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Peripheral and central inflammation in autism spectrum disorders

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ABSTRACT

Recent reports have given a central role to environmental factors in the etiology of autism spectrum disorders (ASD). However, most proposed perinatal factors seem to converge into the activation of the immune system, suggesting that an early inflammatory response could be a unifying factor in the etiology ASD. Here I review the evidence of early immune activation in individuals with ASD, and the chronic peripheral and central alterations observed in the inflammatory response in ASD. This evidence shows that ASD is associated with altered neuroinflammatory processes and abnormal immune responses in adulthood. How these immune alterations can affect developmental programming of adult behavior or directly affect behavior later in life is discussed in the context of both clinical and animal models of research. Recent studies in rodents clearly support a role of elevated cytokines in the behavioral symptoms of ASD, both during development and in adulthood. This article is part of a Special Issue entitled 'Neurodegeneration'.

Introduction

Autism spectrum disorders (ASD) are characterized by reduced sociability, diminished communicative skills and repetitive behaviors or restricted interests, all tend to manifest prior to 36 months (American Psychiatric Association, 2000; World Health Organization, 1994). Prevalence is estimated 1 in 100–200 children born (Baron-Cohen et al., 2009; Centers for Disease Control and Prevention, 2009). However, these figures are in rise as a significant increase in the incidence of autism has been noted in recent years (discussed in Hertz-Picciotto and Delwiche, 2009).

Although several lines of evidence suggest that the disorder is heritable, a recent large study suggests that ASD heritability plays a relatively minor role, which has highlighted a central role for the shared environment component in twin studies (Hallmayer et al., 2011). Moreover, even with the recent advances in whole-genome linkage studies, the identification of candidate genes involved in ASD only appears to account for 10–20% of ASD cases (Abrahams and Geschwind, 2008). Thus attention has shifted to understanding the environmental factors that contribute to the etiology of ASD (Berg, 2009) and how such factors might interact with predisposing alleles during a critical window during neurodevelopment.

The controversy over the association between the measles virus vaccination and autism, triggered after Dr. Andrew Wakefield's report (Wakefield et al., 1998) and scientifically disproved many times (see Flaherty, 2011), has probably delayed and misled the identification of environmental factors that could contribute to the etiology of ASD. However, a number of environmental factors have been identified: heavy metals (namely, lead, mercury, cadmium, and arsenic) (Landrigan, 2010); insecticides (Roberts et al., 2007); phthalates used in vinyl and cosmetics (Larsson et al., 2009); in utero exposure to teratogenic agents such as thalidomide and valproic acid (Moore et al., 2000; Stromland et al., 1994); household cleaning products, such as antibacterial soaps, Western cleanliness and the eradication of diseases (the "hygiene hypothesis") (Becker, 2007); and bacterial or viral infections (Atladottir et al., 2010; Ciaranello and Ciaranello, 1995). The great heterogeneity displayed in ASD may relate at least in part to these diverse environmental factors and the period of exposure in utero and early post partum.

Despite the diversity of potential causal agents, it seems likely that such environmental challenges will converge on some common pathways. One candidate that fulfills these requirements is the host inflammatory response. Research over the past few decades has shown how the immune system can affect brain function and how the brain can regulate the immune system via both neuronal and hormonal pathways (reviewed in Besedovsky and Rey, 2007). In the case of developmental diseases such as ASD, the neuroimmune system could affect not only function, but also development, resulting in long-term alterations and disease (also discussed in Patterson, 2002). The inflammatory response, when elicited during pregnancy, may originate in the mother and then subsequently induce inflammation in the placenta or the fetus (reviewed in Stolp and Dziegielewska, 2009). Similarly, an environmental or genetic factor could affect the inflammatory response in

Abbreviations: ASD, Autism spectrum disorders; ICV, intracerebroventricular; IL-1, interleukin-1; TNF-α, tumor necrosis factor alpha; IFN-α, interferon alpha; sTNFRI, soluble tumor necrosis factor receptor I; LPS, lipopolysaccharide; TGF-β, transforming growth factor beta; BBB, blood–brain barrier; GD, gestational day; PD, postnatal day; MIA, maternal immune activation; PPA, propionic acid.

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the newborn, altering postnatal brain development (Adams-Chapman and Stoll, 2006). To support this, a recent in silico analysis of ASD found that genes previously linked to ASD interact at the level of immune signaling pathways, suggesting that mutations in these genes alter signaling regulation of immune cells during development (Ziats and Rennert, 2011). Here, I review the evidence of altered inflammatory responses in ASD patients, both peripherally and centrally, during development and later in life.

Altered inflammation early in life: an etiological hypothesis of ASD

Clinical evidence of perinatal inflammation

The hypothesis of a role of early inflammation in the etiology of ASD was initially based on the evidence gathered from medical history of autistic patients and from epidemiological studies, that reported a high correlation of ASD with season of birth or the occurrence of viral epidemics. Since then, maternal viral and bacterial infections, and autoimmune diseases have been shown to be associated with the development of ASD.

Prenatal exposure to rubella (Chess, 1971, 1977; Stubbs, 1976), herpes simplex virus (DeLong et al., 1981; Ghaziuddin et al., 1992; Gillberg, 1986; Greer et al., 1989), cytomegalovirus (Ivarsson et al., 1990; Markowitz, 1983; Stubbs, 1978; Yamashita et al., 2003), measles (Ring et al., 1997; Singh and Jensen, 2003) or viral meningitis (Barak et al., 1999; Ring et al., 1997) greatly increases the risk for ASD. This led to the claim that prenatal viral infection is the principal nongenetic cause of autism (Ciaranello and Ciaranello, 1995). Analysis of all children born in Denmark between 1980 and 2005 showed an increased risk for ASD when mothers were hospitalized for viral infections during the first trimester of pregnancy or for bacterial infections during the second trimester (Atladottir et al., 2010). History of maternal autoimmune diseases has also shown association with ASD (Comi et al., 1999). Maternal rheumatoid arthritis or maternal diagnosis of celiac disease increase the risk of ASD in their children (Atladottir et al., 2009), suggesting that prenatal exposure to maternal antibodies or maternal immune alterations can affect the fetal development.

How can infection or autoimmune diseases affect brain development and function? First, maternal immune system activation might affect the normal function of the placenta (altered blood flow for example). Placental pathology (trophoblasts inclusions) has also been associated with autism (Anderson et al., 2007). Second, sera of some mothers of children with ASD present antibodies against CNS proteins, both during gestation and after birth (Braunschweig et al., 2008; Croen et al., 2008; Dalton et al., 2003). Antibodies, particularly IgGs, can be transported across the placenta into the fetal circulation (Malek et al., 1997). Although the blood–brain barrier (BBB) does restrict the passage of antibodies from the circulation into the brain, it is unknown how permeable the developing BBB is to antibody or how factors such as cytokines can facilitate the passage of antibodies across the fetal BBB (Abbott et al., 2010; Saunders et al., 2000). In fact, injection of purified anti-brain IgGs obtained from ASD mothers into pregnant rhesus monkeys resulted in infant monkeys that showed behavioral alterations similar to ASD: stereotypical behaviors and hyperactivity (Martin et al., 2008). So maternal antibodies may reach the fetal brain in some circumstances, alter neural development and affect the behavior of the offspring—at a time point when the fetal immune system is very underdeveloped.

Finally, both viral and bacterial infections and autoimmunity result in increased activation of the maternal immune system. Studies using animal models have contributed to understanding how maternal immune activation (MIA) can affect fetal brain development (see below and Patterson, 2002). MIA alters not only the levels of specific cytokines in the maternal serum, but also in the placenta and in the fetal brain. During development, cytokines and chemokines are expressed at very low levels in the brain, playing a role in neuronal and glial cell migration, differentiation and synaptic maturation (Merrill, 1992). The increase in the levels of certain, specific brain cytokines and/or chemokines in the maternal blood upon MIA could then reach the fetal brain and affect brain development at different levels. For instance, perinatal complications result in increased concentration of IL-1β, IL-6 and TNF-α in the chord blood (Miller et al., 1990; Yoon et al., 1995). It has been reported that the levels of IL-1β in the cord blood are highly predictive of the neurological outcome of newborns that were exposed to neonatal hypoxia (Aly et al., 2006; Liu and Feng, 2010). In addition, a recent study showed increased amniotic fluid levels of the chemokine MCP-1 in ASD (Abdallah et al., 2012). It has been shown using animal models of MIA that the maternal inflammatory response can affect the normal early programming of different behaviors, including sociability, communication and the regulation of stereotypic behaviors (see below); a similar effect on the human brain could be expected (Fig. 1).

Because brain development continues after birth, postnatal infections and postnatal immune activation can also affect neuronal maturation and survival. Extrapolating from the rodent studies (see below), it would be reasonable to expect that early life stimulation of the newborn's immune system can have profound effects on the development and establishment of behavior. However, only few reports on the occurrence of postnatal and early life infections in children later diagnosed with ASD have been published. A study in California found no differences in the overall rate of infections during the first 2 years of life between children diagnosed with ASD and control subjects (Rosen et al., 2007). However, children later diagnosed with ASD were more likely to suffer an infection during the first month of life. A recent report also shows lack of association between early life infections and ASD diagnosis in a Danish population (Atladottir et al., 2012), although in this case the analysis was performed during the first 6 months of life or between 6 and 19 months. More studies are needed to identify whether there is a postnatal period in human development when an infection and/or the host inflammatory response to different pathogens can affect the normal development of the brain structures determining social behavior.

Animal models of perinatal inflammation

Maternal immune activation

Different approaches have been used to study the effects of maternal inflammatory processes on fetal brain development (Depino, 2006): infection with human influenza virus (Fatemi et al., 1999, 2002, 2008; Shi et al., 2003, 2009), use of synthetic dsRNA, poly(I:C), to mimic viral infection (Meyer et al., 2006; Shi et al., 2009; Smith et al., 2007), or injection of lipopolysaccharide (LPS) to mimic bacterial infection (Ashdown et al., 2006; Golan et al., 2005; Graciarena et al., 2010). These stimuli lead to alterations in placental and amniotic fluid cytokines, but also alter the levels of IL-1β, IL-6, TNF-α, IFN-γ and TGF-β1 in the fetal and neonatal brain (Ashdown et al., 2006; Cai et al., 2000; Golan et al., 2005; Graciarena et al., 2010; Meyer et al., 2006). Moreover, prenatal inflammation can have profound long-term effects on the offspring behavior.

In the recent years different behavioral assays were developed and tested to evaluate social responses, communication, restricted interests and repetitive behaviors in mice, in order to model the core symptoms of autism (Crawley, 2007). Using these behavioral paradigms, it has been shown that MIA affects ASD-like behaviors. For example, intranasal infusion of human influenza virus on gestational day (GD) 9.5 resulted in reduced sociability in mice (Shi et al., 2003). Intraperitoneal injection of poly(I:C) at GD12.5 resulted in heightened anxiety and in deficits in social interaction in the mouse, an effect mediated by IL-6 (Smith et al., 2007). Injection of poly(I:C) at GD17 resulted in perseverant behavior in the adult offspring

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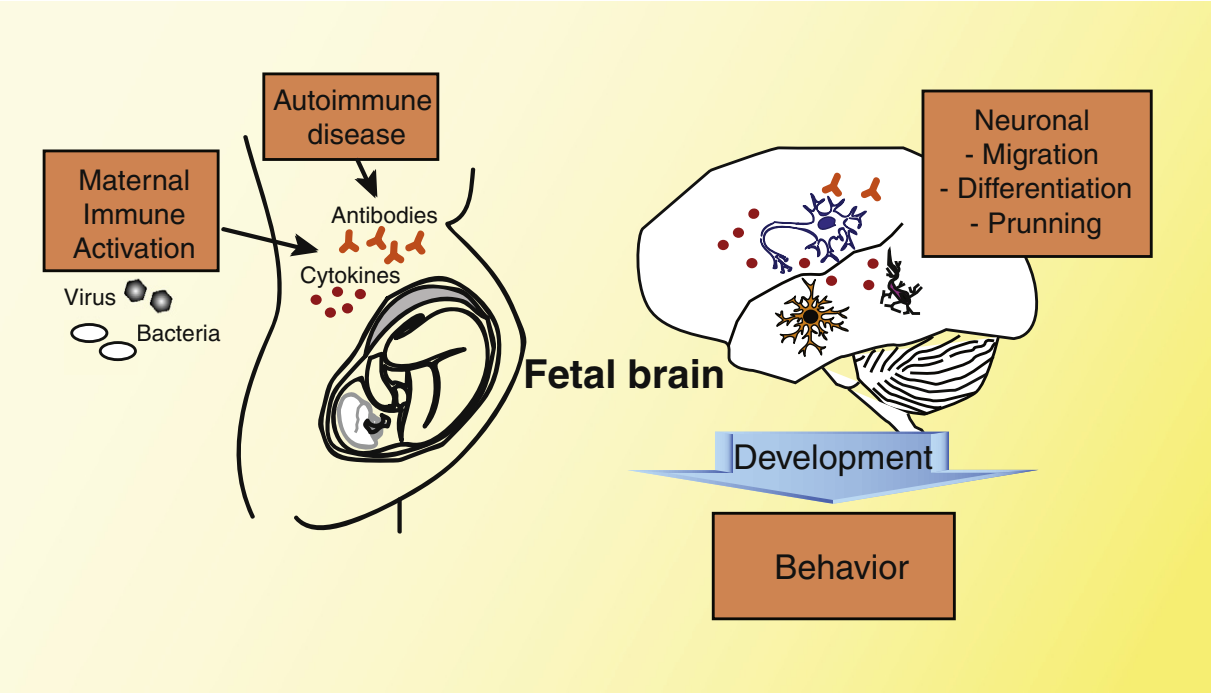

Fig. 1. Early inflammation as an etiological hypothesis for ASD. Increased levels of cytokines and/or antibodies in the maternal circulation accompany maternal immune activation or maternal autoimmune diseases. These proteins can either directly enter into the fetal brain parenchyma or elicit a cascade of events in the placenta, the fetal blood and the fetal brain tissue that lead to the secretion of cytokines by fetal astrocytes and microglia. Cytokines can affect neuronal development, acting on migration, differentiation and pruning processes. This altered development could result in abnormal behavior later in life.

(Meyer et al., 2006), an alteration that was not observed when the inflammogen was injected at GD9. This behavior has homology to the reduced behavioral flexibility observed in ASD patients. The different long-term behavioral effects of MIA at different gestational ages show that different behaviors have different temporal windows of susceptibility. Indeed, a recent report showed that MIA through the injection of poly(I:C) at GD10.5, 12.5 and 14.5 affects the behavior of the offspring later in life, resulting in reduced sociability and increased stereotypic behavior, showing a wider ASD-like behavior (Malkova et al., 2012). This and other similar models using different inflammatory stimuli can be useful to guide the search for the mechanisms underlying this kind of prenatal programming of behavior.

In addition, MIA in rodents resulted in molecular and cellular alterations homologous to those found in ASD, such as a spatially restricted deficit in Purkinje cells (Amaral et al., 2008; Palmen et al., 2004). Different MIA models showed persistence of neuroinflammation or long-term alterations in the immune system of the offspring (Graciarena et al., 2010; Hsiao et al., 2012; Mandal et al., 2011; Samuelsson et al., 2006), recapitulating the dysfunctions in the immune system frequently observed in ASD patients (see below). Therefore, these models could also be useful to study whether and how these persistent alterations of immune function contribute to the signs of ASD (see below).

Postnatal inflammation

Studying the neonatal rodent brain, it was shown that two developmental features that are found in human premature neonates – the discontinuous temporal organization of the cortical activity and the "immature" patterns of activity that precede the activity-dependant maturation of cortical and hippocampal circuits – are also present in the neonatal rat and mouse brain (Khazipov et al., 2004; Leinekugel et al., 2002). Owing to the temporal differences in the maturation of the brain regions in rodents and humans (Rodier, 1980), it was suggested that for certain regions of the brain such as the cortex the neonatal mouse is a better model for events occurring at the fetal stage in humans (Khazipov and Luhmann, 2006). We and other groups have studied the effects of administering inflammatory stimuli directly into the newborn, at different postnatal ages (Lucchina et al., 2010; Shanks et al., 2000).

In mice, injection of LPS at postnatal day 3 (PD3) increased their anxiety and risk assessment behavior in adulthood and reduced the HPA axis response to LPS, resulting in less plasma corticosterone 2 h after injection (Lucchina et al., 2010), showing a long-standing effect on both behavior and the response to inflammatory stimuli. Injection of LPS at PD5 increased the reactivity to social stimulation later in life—LPS-exposed animals showing a startle response, jumping or kicking, in response to the partner (Granger et al., 1996). In the rat, injecting LPS at PD4 increased the levels of IL-1β in the hippocampus and the parietal cortex, and leads to contextual long-term memory impairment after a LPS challenge in adulthood (Bilbo et al., 2005). LPS-treatment at PD5 resulted in increased or decreased social exploration, depending on the amount of care received postnatally: LPS-treated neonates that received more nursing developed as adults showing more propensity to explore new partners than those that received less care (Hood et al., 2003).

As for MIA, postnatal inflammation can also alter the programming of social behavior. Whether the cellular and molecular mechanisms that mediate these long-term behavioral effects are similar after pre- and postnatal inflammation, needs to be further studied. Such studies could further contribute to understanding the etiological factors that contribute to ASD.

Effects of peripheral and central inflammation on the pathophysiology of autism

Clinical evidence of chronic inflammation in ASD

Clinical and postmortem data show that in ASD inflammatory processes are not restricted to the perinatal period, and probably remain altered throughout ASD pathology. Chronic inflammatory diseases and the abnormal response to infection of different blood cell populations have been described in ASD children and adults. ASD patients suffer from chronic gastrointestinal disturbances (Hornig et al.,

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2008; Parracho et al., 2005; Wang et al., 2011), and peripheral blood mononuclear cells and lymphoblasts from ASD children produced excessive proinflammatory cytokines (IL-1β, IL-6 and TNF-α) both basally (Malik et al., 2011) and after LPS stimulation (Jyonouchi et al., 2001) when compared with controls. Astrogliosis and microglial activation, along with increased expression of cytokines in different regions of the autistic brain at different ages show that ASD patients present an altered neuroinflammatory response through their lives. ASD patients show increased astro- and microgliosis in the cortex and the cerebellum (Morgan et al., 2010; Vargas et al., 2005). Moreover, increased expression of IL-6, TNF-α, MCP-1, TGF-β1, IFN-γ, IL-8 and other genes associated with the immune response have been reported in those brain regions and in the cerebrospinal fluid (Chez and Guido-Estrada, 2010; Chez et al., 2007; Garbett et al., 2008; Li et al., 2009; Vargas et al., 2005). Thus aberrant inflammatory processes may be an ongoing etiological factor in ASD that might affect behavior and other symptoms throughout the life of a patient (Fig. 2).

This raises the question as to how a disease initiated early in life can result in long-lasting alterations of the immune response? It is possible that chronic viral infections might give rise to such modifications. Polyomaviridae can be vertically transmitted from the mother to the fetus, and reach the developing brain owing to its neurotropism. In

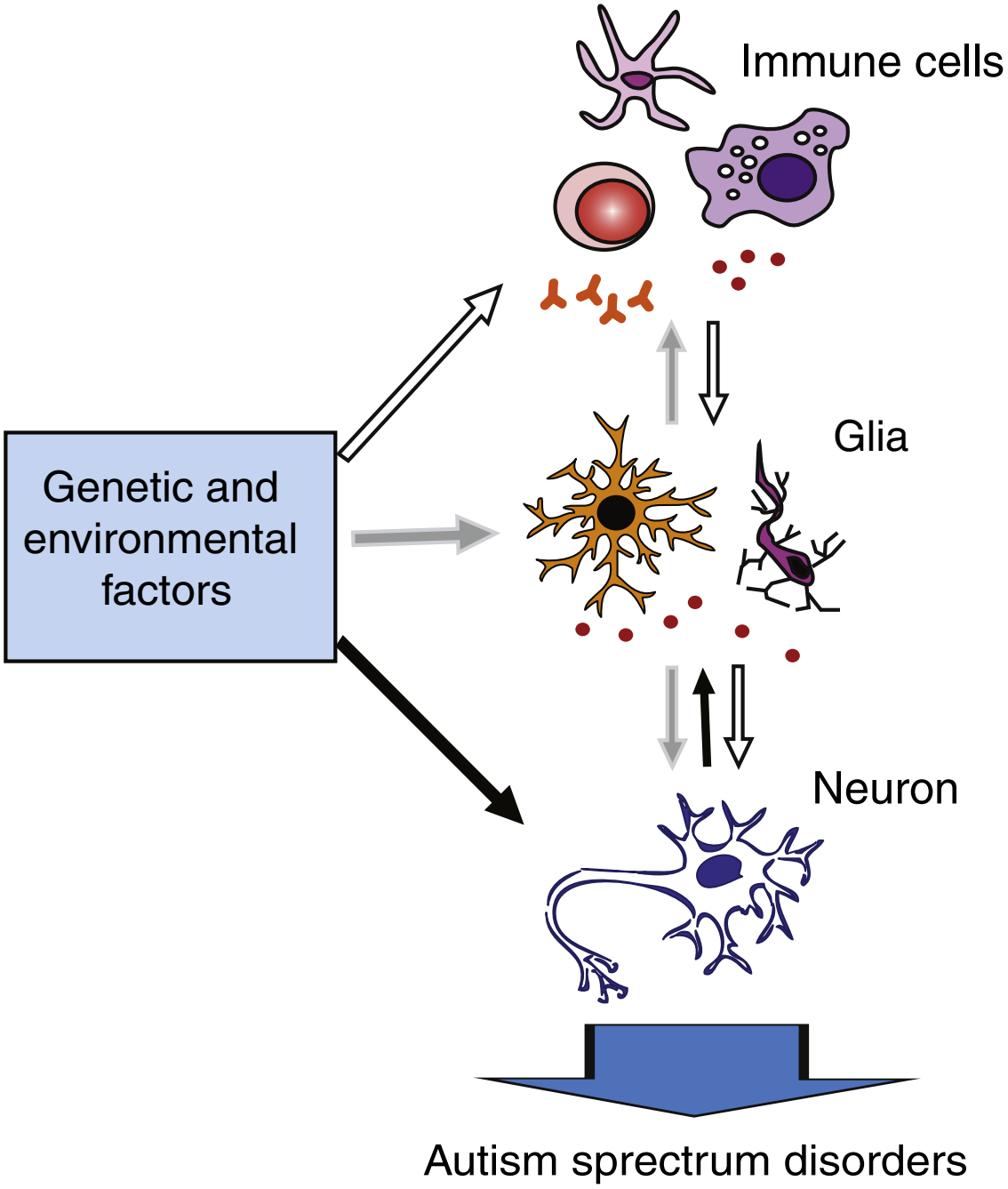

Fig. 2. Role of inflammation on modulating ASD symptoms. Chronic neuroinflammation can be directly elicited by genetic and environmental factors and modulate neuronal function and the immune response (gray arrows). Alternatively, perinatal factors could alter the peripheral immune response chronically, which would in turn activate glial cells, and then affect the physiology of neurons (white arrows). Finally, genetic and environmental factors could directly affect neuronal function and this result in chronic neuroinflammation (black arrows). In all these scenarios neuroinflammation would modulate neuronal function at different ages in ASD.

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fact, Polyomaviridae infections have been detected in the neocortex of autistic patients (Lintas et al., 2010), and, although not reported in that study, they could cause chronic inflammation in the brain. Other chronic viral and bacterial infections could underlie the chronic inflammatory status observed in ASD patients. Indeed, there is unlikely to be one sole causal agent. For example, both virus and bacteria have been associated with the high incidence of gastrointestinal problems observed in ASD. Measles virus has been associated with different gastrointestinal diseases, including ileal lymphonodular hyperplasia and enterocolitis (Uhlmann et al., 2002). Although other studies were not able to replicate this association (D'Souza et al., 2007; Hornig et al., 2008), these studies led to the description of an increased prevalence of gastrointestinal problems in children with ASD (Hornig et al., 2008; Wang et al., 2011). Analysis of the gut flora has shown that patients with ASD present a higher incidence of Clostridia, toxin-producing bacteria, than control groups (Parracho et al., 2005). When the intestinal mucosa barrier is compromised, bacteria can translocate from the gut to the circulation. The analysis of serum levels of endotoxin in severe autism patients showed a significant increase in the concentration of endotoxin units when compared to healthy volunteers (Emanuele et al., 2010). Interestingly, the authors showed that endotoxin levels could predict the scores obtained by the patients in the Socialization Domain.

Children with ASD that have anti-measles or anti-human herpes virus antibodies also presented anti-CNS antibodies (anti-myelin basic protein and anti-neuron-axon filament protein antibodies) that were not observed in control sera (Singh et al., 2002, 1998). Although it is not clear how these antibodies could contribute to the pathogenesis of ASD, evidence coming from autoimmune diseases such as Systemic Lupus Erythematosus (SLE), Sydenham's chorea and other pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) shows that the presence and titer of anti-CNS antibodies correlate with neuropsychiatric symptoms (Libbey and Fujinami, 2010). More research is still needed to identify the pathobiologic processes and biologic activity of these anti-CNS antibodies and how they could affect behavior.

Alternatively, long-lasting alterations in the immune response can be independent of chronic infections or autoimmune disorders, but actually reveal an abnormal immune system. Some reports show that ASD patients present with elevated serum levels of IL-1, IL-6, IL-1ra and sTNFRII (Croonenberghs et al., 2002; Suzuki et al., 2011; Zimmerman et al., 2005). Studying the expression patterns in the lymphocytes of ASD patients and nonaffected siblings showed differential patterns in genes related to inflammation and neurodevelopment (Hu et al., 2009). Peripheral blood mononuclear cells from ASD patients secrete higher levels of TNF-α, IL-6 and IL-1β than controls (Jyonouchi et al., 2001; Malik et al., 2011). But they also secrete higher levels of IL-1ra, sTNFRI, and sTNFRII, molecules that limit the inflammatory response, along with the anti-inflammatory cytokine IL-10 (Croonenberghs et al., 2002; Jyonouchi et al., 2001). Moreover, upon their stimulation with LPS or other Toll-receptor ligands, monocytes from ASD patients showed aberrant innate immune responses, with excessive production of proinflammatory cytokines (Enstrom et al., 2010; Jyonouchi et al., 2002). These heterogeneous data suggest that the immune alterations in ASD are complex, comprising a pro-inflammatory state and an altered anti-inflammatory response, which would probably result in abnormal temporal patterns of immune activity.

The persistent pro-inflammatory status observed in ASD might have a genetic basis. For example, a polymorphism in the gene coding for the tyrosine kinase receptor MET increases the risk for autism and is a negative regulator of immune responses (Enstrom et al., 2010). On the other hand, immune alterations could represent a long-term maladaptation to early events, which could be mediated by epigenetic modifications of cytokine promoters, altered receptor signaling or other still unknown mechanisms. Evidence from laboratory animals shows indeed that early peripheral or maternal immune activation can lead to long-term alterations in the immune response and in glial activation status (Boisse et al., 2004; Graciarena et al., 2010; Lucchina et al., 2010; Shanks et al., 2000; Williams et al., 2011).

The chronic alterations in the inflammatory and immunological responses in patients with autism suggest that this can constitute an endophenotype for ASD. Exploring this hypothesis, Saresella studied autistic children and their healthy siblings in comparison with healthy children (Saresella et al., 2009). Results show that both autistic children and their siblings present similar immune dysregulation, suggesting that this could indeed constitute an endophenotype. However, the genetic or epigenetic mechanisms underlying this endophenotype are still not clear and still need to be investigated. Interestingly, these findings could also signify that previous studies comparing autistic patients with their healthy siblings would actually hide interesting phenomena, common to both groups. Those results should be revised in light of these new findings.

How can these chronic alterations of the immune response affect behavior? Peripheral cytokines are known to affect different behaviors, including sickness behavior and depression (reviewed in Konsman et al., 2002). Evidence shows that they do so by increasing the expression of cytokines into the brain. Because both the neuroinflammatory processes and the increased immune response observed in ASD would comprise high levels of cytokines in the brain, these proteins could affect behavior. However, whether the high peripheral and/or central cytokine expression and the inflammatory response observed in ASD are responsible of some of the behavioral symptoms of the disorders remains to be clarified. Interestingly, it was shown that fever reduces irritability, hyperactivity, stereotypical behaviors, and inappropriate speech in ASD patients, an effect that is not a function of illness severity (Curran et al., 2007). Behavioral changes could be a direct consequence of fever, but they could also result from high cytokine levels. Chronic treatment of Hepatitis B or C viral infection with IFN-α often results in depression (Myint et al., 2009), a disorder that shows high comorbidity with ASD. Similar effects are observed when IL-2 is used to treat certain cancers. So peripheral cytokines, when chronically augmented, can have profound, long-term effects on human behavior, even resulting in neuropsychiatric disorders. Although we have no data on the behavioral effects of physiological chronic increments of cytokines in humans, data from rodent models suggest that cytokines could indeed affect ASD behavioral symptoms.

Effect of peripheral and central inflammation in juvenile and adult animals on ASD-like behavior

In the last decades, the behavior associated with sickness and disease has been well characterized. Proinflammatory cytokines, such as IL-6, TNF, and IL-1, are known to be key factors in the generation of reprioritized behaviors. The difference between sickness behaviors and ASD-like behaviors is, quite clearly, that ASD is chronic and seemingly irreversible. ASD-like behaviors that are similar to sickness behaviors include reduced social interaction, increased stereotypical behaviors and depression. Considering the persistent high expression of cytokines observed in ASD patients, it would be relevant to evaluate whether peripheral cytokines can affect ASD-like behaviors.

Peripheral inflammation reduces the levels of social exploration in laboratory rodents (Bluthe et al., 1994) and certain cytokines can mediate this effect. For example, both peripheral and central IL-1 reduce social exploration in the mouse (Bluthe et al., 2000; Konsman et al., 2008), and this effect is at least partially dependant on IL-6 expression. Central IL-4 expression appears to have a dual effect on the reduced social exploration observed after peripheral LPS injection: it further reduces social exploration when it is co-administered with LPS, but it attenuates the effect of LPS when it is injected 12 h before (Bluthe et al., 2002). IL-4 is regarded by many as an anti-inflammatory cytokine and counteracts the activities of proinflammatory cytokines, but, in regard to behavior, it seems that it cannot be assumed that

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proinflammatory cytokines will induce sickness behavior and anti-inflammatory cytokines will abrogate the response. Whether persistent cytokine expression, of any type, can result in reduced sociability through the same mechanisms that are involved during sickness behavior acutely is currently unknown. Models in which chronic cytokine expression, and specific inhibition, is achieved are required to shed light on the mechanisms involved in modulating long-term alterations in social behavior and may help to identify other behaviors that might serve to support the link between ASD and aberrant cytokine expression.

As a developmental disorder, it is not surprising that most animal models of ASD have been designed to recapitulate this characteristic. Only few reports have studied the effects of juvenile or adult activation of the immune system on behaviors related to ASD. Recently, it was shown that the BTBR mouse strain, which shows an autism-like phenotype when compared with other strains (i.e. reduced sociability and increased repetitive behavior Moy et al., 2007), present anti-CNS antibodies and neuroinflammation (Heo et al., 2011). It has yet to be determined whether these immune alterations are actually generated the ASD-like behavior or whether they are the result of another, unidentified component. Studies of neuroinflammation reported scattered effects on behavior, and a comprehensive battery of tests that would model ASD symptoms are lacking on these experimental paradigms (Moy and Nadler, 2008; Moy et al., 2007). To our knowledge, only neuroinflammation by intracerebroventricular (icv) injection of propionic acid and overexpression of TGF-β1 in the hippocampus have been evaluated as inflammatory rodent models of ASD, both showing high face validity.

Propionic acid (PPA) is an intermediary of cellular fatty acid metabolism that is present in a variety of foods. It is present in high concentration in the gut and is the major metabolic end product of enteric bacteria. It readily crosses lipid membranes, including the gut–blood barrier and the BBB. Because PPA is augmented during the gastrointestinal infections that are often observed in ASD, different groups have tested the effects of increasing peripheral or central PPA levels on ASD-like phenotypes in rodents. Intracerebroventricular (icv) injections of PPA into adult rats induced neuroinflammation, impaired social behavior, caused seizures, and resulted in repetitive and abnormal motor movements (MacFabe et al., 2007; Shultz et al., 2009, 2008). Also when PPA is injected in juvenile rats, neuroinflammation is observed in the hippocampus and animals show reduced social behavior and impaired reversal learning (MacFabe et al., 2011). This evidence provides support for the face validity of adult PPA treatment as a rat model of ASD. However, whether these effects are specific to PPA treatment or whether they might be generic and observable with other proinflammogens applied icv, remains to be determined.

Following the observation by Vargas et al. (2005) who showed that TGF-β1 levels were elevated in the autistic brain, we examined the role of TGF-β1 in the rodent brain in modulating behaviors (Depino et al., 2011). As the human studies showed that TGF-β1 was augmented in the ASD brains post mortem, we evaluated the effect on behavior of overexpressing this cytokine in the adult mouse hippocampus. Surprisingly, we found that this treatment resulted in increased sociability and reduced repetitive behavior (self-grooming), showing a phenotype that appeared opposite to expectations. This led us to speculate that the elevated TGF-β1 might be a homeostatic response to the autistic phenotype. However, when we overexpressed TGF-β1 in the postnatal hippocampus (starting at PD14) and tested the animals in adulthood, TGF-β1 treated mice showed reduced sociability and increased repetitive behavior, showing an ASD-like phenotype. Moreover, these mice showed increased depression-related behavior, a symptom commonly observed in ASD.

The studies discussed here support the existence of windows in human development when neuroinflammation in early life might induce ASD-like behaviors in adulthood. These studies also reveal the difficulties associated with investigating the link between cytokine expression and ASD when the same cytokine can have opposite effects during development. Future research is required to identify other cytokines that might affect perinatal programming of adult behaviors, but it is clear that conditional mutants will be needed to explore the existence of these windows.

Conclusions

In light of the recent findings, studies on ASD have now become more focused on environmental factors. Remarkably, most proposed perinatal factors seem to converge on immune activation. As reviewed here, cytokines appear to have an important role in programming behavior and they have the ability to access the brain at different ages to affect brain development and function. Identifying critical periods, the specific cytokines involved, and, most importantly, how the architecture of the brain is affected by these factors is essential to enable the development of preventive and curative treatment strategies.

A recent open-label clinical trial showed that treatment with the anti-inflammatory drug minocycline resulted in significant behavioral improvement in Fragile X syndrome patients (Paribello et al., 2010). Whether these results were attributable to the anti-inflammatory action of minocycline or to other effects of this drug need further clarification, but this study opens the possibility of treating the immune system in neurodevelopmental disorders. The availability of different mouse models of Fragile X syndrome has been critical to the design of these clinical trials (Bilousova et al., 2009). Advances in modeling ASD in rodents are urgently needed to understand the role of peripheral and central inflammation both at the etiology of the disorder and in the pathophysiology.

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