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Perinatal Immune Activation and Risk of Autism

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1. Introduction

He could fit in the palms of both hands, seemed to look at you beseechingly while you rushed to thread a vein and snake a tube down a tiny nostril of this 24 week preemie. Already exposed to the prenatal stress that culminated in premature delivery, he has been further exposed to the stress associated with the separation from his mother and multiple medical interventions. Like other premature babies, he is more vulnerable to invasive infections from bacteria and viruses; moreover, the delayed development of his gut-blood-brain barriers could expose him to potential neurotoxins.

Such infants are up to 4 times more likely to develop autism. If their mothers had allergies, mastocytosis or an autoimmune disease, this risk almost doubles.

Autism Spectrum Disorders (ASD) are pervasive developmental disorders that include Autistic Disorder and Asperger's Disorder, although Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) is frequently included (Johnson & Myers, 2007). ASD are characterized by variable deficits in social skills, stereotypic behaviors, and a wide range of behavioral and learning problems. ASD manifest during early childhood and at least 30% present with sudden clinical regression of development around 3 years of age (Matson J.L. & Kozlowski A.M., 2010; Zappella, 2010). Over the last 20 years, there has been an impressive rise in ASD with current prevalence estimates of 1/100 children (Fombonne, 2009; Kogan et al., 2009).

In the majority of cases, the cause of ASD is unknown (Levy et al., 2009). Some autism susceptibility genes have been identified (Weiss et al., 2009), but gene interactions with environmental factors are increasingly suspected (Deth et al., 2008; Herbert, 2010). Recent reviews have focused mostly on genomic screens that suggest there are multiple gene interactions in autism; however no gene abnormality alone can explain the apparent increase in ASD prevalence (Durkin et al., 2010; Herbert, 2010; Miles, 2011). Increasing evidence suggests that there are different ASD endophenotypes, even within the ASD spectrum (Palmieri & Persico, 2010).

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Intrauterine conditions in combination with external environmental triggers or specific genotypes, may lead to developmental disturbances. Indeed, an epidemiologic study, nested within a cohort of 698 autistic children in Denmark, concluded that prenatal environmental factors and parental psychopathology are associated with the risk of autism and these factors seem to act independently (Larsson et al., 2005). It is also recognized that tuberous sclerosis, a neurocutaneous disorder, involves autistic symptoms in approximately 40-45% of cases (Smalley, 1998). It has been proposed that this partial penetrance may be the result of an interaction between gene mutations and environmental factors, such as gestational immune activation (Ehninger et al., 2010). An early environmental insult, such as prenatal infection could cause long-term changes in neural function by altering epigenetic programming. Studies on rodents suggest that during early development, environmental signals can activate intracellular pathways, leading to epigenetic changes and consequently changes in neural function (Zhang & Meaney, 2010). In fact, variations in early maternal care affect stress responses in the offspring by altering the methylation status of the glucocorticoid receptor gene promoter (Weaver et al., 2004).

2. The role of prematurity

Premature births (delivery prior to 37 weeks gestation) currently account for 12.7% of all births in the United States, a rise of approximately 20% in the past two decades (MacDorman et al., 2010). Although infants less than 28 weeks gestation are at the highest risk for long-term neurologic problems, infants born between 32 and 36 weeks are increasingly recognized to be at risk for neurologic injury, such as leukomalacia and gray matter damage (Adams-Chapman, 2006; Argyropoulou, 2010; Okumura et al., 2010; Volpe, 2009). Clinical, epidemiological and experimental studies have revealed that key factors, such as inflammation and oxidative stress contribute considerably to white- and grey-matter injury in premature infants, whose brains are particularly susceptible to damage (Kaindl et al., 2009). In infants surviving premature birth, cerebellar hemorrhagic injury is also associated with a high prevalence of neurodevelopmental disabilities (Limperopoulos et al., 2007). The resulting long-term neurologic complications may include learning difficulties, behavioral and socio-emotional concerns, and poor general health outcomes. These vulnerable near-term (late preterm) infants make up the greatest number of premature births and account for the significant increase in the rate of prematurity in the recent years (Martin, 2011). Although the etiology of premature delivery is often unknown, chronic *in utero* inflammation or infection are well-described conditions that lead to preterm labor and birth (Dubicke et al., 2010; Snegovskikh et al., 2009; Thaxton et al., 2010). Inflammation itself has been strongly associated with adverse neurodevelopmental outcomes in premature infants (Lin et al., 2010; Rovira et al., 2011). An additional 5-8% of deliveries are complicated by pre-eclampsia or gestational diabetes, which may lead to placental insufficiency, abnormal growth, and postnatal metabolic imbalance. Excessive production of cortocotropin releasing hormone (CRH) has also been linked to preterm labour (Campbell et al., 1987; Warren et al., 1992). A number of cytokines are known to cause in vitro secretion of CRH from cultured placental trophoblasts, including IL-1 and IL-6 (Petraglia et al., 1990). In turn, CRH stimulates release of IL-6 from peripheral blood mononuclear cells, which infiltrate the fetal membranes and the placenta in increasing numbers during intrauterine infection (Angioni et al., 1993).

Recent reports suggest a potential association between preterm birth and autism. In particular, one retrospective study investigated preterm children born in Atlanta, GA (1981-93) who survived to three years of age, and identified rates of autism through the

Metropolitan Atlanta Developmental Disabilities Surveillance Program. Preterm birth prior to 33 weeks gestation was associated with a two-fold higher risk of autism in all infants (Limperopoulos et al., 2008). Interestingly, this study reported a gender-specific, four-fold increased risk for autism accompanied by mental retardation in preterm girls with low birth weight (LBW) (<2500 g at birth). Another study performed a prospective follow-up assessment on 91 ex-preterm very low birth weight (VLBW) infants (<1500 g at birth) at the mean age of 22 months and found 26% of these children to have a positive Modified Checklist for Autism in Toddlers (M-CHAT) test (Kinney et al., 2008). A more recent study found that 21% of infants (212/988) born before 28 weeks of gestation screened positive using M-CHAT (Kuban et al., 2009) as compared to 5.7% of healthy children 16-30 months old (Kleinman et al., 2008). Much higher rates of positive testing on M-CHAT were found in premature children with motor or sensory impairment (Kuban et al., 2009). It should be noted, however, that a positive CHAT test must be confirmed with more specific diagnostic tools, such as the Autism Diagnostic Observation Schedule-Generic (ADOS-G, a patient observational tool) or the Autism Diagnostic Interview-Revised (ADI-R, a parent interview tool) which provide a more reliable diagnosis for ASD. A prospective study of all births less than 26 weeks gestation in 1995 in the United Kingdom and Ireland concluded that ex-preterm children are at increased risk for ASD in middle childhood, compared with their term-born classmates, after psychiatric, clinical, IQ and SCQ (Social Communication Questionnaire) evaluations (Johnson et al., 2010).

A cohort of 164 families with autistic children (Brimacombe et al., 2007) concluded that the increased risk of autistic disorders related to prematurity is primarily attributed to perinatal complications that occur more commonly among preterm infants, results also confirmed in a Swedish population-based case-control study (Buchmayer et al., 2009). A meta-analysis on prenatal risk factors for autism argued that evidence is insufficient to implicate individual prenatal factors in autism etiology, because many of the studies examined all available prenatal data using designs with methodological weaknesses, so that significant associations may have been observed by chance after multiple testing (Gardener et al., 2009). Findings from population-based studies suggest that suboptimal birth conditions are not independent risk factors for infantile autism, but rather clusters of them increase the risk of ASD (Maimburg & Vaeth, 2006). Finally, a more recent cohort study on infants born in Canada between 1990-2002 concluded that perinatal risk factors including prenatal, obstetrical and neonatal complications, have a lesser overall effect on autistic outcomes among the genetically susceptible pediatric population, compared to children with low genetic susceptibility (Dodds et al., 2010). Reviews of studies evaluating neurobehavioral outcomes following preterm birth reveal a "preterm behavioral phenotype" characterized by symptoms of inattention, anxiety and social difficulties (Johnson & Marlow, 2011; Limperopoulos, 2009).

3. Maternal autoimmune diseases

The relationship between ASD and familial autoimmunity has long been recognized (Money et al., 1971), and has been supported by at least three large population-based studies discussed below; these studies utilized medical records and physician data to determine autoimmunity in families of ASD and typically-developing children.

One case-control study nested within a cohort of infants born in California between 1995-1999, examined the association of "immune-related conditions" with ASD using health records and reported that prevalence of maternal psoriasis, asthma, hay fever and atopic dermatitis during

the second trimester of pregnancy correlated with over two-fold elevated risk of ASD in their children (Croen et al., 2005). The second cohort consisted of the pediatric population born in Denmark from 1993 through 2004 (n=689,196), in which 3,325 children were diagnosed with ASD including 1,089 cases of infantile autism. The study confirmed an association between family history of type 1 diabetes and infantile autism, as well as rheumatoid arthritis and ASD; it was also the first to show a significant association between maternal celiac disease and ASD (Atladottir et al., 2009). A significant association between parental rheumatic fever and ASD, as well as several significant correlations between maternal autoimmune diseases and ASD were investigated across 3 Swedish registries by means of a case-control study (n=1,227 ASD cases matched with 25 controls each) (Keil et al., 2010). Auto-antibodies against brain proteins have been reported in a number of mothers with children who developed autism (Croen et al., 2008). A possible explanation for the link between maternal immune dysregulation and ASD would be the transfer of maternal autoantibodies to the developing fetus during pregnancy (Braunschweig et al., 2008; Croen et al., 2008; Singer et al., 2008; Zimmerman et al., 2007), resulting in abnormal neurodevelopment. This phenomenon was manifested in the offsprings of pregnant mice after their transfection with human systemic lupus erythematosus autoantibodies (Lee et al., 2009). A preliminary report also indicated that mothers with a diagnosis of mastocytosis during pregnancy had a high chance of having one or more children with autism (Theoharides, 2009).

Results from animal modeling studies clearly indicate that maternal immune activation (MIA) can cause both acute and lasting changes in behavior and CNS structure and function in the offspring (Boksa, 2010). Administration of bacterial lipopolysaccharide (LPS), a cell wall component from Gram-negative bacteria, activates Toll-like receptor-4 (TLR-4) on immune cells leading to synthesis and release of TNF (Varadaradjalou et al., 2003), IL-1 and IL-6 (Supajatura et al., 2002). It was recently shown that IL-1 receptor antagonism prevented neurodevelopmental anomalies in pregnant rats after systemic end-of-gestation exposure to LPS (Girard et al., 2010). In addition to its direct detrimental effect on the placenta and fetal brain tissue, IL-1 induces selective release of IL-6 from mast cells (Kandere-Grzybowska et al., 2003). IL-6 appears critical for fetal brain development and social behavior development, as demonstrated in a poly(I:C) mouse model for MIA, where co-administration of anti-IL-6 antibody prevented the social deficits and associated gene expression changes in the brain of the offspring (Smith et al., 2007).

However, human studies investigating the role of prenatal infection in the pathogenesis of autism are limited, and mostly focused on viral infections (Chess, 1977; Libbey et al., 2005; Wilkerson et al., 2002). A recent nationwide study in Denmark including children born from 1980 through 2005 points to an increased risk for ASD after maternal viral infection in the first trimester of pregnancy (adjusted hazard ratio = 2.98; CI: 1.29-7.15) or maternal bacterial infection in the second trimester of pregnancy (adjusted hazard ratio = 1.42; CI: 1.08-1.87) (Atladottir et al., 2010). Moreover, a number of rotaviruses have been isolated from asymptomatic neonates (Dunn et al., 1993). Viral double-stranded RNA like poly(I:C) induces release of TNF and IL-6 without degranulation from mast cells through viral TLR-3 (Kulka et al., 2004).

4. Autoimmunity in ASD children

A recent study implied the presence of an endophenotype with complex immune dysfunction is present both in autistic children and their non-autistic siblings (Saresella et al., 2009). Brain-

specific auto-antibodies are present in the plasma of many ASD individuals (Cabanlit et al., 2007; Singh et al., 1997; Singh & Rivas, 2004). Such auto-antibodies suggest a loss of self-tolerance to neural antigens during early neurodevelopment, but their precise role in autism remains unknown (Enstrom et al., 2009; Mostafa et al., 2008; Mostafa & Kitchener, 2009; Wills et al., 2007). They may indicate disruption of the blood-brain barrier (BBB), at least in a subgroup of patients. The presence of an auto-inflammatory response is also supported by the detection of certain inflammation markers. For instance, TNF was high in the cerebrospinal fluid (CSF) (Chez et al., 2007), and IL-6 gene expression was increased in the brain (Li et al., 2009) of autistic patients. CSF and microglia of ASD patients had high levels of macrophage chemoattractant protein-1 (MCP-1) (Vargas et al., 2005), which is also a potent chemoattractant for mast cells (Conti et al., 1997). In contrast, ASD plasma levels of transforming growth factor-beta1 (TGF-β1) were low (Ashwood et al., 2008), which is important in view of the fact that TGF-β1 inhibits mast cell function (Gebhardt et al., 2005). Many children with ASD also report gastrointestinal symptoms (Buie et al., 2010). In a few studies, examination of intestinal biopsies from children with regressive autism reveals features of an autoimmune mucosal pathology, that is not seen in other conditions or inflammatory bowel diseases (Ashwood et al., 2003; Torrente et al., 2002).

Many of the epidemiologic, biochemical and pathologic findings could be explained through activation of mast cells, immune cells important in both innate and acquired immunity (Galli et al., 2005), as well as in inflammation (Theoharides & Kalogeromitros, 2006). Mast cells are well-known for their leading role in allergic reactions, during which they are stimulated by IgE binding to high-affinity receptors (FcεRI), aggregation of which leads to degranulation and secretion of numerous pre-stored and newly-synthesized mediators, including IL-6 and TNF (Blank & Rivera, 2004; Kraft & Kinet, 2007; Schroeder et al., 1995; Schwartz, 1987; Serafin & Austen, 1987; Stone et al., 2010; Torigoe et al., 1997). In addition to IgE, many substances originating in the environment, the intestine or the brain can trigger mast cell activation (Theoharides et al., 2011). These include non-allergic environmental, infectious, neurohormonal and oxidative stress-related triggers, involving release of mediators selectively, without degranulation (Theoharides et al., 2007b). For instance, LPS activates TLR-4 on mast cells and induces selective release of TNF (Varadaradjalou et al., 2003), while IL-1 induces selective release of IL-6 (Kandere-Grzybowska et al., 2003).

Environmental toxins have been implicated in developmental neurotoxicity (Grandjean & Landrigan, 2006) and also in mast cell activation. In particular, polychlorinated biphenyl (PCB) (Hertz-Picciotto et al., 2008) and mercury (Young et al., 2008) have been associated with ASD, and both also activate mast cells (Asadi et al., 2010; Kempuraj et al., 2010; Kwon et al., 2002). Other mast cell triggers include bacterial and viral antigens, as well as peptides such as neurotensin (NT), which we reported to be increased in serum of young children with autism (Angelidou et al., 2010), and to induce mast cell release of extracellular mitochondrial DNA, which was also increased in the serum of these ASD patients (Zhang et al., 2010). This finding may be in addition to mitochondrial dysfunction reported in ASD (Giulivi et al., 2010; Palmieri & Persico, 2010). Given the fact that NT activates mast cells (Theoharides et al., 2004) and abundant NT is located in the gut (Castagliuolo et al., 1996), its elevated levels might lead to gut dysfunction in a cohort of autistic patients. NT also augments the action of CRH, which stimulates selective release of vascular endothelial growth factor (VEGF) (Cao et al., 2005). In fact, CRH acts synergistically with NT to increase vascular permeability (Donelan et al., 2006).

Mast cell-derived cytokines can also increase BBB permeability (Abbott, 2000; Theoharides & Konstantinidou, 2007). BBB disruption has been documented in brain inflammatory diseases, such as multiple sclerosis, where it *precedes* any pathological or clinical symptoms (Minagar & Alexander, 2003; Soon et al., 2007; Stone et al., 1995). We speculate that perinatal mast cell activation, in response to allergic or non-immune triggers, could disrupt the gut-blood-brain barriers (Theoharides & Doyle, 2008) and permit neurotoxic molecules to enter the brain and result in brain inflammation, thus contributing to ASD pathogenesis (Fig. 1) (Theoharides et al., 2008). It is intriguing that mast cell-derived IL-9 induces intestinal permeability and predisposes to oral antigen hypersensitivity in children (Forbes et al., 2008), while it also exacerbates newborn brain toxic lesions (Dommergues et al., 2000). Moreover, IL-33 can synergize with SP (Theoharides et al., 2010) and SCF (Drube et al., 2010) in stimulating mast cell TNF release, while it also activates glial cells to secrete pro-inflammatory cytokines (Yasuoka et al., 2011). The possible involvement of mast cells (Theoharides et al., 2011) in ASD is also supported by the fact that many children with ASD report "allergic-like" symptoms (Angelidou et al., 2011).

5. Perinatal stress

Mast cells have been implicated in inflammatory conditions that worsen by stress (Theoharides & Cochrane, 2004) and in regulating BBB permeability (Esposito et al., 2002). It was shown that early life stress due to maternal separation resulted in an altered brain-gut axis; it was sufficient to cause an increase in the blood concentrations of pro-inflammatory cytokines after a challenge with LPS, and also an increase in plasma corticosterone (O'Mahony et al., 2009). The timing of prenatal stressors was investigated in a case-control study, recording mothers' reports on exposure to stressors during each 4-week block of pregnancy. A higher incidence of stressors at 21-32 weeks gestation was found in autism, in consistency with the embryological age at which pathological cerebellar changes in autism are seen (Beversdorf et al., 2005).

We propose that prenatal or perinatal stress may contribute to the development of ASD through excessive release of CRH. CRH is typically secreted from the hypothalamus, but it can also be secreted from the skin (Slominski et al., 2006) and nerve endings (Skofitsch et al., 1985), where it exerts pro-inflammatory effects (Chrousos, 1995; Slominski et al., 2001; Theoharides et al., 2008). CRH can also be released from immune cells (Karalis et al., 1997) and mast cells (Kempuraj et al., 2004). In fact, CRH released from hair follicles can trigger mast cell proliferation (Ito et al., 2010). This form of tissue CRH sometimes called "immune CRH" may have an immunomodulatory role as an autocrine/paracrine mediator of inflammation during reproduction (Kalantaridou et al., 2007). One of the early effects of immune CRH is the activation of mast cells and the release of several pro-inflammatory cytokines (Theoharides et al., 2004). CRH was increased in the serum of mothers who delivered preterm babies and correlated with their level of anxiety during that period of pregnancy (Makrigiannakis et al., 2007). Maternal serum CRH can cross the placenta, and potentially high amounts of CRH could be produced by the placenta itself in response to external or intrauterine stress (Grammatopoulos, 2008; Torricelli et al., 2011). CRH can then disrupt the BBB (Theoharides & Konstantinidou, 2007), which appears to be compromised in ASD patients, as indicated by the presence of autoantibodies against encephalogenic peptides (Cabanlit et al., 2007; Goines & Van de Water J., 2010; Singer et al., 2006; Vojdani et al., 2002; Wills et al., 2008). BBB disruption due to stress is dependent on both CRH

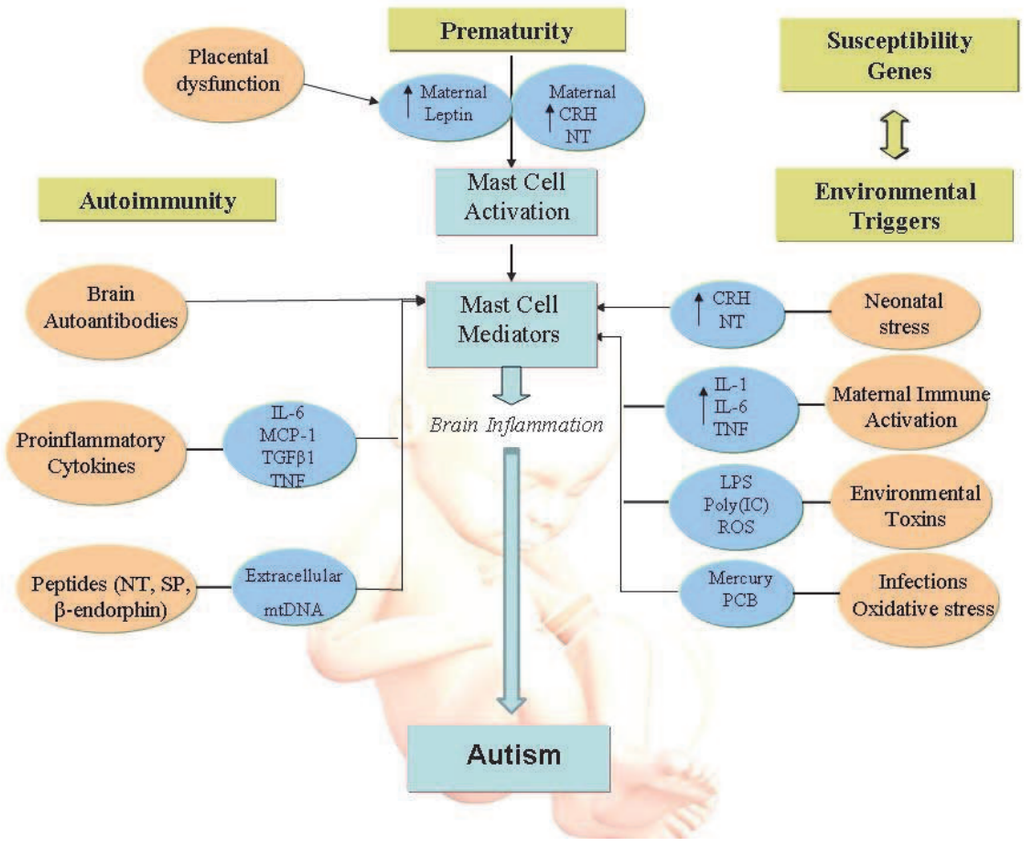

Fig. 1. Diagrammatic depiction of how perinatal immune activation may contribute to brain inflammation and autism. CRH, corticotropin-releasing hormone; IL, interleukin; LPS, lipopolysaccharide; MCP-1, macrophage chemoattractant protein-1; mtDNA, mitochondrial DNA; NT, neurotensin; PCB, polychlorinated biphenyl; poly(IC),polyinosinic:polycytidylic acid; ROS, reactive oxygen species; SP, substance P; TGFβ1, transforming growth factor-beta1; TNF, tumor necrosis factor

(Esposito et al., 2002) and mast cells (Esposito et al., 2001) and is associated with high serum IL-6 that is also mast cell-dependent (Theoharides & Konstantinidou, 2007).

The effect of CRH may be relevant to the behavioral manifestations of ASD. ASD patients had high anxiety levels and were unable to handle stress appropriately (Gillott & Standen, 2007). Evening cortisol levels positively correlated to daily stressors in children with autism (Corbett et al., 2009). Moreover, increase in age of autistic children correlated with increased cortisol levels during social interaction stress (Corbett et al., 2010). CRH has also been shown to increase intestinal permeability of human colonic biopsies, while maternal separation stress and CRH are associated with a dysfunctional mucosal barrier in rodents (Soderholm et al., 2002). A short period of restraint (Chandler et al., 2002) or maternal deprivation stress (Teunis et al., 2002) also increased the severity of experimental autoimmune encephalomyelitis.

The presence of maternal stress may explain why children born within a year of the first child that developed autism had a much higher chance of developing autism than if they were born two years later (Cheslack-Postava et al., 2011). Increased circulating CRH, directly or through immune cell release of other inflammatory and vasoactive molecules, can disrupt

the gut-blood-brain barriers during gestation and/or infancy and permit absorption of intestinal-derived inflammatory and neurosensitizing mediators.

6. Other perinatal risk factors

High weight gain in pregnancy has been considered an independent risk factor for autism in the offspring (Stein et al., 2006). Even though a clear mechanism is lacking, leptin is suspected to play a major role. Obese subjects have higher leptin levels than normal weight subjects (Considine et al., 1996; Dardeno et al., 2010). Additionally, it has been suggested that elevated plasma leptin levels during pregnancy are indicative of placental dysfunction (Hauguel-de et al., 2006). Placental insufficiency, possibly associated with anoxia, may also contribute to autism in the offspring (Glasson et al., 2004).

Elevated plasma leptin levels were reported in children with regressive autism (n=37), compared with typically-developing controls (n=50) (Ashwood et al., 2007). One group also measured the variation of circulating leptin at baseline and after one year of follow-up in 35 patients with "classic autism" (according to DSM-IV criteria) aged 14.1±5.4 years old. The authors reported significantly higher leptin values in the patients versus the controls (24.1±17.8 ng/ml vs 9.8±3.2 ng/ml at baseline; 33.5±21.4 ng/ml vs 11.1±3.9 ng/ml at one year), and leptin concentrations were not associated with obesity or pubertal status (Blardi et al., 2010). It is still unclear, however, if the alteration of leptin levels in autism is a primary event or a finding attributable to the disease. Plasma levels of leptin have also been investigated in patients with Rett syndrome (n=16), where it was found that leptin was significantly increased compared to healthy controls (n=16), but also did not correlate with obesity (Blardi et al., 2008), suggesting that there may be more to the actions of leptin in neurodevelopment than weight balance.

The immunomodulatory properties of leptin were first reported on a mouse model, in which obese mice were found to have impaired cell-mediated and humoral immunity, attributed to possible lack of leptin (Chandra, 1980). The epigenetic status in adulthood was shown to be directionally dependent on prenatal nutritional status (Gluckman et al., 2007) and neonatal leptin administration late in the phase of developmental plasticity was able to reverse the developmental programming in rats (Vickers et al., 2005). Mast cells also express leptin and leptin receptors, a finding implicating paracrine or autocrine immunomodulatory effects of leptin on mast cells (Taildeman et al., 2009). Locally released leptin from T lymphocytes doesn't seem to play a major role in immunoregulation in mouse models of intestinal inflammation, suggesting other sources of leptin as critical in modulation of the inflammatory response (Fantuzzi et al., 2005). Despite evidence supporting the role of leptin in immune processes (Lago et al., 2008; Matarese et al., 2005), its precise role in inflammation remains incompletely understood.

7. Oxidative stress and prematurity

A variety of events associated with poor fetal growth or preterm birth are also associated with oxidative stress. These include maternal infection and inflammation that lead to increased lipid peroxidation, but more importantly to alterations in the expression of many genes associated with adverse perinatal outcomes (Ingelfinger, 2007).

Considerable evidence indicates that oxidative stress may be increased in patients with ASD, possibly due to their decreased ability to neutralize free radicals. An earlier study

showed increased levels of plasma malondialdehyde, a marker of oxidative stress, ($p<0.05$) in the blood of mothers who delivered preterm and in the cord blood of their preterm neonates, compared to the levels in samples from term deliveries (Joshi et al., 2008). Preterm birth is associated with increased generation of reactive oxygen species (ROS), which places these infants in high risk for injury (Davis & Auten, 2010). In fact, a recent study identified an increase in the oxidative stress marker non-protein bound iron (NPBI) in the cord blood of 168 preterm newborns of gestational age 24-32 weeks (Perrone et al., 2010), suggesting that early identification of neonates at-risk is possible.

The impact of environmental oxidants in the etiology of autism is associated with brain region-specific changes in oxidative stress markers, such as 3-nitrotyrosine (3-NT) and neurotrophin-3 (NT-3), in ASD (Sajdel-Sulkowska et al., 2008; Sajdel-Sulkowska et al., 2011). Deficiencies in anti-oxidant enzymes might, in certain cases, be associated with mercury toxicity, which was shown to be tightly bound to and inactivate thioredoxin (Carvalho et al., 2008). In fact, cytosolic and mitochondrial redox imbalance was found in lymphoblastoid cells of ASD children compared to controls, an event exaggerated by exposure to thimerosal (James et al., 2009).

Several studies have suggested a link between oxidative stress and the immune response (Viora et al., 2001). Because immune cell functions are specially linked to ROS generation, their normal functioning is largely dependent on the oxidant/antioxidant balance. A strong association between oxidative stress and autoimmunity was shown in a group of 44 Egyptian autistic children, 88.64% of whom had elevated plasma F2-isoprostane (a marker of lipid peroxidation) and/or reduced glutathione peroxidase (an anti-oxidant enzyme), compared to 44 age-matched controls. Anti-neuronal antibodies were found in 54.5% of the same cohort, implying immunomodulation (Mostafa et al., 2010). Several groups have hypothesized that oxidative stress is the mechanism by which prenatal LPS affects offspring neurodevelopment (Lante et al., 2008; Paintlia et al., 2008). Potential therapies for oxidative stress and ROS-induced morbidities in the preterm infant include both enzymatic and nonenzymatic antioxidant preparations (Lee & Davis, 2011), such as the naturally-occuring flavonoids quercetin and luteolin (Cotelle, 2001; Middleton, Jr. et al., 2000). Quercetin inhibits mast cells (Kandere-Grzybowska et al., 2006), and also inhibited and reversed acute stress-induced autistic-like behavior and the associated reduced brain glutathione levels in mice (Kumar & Goyal, 2008). Luteolin can also block mast cell activation and superstimulation of activated T-cells (Kempuraj et al., 2008; Theoharides et al., 2007a). Luteolin and its structural analog diosmin prevented MIA-induced behavioral deficits in the mouse offspring by blocking the IL-6-induced JAK2/STAT3 (Janus tyrosine kinase-2/signal transducer and activator of transcription-3) signaling pathway, both *in vivo* and *in vitro* (Parker-Athill et al., 2009). A luteolin-containing dietary supplement, Neuroprotek® was recently made available to help the body reduce brain inflammation.

8. Conclusion

A number of findings suggest the presence of different biological endophenotypes in ASD (Persico et al., 2008), as well as between early-onset and regressive autism, with the latter being associated with poorer outcomes in social reciprocity, verbal IQ and more gastrointestinal symptoms, according to caregiver interviews (Richler et al., 2006).

Increasing evidence indicates that perinatal immune activation, in the mother and/or the fetus, could adversely affect neurodevelopment. Moreover, mast cell activation during this

period by environmental, infectious, neurohormonal and immune triggers appears to be involved in gut-blood-brain barrier disruption and subsequent brain inflammation. Reduction of stress during gestation and infancy, potential use of specific CRH receptor antagonists, as well as drugs that could prevent BBB disruption, or block brain inflammation may prove useful in at least a subgroup of infants at high risk for developing autism. These goals may be at least partly achieved by the use of mast cell blockers. Unfortunately, there are no clinically effective mast cell inhibitors, and the available disodium cromoglycate (cromolyn) has proven a weak inhibitor of human mast cells (Theoharides & Kalogeromitros, 2006). Instead, flavonoids such as luteolin are anti-inflammatory and neuroprotective (Dirscherl et al., 2010), and can inhibit mast cell activation (Asadi et al., 2010).

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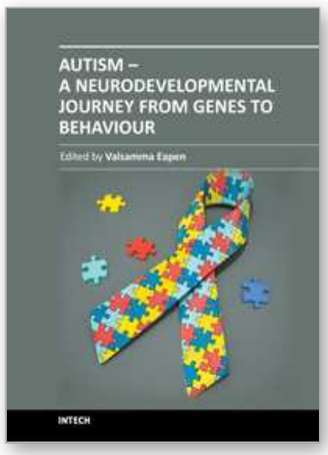

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The book covers some of the key research developments in autism and brings together the current state of evidence on the neurobiologic understanding of this intriguing disorder. The pathogenetic mechanisms are explored by contributors from diverse perspectives including genetics, neuroimaging, neuroanatomy, neurophysiology, neurochemistry, neuroimmunology, neuroendocrinology, functional organization of the brain and clinical applications from the role of diet to vaccines. It is hoped that understanding these interconnected neurobiological systems, the programming of which is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems, would no doubt assist in developing interventions that accommodate the way the brains of individuals with autism function. In keeping with the multimodal and diverse origins of the disorder, a wide range of topics is covered and these include genetic underpinnings and environmental modulation leading to epigenetic changes in the aetiology; neural substrates, potential biomarkers and endophenotypes that underlie clinical characteristics; as well as neurochemical pathways and pathophysiological mechanisms that pave the way for therapeutic interventions.

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