coordinative or independent role in mediating the abnormal brain development in autism. Furthermore, the signaling pathway through which IL-6 affects neurons in the autistic brain and the neuropathological effect of IL-6 in young autistic patients are topics of great value for future studies. It is worth noting that while a neuroimmune explanation for the pathophysiology of autism is excited, attention also needs to be paid to the genetic factors, environmental risk factors and other factors.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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