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Redox Regulation and the Autistic Spectrum: Role of Tryptophan Catabolites, Immuno-inflammation, Autoimmunity and the Amygdala

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Abstract: The autistic spectrum disorders (ASD) form a set of multi-faceted disorders with significant genetic, epigenetic and environmental determinants. Oxidative and nitrosative stress (O&NS), immuno-inflammatory pathways, mitochondrial dysfunction and dysregulation of the tryptophan catabolite (TRYCATs) pathway play significant interactive roles in driving the early developmental etiology and course of ASD. O&NS interactions with immuno-inflammatory pathways mediate their effects centrally *via* the regulation of astrocyte and microglia responses, including regional variations in TRYCATs produced. Here we review the nature of these interactions and propose an early developmental model whereby different ASD genetic susceptibilities interact with environmental and epigenetic processes, resulting in glia biasing the patterning of central interarea interactions. A role for decreased local melatonin and N-acetylserotonin production by immune and glia cells may be a significant treatment target.

Keywords: Autism, Oxidative stress, Nitrosative stress, glia, Immuno-inflammation, tryptophan, melatonin.

INTRODUCTION

Autism is a neuroimmune developmental disorder, with variable presentations that are generally thought to represent subgroups or collections of different, but related disorders. As a consequence the term autistic spectrum disorders (ASD) is often used. ASD is characterized by deficits in social communication coupled to repetitive stereotypies with associated difficulties in: social interaction; language, communication and imaginative play; and a narrow range of interests and activities. ASD susceptibility is strongly genetically determined, with genes accounting for 35-80% of susceptibility, although considerable debate centres on whether ASD as a whole [1] or independent dimensions [2] are heritable. Over 234 separate genetic loci contribute to ASD risk [3], many *via de novo* point mutations linked to older parental age [4]. Much of the genetic influence is mediated *via* effects in early developmental processes. Around one third of ASD children show developmental regression [5], although some evidence of developmental delay prior to regression is usually evident [6].

The role of environmental factors and their interactions with genetic susceptibilities has generated considerable interest in recent years, especially given the growing ASD prevalence in the USA and other countries. Recent estimates of prevalence in the USA show a dramatic rise, with 1 in 88 children being classed as having ASD [7], although partly due to improved detection and altered ASD criteria [8]. Environmental risk factors for ASD include viral infection around the second year of life and maternal weight gain in pregnancy [9]. A recent extensive analysis of genetic and environmental influences in twins produced a best-fit model showing a 37% genetic and 55% shared environment effect [10]. The interactions of environmental factors with gene susceptibilities have been relatively overlooked [11]. Here we look at the role of oxidative and nitrosative stress (O&NS) and its interaction with immuno-inflammatory and tryptophan catabolite (TRYCAT) pathways in the etiology, course and treatment of ASD and as to how such factors interact with, and drive, ASD genetic susceptibility factors.

ASD: EARLY DEVELOPMENTAL ETIOLOGY

Prenatal and Perinatal Risk Factors

Perinatal risk factors for ASD include: fetal distress, breech presentation, planned cesarean section, gestational diabetes, multiple birth, umbilical-cord complications, birth injury or trauma, maternal bleeding, low birth weight, summer birth, small for gestational age, maternal medication, low 5-minute Apgar score, meconium aspiration, neonatal anemia, ABO or Rh incompatibility, and hyperbilirubinemia [12-14]. In a study of over 87,000 births, pre-eclampsia significantly increased the risk of ASD (OR = 1.69, p = .0005) [15]. Preterm births are rising in the USA, accounting for 15% of births [16]. An additional 5-8% of births are complicated by preeclampsia or gestational diabetes, with consequences for obstetric outcome [17]. An association of offspring ASD is linked to single nucleotide polymorphisms (SNP) in glutathione S-transferase P1 (GSTP1), suggesting that maternal antioxidant regulation prenatally modulates offspring ASD likelihood [18], highlighting the importance of O&NS in the etiology of ASD.

The role of maternal prenatal infection in ASD risk overlaps the etiology of ASD with that of schizophrenia [19].

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Increased mid-gestation interferon-gamma (IFN-γ), interleukin (IL)-4 and IL-5 in the maternal serum raises offspring ASD risk, suggesting a role for altered maternal immune responses [20]. In foetal rodent brains at 6hrs after maternal viral infection, IL-1β, IL-13 and vascular endothelial growth factor (VEGF) are increased, with only IL-1β continuing to be raised at 24 hours [21]. These authors also show that the response to the same viral mimetic is significantly different at post-natal day 4, with relatively little evidence of increased central IL-1β, suggesting that foetal IL-1β may be of particular importance. Interestingly the offspring of rodent maternal viral infection show significant alterations in immune system functioning, including decreased immuno-suppressive regulatory T-cells and increased IL-17 and IL-6 production by CD4+ T-cells [22]. Irradiation of these rodents and replacement with immunologically normal bone marrow prevents the development of ASD-type behaviours, suggesting that immuno-inflammatory pathways are significant drivers of maternal infection induced ASD risk. The association of maternal infection with ASD [23] contributes to increased ASD summer births [12], and mediates the effects of decreased vitamin D in offspring ASD susceptibility.

Other perinatal ASD risk factors include pre-pregnancy obesity and excessive pregnancy weight gain [24]. Increased obesity in western cultures is therefore likely to contribute to rising ASD prevalence. In rodents maternal high fat diet modulates offspring opioids, μ-opioid receptor and dopamine transporter levels [25], increasing obesity susceptibility *via* the μ-opioid receptor regulation of food and fat intake, driven by μ-opioid receptor effects in the hypothalamic paraventricular nucleus, nucleus accumbens and amygdala [26-28]. In ASD young children and adolescents in the USA there is a twofold increase in obesity versus general population [29,30]. ASD is also associated with increased hyperlipidemia [31], triglycerides and LDL cholesterol [32]. Prenatal maternal obesity, in increasing offspring obesity, will therefore contribute to pro-inflammatory ASD risk factors.

However, the μ-opioid receptor also regulates separation anxiety and attachment [33,34] as well as modulating the effects of social reward in the nucleus accumbens [35]. Opioids are increased in ASD [36], with β-endorphin positively correlating with ASD symptom severity [37]. Treatment with the opioid receptor antagonist, naltrexone, improves social interactions and some repetitive behaviours and language deficits in ASD children [38]. As such maternal obesity and high fat diet intake during pregnancy are likely to modulate many facets of ASD, including psychiatric comorbidities and social attachment, partly *via* the regulation of opioids and dopamine.

Mutations in phosphatase and tensin homolog (PTEN) associate with increased ASD risk, being especially relevant to increased macrocephaly and cancer in ASD. Inhibitory mutations in PTEN are commonly associated with many cancers, in part driven by increased phosphatidylinositol 3-kinase (PI3K)/Akt pathways, altering the regulation of Notch and cell proliferation. As such PTEN mutations may have particular relevance to ASD macrocephaly. PTEN mutations will also interact with μ-opioid receptor activity. Functionally inhibitory PTEN mutations, by increasing the PI3K/Akt pathway may also not only increase neurogenesis, macrocephaly and cancer risk, but also accelerate the desensitization of the μ-opioid receptor following chronic activation [39]. As such the genetic and epigenetic regulation of PTEN may be a significant modulator of μ-opioid receptor activity and effects, contributing to heterogeneity in opioidergic regulation, including in interaction with maternal high fat diet.

Given the predominance of ASD in males, testosterone effects prenatally are being extensively investigated. Preliminary data show foetal testosterone, as measured in amniotic fluid, but not postpartum testosterone at 3-4 months, associates with ASD risk [40,41], including correlations with eye contact [42] and empathy [43]. Interestingly foetal testosterone increases dopamine driven behavioural approach in later childhood for positively valenced facial cues [44], not directly relevant to ASD, but suggesting impacts on dopamine regulation of amygdala-cortex and amygdala-sensory interactions in ASD, as detailed below. Two/four digit ratio is often used as a proxy for prenatal testosterone, with data using this ratio generally supporting a role for prenatal testosterone in ASD [45]. Fetal testosterone and the aromatase conversion of testosterone to estrogen are therefore likely to have significant impacts on early ASD associated processes.

Environmental toxins have a role in the etiology of ASD [46], as with many other medical conditions, including Parkinson's disease [47]. Recently it has been proposed that perfumes and perfumed products prenatally may contribute to mutagenic, neurotoxic and neuromodulatory changes in the offspring, even at femtomolar levels [48]. As to how such products would interact with the known prenatal ASD susceptibility effects of valproate, mercury, antidepressants and decreased vitamin D requires investigation.

Maternal Medication

Psychotropic medication use in pregnancy and during the period of lactation postnatally can have significant impacts on the foetus and neonate [49]. Children born to mothers exposed to valproate, especially in the first trimester, have an 8-fold increased risk of ASD [50]. Maternal antidepressants use in pregnancy, especially in the first trimester, also increases offspring ASD risk, although to a lesser extent than valproate [51]. In a Swedish population based nested control study, selective serotonin reuptake inhibitors (SSRIs) or tricyclic use during pregnancy increased the risk of ASD without intellectual disability, accounting for 0.6% of cases [52].

Vitamin D

Urban residence, living at high latitude or in areas of high precipitation are all environmental risk factors for ASD and all are associated with decreased vitamin D (vit D) [53]. ASD is also more prevalent in people with black ethnicity [54], suggested to be a consequence of decreased vit D prenatally [55,56]. Reduced levels of vit D are also evident in autistic children [57], which associates with decreased bone mineral density, lowered dietary vit D intake and

decreased outdoor exercise [58]. vit D is also protective against O&NS and O&NS induced DNA damage [59], suggesting that decreased vit D will contribute to increased mutation rates.

Decreased maternal vit D in very early pregnancy raises the risk of preeclampsia, which modulates offspring ASD risk [60]. Vit D also decreases T-helper (TH)17 differentiation, and therefore relevant to both mother and offspring response to infection. Maternal infection in rodent pregnancy increases offspring TH17 response. As such vit D will modulate the likelihood and consequences of maternal viral infection as well as the likelihood and consequences of first or second year viral infection in the offspring. This would suggest a two-hit type model, whereby decreased maternal vit D and increased maternal infection acts as first hit to a later viral infection in the first or second postnatal year in the offspring, where a continued decrease in vit D would increase viral infection risk, coupled to a more prolonged pro-inflammatory TH17 response. It requires investigation as to whether decreased prenatal vit D would interact with maternal infection during pregnancy to alter TH17, and perhaps wider immune responses to viral infection in the offspring around the first or second year. The human adaptive immune response is not developed in the first six months postnatally, where a heightened innate immune response is evident. As such a viral infection around the first year postnatally is likely to be the first major adaptive immune response. A prolonged and excessive TH17 driven response at this time is likely to contribute to regression, which is evident in about one third of ASD presentations [5].

Perinatal Mercury

Maternal prenatal mercury levels have sharply increased in recent decades, with foetal cord blood levels being significantly increased versus maternal levels [61,62]. This suggests that prenatal mercury, which can induce many of the changes evident in ASD, including increased O&NS and immuno-inflammation, as well as decreased endogenous anti-oxidants and mitochondrial functioning, may play a significant role in the etiology of ASD. As to whether mercury interacts with the consequences of prenatal infection in the offspring is unknown, although not unlikely given that mercury significantly modulates murine viral immune response [63,64] and viral infection increases brain mercury levels [65]. SNPs in genes involved in mercury regulation associate with ASD [66]. It also requires testing as to whether mercury has any impact on the development of foetal gamma-delta (γδ) T cells and prenatal epigenetic regulation.

Other Prenatal Toxins

Other heavy metals, including cadmium and lead [66], may also interact with ASD susceptibility genes to modulate the early developmental processes driving increased ASD risk, including in interaction with PTEN and miR-21, as detailed below. Likewise persistent organic and other air pollutants exposure perinatally can increase offspring ASD risk [67,68]. As to how these metals and persistent organic pollutants interact with maternal and offspring immune responses to infection requires investigation.

EARLY DEVELOPMENTAL CO-ORDINATING PROCESSES

Epigenetics

Many of the above perinatal susceptibility factors will mediate their effects *via* changes in co-ordinated gene expressions, including *via* micro-RNAs (miRNAs) and epigenetic regulating processes. A number of single gene genetic syndromes that show ASD-like features, including Rett, Fragile X, Prader-Willi and Angelman syndromes, also mediate many of their effects *via* changes in epigenetic dysregulation [69]. SNPs in a gene associated with the epigenetic driven methylation is linked to ASD [70]. Decreased retinoic acid-related orphan receptor alpha (RORα) in ASD is epigenetically driven [71], with consequences for aromatase regulation and sex differences in susceptibility to ASD [72]. Gonadol hormone effects in ASD are mediated in part *via* the regulation of oxytocin, which significantly modulates social interactions and is decreased in ASD. The oxytocin receptor level is strongly epigenetically determined, primarily *via* DNA methylation [73]. The role for perinatal epigenetics in regulating ASD risk is an area of intensive research [74].

MicroRNAs

Accumulating data highlights the importance of miRNAs in co-ordinating patterned gene changes, including in ASD. The macrocephaly and ASD susceptibility gene, PTEN, is significantly regulated by a number of miRNAs, including miR-21 [75] (Vaishnavi *et al.*, 2013), suggesting that perinatal ASD risk factors can mediate their effects *via* miRNA co-ordinations that include the regulation of ASD susceptibility gene levels. Heavy metal toxicity, especially lead, is partly mediated *via* the regulation of miR-21 [76] as well as the downregulation of the ASD, and especially Rett syndrome, associated methyl-CpG-binding protein 2 (MeCP2) [77]. Increased lead, as with mercury, is associated with ASD [78] and may be an early developmental contributor to increased amyloid B in later life ASD [79]. Lead has differential consequences on gene transcription in ASD versus controls [80]. This could suggest an association of heavy metals with the regulation of PTEN, contributing to macrocephaly and cancer susceptibility in ASD, driven in part by miR-21. The role of specific miRNAs in co-ordinating early developmental processes in ASD requires investigation.

Amygdala Interactions with Cortex and Sensory Processing

Higher order co-ordination can also be driven by factors influencing structural and connectivity development. The relatively early development of some amygdala nuclei, allows factors acting on the amygdala to influence the development of other brain areas, especially the cortex [81]. Some of the impacts of PTEN mutations, stress driven cortisol and susceptibility gene SNPs, as well as epigenetic and miRNA co-ordination may be mediated in part by their regulation of amygdala driven influences on the development of other brain regions and wider area to area patterned activity.

ASD prenatal susceptibility factors such as maternal high fat diet/pregnancy weight gain [25] and testosterone [44], in regulating dopaminergic activity, may be acting on amygdala driven regulation of, and interaction with, other CNS regions. Dopamine, *via* the dopamine D1r, regulates cortex-amygdala interactions. The activation of the D1r on paracapsular cells of the intercalated masses encapsulating the amygdala leads to the hyperpolarization of paracapsular cells *via* the potassium inwardly-rectifying channel activation [82] leading to decreased cortex inhibitory feedback to the amygdala [81]. This results in heightened and prolonged amygdala activity, which may be especially important in early development, given earlier amygdala nuclei maturation that allows the amygdala to regulate the development of other brain regions. SNPs in the dopamine D1r are risk alleles for ASD [83]. 2 to 4 year olds with ASD show enlarged amygdala volume at baseline and an accelerated rate of growth at one-year follow-up, independent of total brain volume [84]. Although subject to some heterogeneity, this suggests an important role for the amygdala in the etiology of ASD. Given the influence of the amygdala on the development of other brain areas, factors acting to influence dopamine activity in the intercalated masses may have an important influence on wider brain development and patterned interarea connectivity. Changes in amygdala volume, functioning and interactions with the cortex have long been thought relevant in ASD [85], supported by more recent fMRI data [86]. In individuals with high eye gaze aversion, amygdala activity is especially high when eye gaze is manipulated to facial regions [87], suggesting that ASD symptoms may feedback on amygdala activity and developmental influence.

As well as activating the D1r in parcapusular cells, dopamine also activates the lateral amygdala D2r. The D2r potentiates sensory inputs from the thalamus and association-sensory cortex, including the superior temporal gyrus [88], an area showing alterations in ASD [89]. This suggests that any dopamine driven changes in cortex-amygdala interactions will be co-ordinated with heightened sensory input and influence in the lateral amygdala. The lateral amygdala is the site for fear memory storage, suggesting that D2r potentiation of sensory inputs may have particular relevance to fear/anxiety processing, as well as to PTSD-like flashbacks and hallucinations. The lateral amygdala D2r may then be relevant to the high levels of psychosis in ASD and to the efficacy of antipsychotics [90]. The close correlation between sensory over-stimulation and anxiety in ASD [91] may then be mediated by D2r regulation at the amygdala interface of sensory and affective processing. A D2r SNP is a susceptibility allele for ASD as are SNPs at dopamine-regulated and cyclic-AMP-regulated phosphoprotein of 32kD (DARPP-32), with D2r and DARPP-32 alleles having additive interactions linked to more severe social interaction problems, communication deficits and increased stereotypies [92]. Such data highlights the relevance of altered dopamine transmission, *via* both D1r and D2r activation in ASD. An increase in the dopamine metabolite homovanillic acid is evident in the CSF in ASD children [93], suggesting increased levels of dopamine activity in early development.

However, decreased dopamine levels in the ASD frontal cortex [94] suggests that the distribution of dopamine is altered in ASD. The release of cortex dopamine, as well as glutamate and acetylcholine, is induced by activation of the alpha7 nicotinic acetylcholine receptor (α7nAChr) [95], which is inhibited by cortisol and pro-inflammatory cytokine induction of the TRYCAT, kynurenic acid (KYNA). There is also a significant epigenetic regulation of the α7nAChr gene (CHRNA7) in ASD [96], with significantly decreased α7nAChr in the frontal cortex in ASD, coupled to significantly decreased α4 and B2 nicotinic receptor subunits [97]. Decreased levels of melatonin in ASD will also contribute to α7nAChr down-regulation, given that melatonin increases α7nAChr levels and activity [98]. As such, factors acting to differentially decrease cortex dopamine, if coupled to raised levels of amygdala dopamine, will contribute to a decrease in cortex negative feedback to the amygdala, heightening amygdala influence on brain development and processing, including thought and behavioural outputs.

Infection, stress or epigenetic influence on levels of TRYCAT pathway activation can also modulate the influence of dopamine on cortex-amygdala interactions. In rodents, prenatal infection with the viral mimetic PolyI:C, increases levels of midbrain dopamine neurons in the foetus [99]. KYNA in the ventral tegmental area (VTA) increases dopaminergic activity at other sites, including the amygdala, *via* VTA GABAergic activity inhibition [100]. The influenza A virus increases KYNA prenatally, which is associated with later alterations in sensory processing in rodents, including altered prepulse inhibition (PPI) [101, 102]. Alterations in amygdala activation can decrease PPI, in part *via* altered outputs to the ventral pallidum *via* the nucleus accumbens [103]. As to whether this is relevant to decreased PPI in subgroups of ASD requires investigation [104], especially given the association of decreased PPI in ASD with repetitive behaviours [105].

Wider dopaminergic regulation is also relevant in ASD. A gain of function mutation in the G-protein coupled receptor-37 (GPR37) associates with ASD [106]. The GPR37 is a significant regulator of dopamine transporter function and modulates brain development [107]. However, mutations in GPR37 are not invariably associated with ASD, suggesting that it plays a role but only when expressed concurrent to other genetic and/or epigenetic driven variations [106]. As to whether the GPR37 mutation impacts amygdala function and interactions with the cortex and sensory processing requires investigation. Cerebellar dysfunction is common in ASD. In rodent models, cerebellar dysfunction significantly decreases the levels of dopamine efflux to the cortex [108], contributing to cognitive deficits *via* sub-optimal cortex activation, as well as altering cortex-amygdala interactions.

In the rodent the amygdala projects into all layers of cortex until around postnatal day 2. At this time amygdala projections retract, leaving only projections into layers II and V [81,109]. Early amygdala activity is important in co-ordinating cortex development, with later amygdala input being restricted to layers II and V. In schizophrenia, highly associated with prenatal infection [19], most cortex changes

occur in Layers II and V [81]. Changes in cortex Layers II and V are evident in ASD [110] (Simms *et al.*, 2009), including increased apical spine density on pyramidal neurons [111], although changes may not be as Layer-localized as in schizophrenia, perhaps suggesting that earlier alterations in amygdala influence may be more relevant in ASD [81].

Oxytocin is decreased in ASD, contributing to social interaction deficits. Oxytocin receptors are especially dense in the amygdala. A single intra-nasal oxytocin administration alters the levels of amygdala activity under fMRI in a face-processing task [112], suggesting oxytocin impacts on amygdala-cortex interactions. In the rodent mPFC, especially Layer V, oxytocin initially suppresses glutamatergic activity, before increasing α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor linked plasticity [113]. As such oxytocin modulates the cortex and amygdala, their interaction and plasticity, in turn modulating behaviour and thought outputs in response to stress induced amygdala activation. The early regulation of amygdala oxytocin release requires investigation.

Altered amygdala activity is also evident in animal models of ASD, including *via* the prenatal and early postnatal administration of valproate [114]. Valproate increases the excitatory/inhibitory balance in the lateral amygdala, mediated by presynaptic facilitation. As to whether valproate increases D2r activation in the lateral amygdala, thereby potentiating sensory inputs requires investigation. In a single case study of an ASD youth, deep brain stimulation (DBS) in the basolateral amygdala, but not at other amygdala sites improved emotional, social and cognitive aspects of ASD, as well as self-injurious behaviours [115], suggesting that the early developmental influences on amygdala activity and amygdala-cortex interactions may be subject to clinically significant interventions in later years.

Overall many factors acting on early developmental processes are relevant to the etiology of ASD, including prenatal infection, decreased vit D, maternal psychotropic medication and dietary factors. All of these susceptibility factors act on processes that can differentially co-ordinate changes in different cells and brain regions, including *via* epigenetic processes and miRNAs, as well as on higher order co-ordination *via* amygdala activity and interactions with cortex and sensory processing. Many of these processes are driven by changes in O&NS and immuno-inflammation, which continue to show dysregulation in later manifestations of ASD.

O&NS

Oxidants

Many oxidants and indicants of oxidative stress are increased in ASD, both centrally and peripherally, including thiobarbituric acid-reacting substances (TBARS), lipid hydro-peroxides, 4-hydroxy nonenal (4HNE), malondialdehyde, protein carbonyls, sulfhydryl groups, xanthine oxidase, total peroxide content and oxidative stress index, with these showing a negative correlation with ASD functioning [116-119]. Significantly increased plasma nitric oxide (NO), malondialdehyde, protein carbonyl, and lactate to pyruvate ratio are evident in ASD children [120]. To decrease the influence of blood withdrawal stress on parameters measured, urinary measures have been used in many studies, similarly showing significantly increased TBARS, lipid hydroperoxides, 4HNE, protein carbonyls, sulfhydryl groups, total peroxide content and oxidative stress index in ASM 4-10 year olds [116]. This is concurrent to decreased urinary antioxidant excretion.

Likewise increased nitration of proteins is evident in ASD, negatively correlating with functioning [121]. Post-mortem studies show varying 3-nitrotyrosine (3-NT) levels in different CNS regions in ASD, suggesting that ongoing local processes and/or early developmental influences on sub-region development drive local changes in O&NS [122]. Increased 3-NT is evident in the cerebellum and cortex sub-regions, showing a partial overlap with local glutathione (GSH) changes and correlating with symptom severity [123]. Raised lipid peroxidation and associated oxidants, 4HNE and 8 isoprostane in ASD can be coupled to increased non-protein bound iron [124]. Increased free iron contributes to O&NS *via* activation of the Fenton reactions. In association with this lipid mediators of inflammatory processes, including prostaglandin E2 (PGE2) and cysteinyl leukotriene are also raised [125]. Plasma levels of NO are increased in ASD, correlating positively with increased vasoactive intestinal peptide and IFN-γ [126], highlighting correlated changes in cytokines, O&NS and neuropeptides. Overall, O&NS association with level of functioning suggests an O&NS role in the etiology and/or course, as well as in the treatment, of ASD.

Anti-oxidants

As well as increased O&NS, ASD shows decreased endogenous antioxidants, including superoxide dismutase (SOD) and catalase [119,121], but especially GSH [117]. Negative correlations between ASD severity and plasma GSH, catalase and SOD, as well as serum NAD+ and ATP levels are also evident [127], suggesting redox dysregulation in association with mitochondrial dysfunction. A decrease in total antioxidant capacity is also found in adolescents with Asperger's symdrome [128], indicating that redox alterations are relevant across the spectrum of severity of ASD-like symptoms.

Decreased endogenous antioxidants are relevant to wider aspects of ASD, including gastrointestinal and immune alterations [129]. A recent systematic review and meta-analysis of blood antioxidants in ASD showed: decreased GSH by 27%, glutathione peroxidase by 18%, methionine by 13% and cysteine by 14%; increased oxidised glutathione (GSSG) by 45%; no differences in SOD, homocysteine or cystathionine [130]. Decreased GSH is evident in resting peripheral blood mononuclear cells, activated CD4+ T cells and monocytes as well as in the serum of ASD children [131]. Decreased serum GSH correlates with ASD severity [132]. Averaging across ten ASD studies that measured GSH gives a substantial average decrease of 37% in ASD [129]. A similar decrease in GSH and increased GSSG and decreased GSH/GSSG ratio are also evident in the cortex and cerebellum at autopsy versus matched controls [133]. This is accompanied by increased 3-NT, a biomarker of oxidative

protein damage and 8-oxo-deoxyguanosine, an indicant of oxidative DNA damage, as well as decreased aconitase, an indicant of mitochondrial superoxide production [133]. Decreased GSH is also evident in ASD lymphoblastoid cell mitochondria versus controls [134]. The glutathione pathway shows a number of ASD susceptibility SNPs, which modulate anti-oxidant responses to oxidative challenge [135]. Overall this suggests that decreased antioxidants, especially GSH, are intimately associated with indicants of oxidative damage and mitochondrial dysfunction in ASD.

Decreased GSH is driven by an impaired uptake of its precursor cysteine, including in the ASD gastrointestinal tract [129]. Decreased plasma cysteine in ASD correlates with decreased plasma GSH [136]. This may be partly driven by O&NS, which decreases excitatory amino acid transporter (EAAT)3 uptake of cysteine in neurons [137], gastrointestinal tract and immune cells [129]. The induction of endogenous anti-oxidants by nuclear factor-erythroid 2 (NF-E2) p45-related factor-2 (Nrf2) increases neuronal GSH *via* increased EAAT3 [138]. This is mediated by the uptake of glutamate by EAAT3 and rapid efflux *via* the cystine-glutamate antiporter (CysGluX) in exchange for cystine, which is rapidly converted to cysteine [139]. As such cooperation between EAATs and CysGluX is crucial to GSH maintenance and can be modulated by O&NS.

Although changes in redox status and GSH levels occur in different organs and tissues in ASD, some brain sub-regions may be more highly affected [123]. A 40% decrease in GSH and GSH/GSSG ratio is found in the cerebellum and temporal cortex, but not in the frontal, occipital or parietal cortices in ASD versus controls [123], which partially overlaps with levels of increased 3-NT [122]. Given that astrocytes are the major source of GSH generation, including in the provision of GSH substrates for neuronal GSH resynthesis, this could suggest area specific changes in astrocytes and their regulation of neuronal activity, contribute to altered interarea patterning in ASD. Astrocyte cystine uptake is *via* the CysGluX. As to whether the necessary breakdown of GSH by gamma-glutamyltranspeptidase (γGT) into constituents that can be taken up by neurons is altered *via* variations in NO locally [140] requires investigation. As such a dysregulation of astrocyte GSH substrate provision and neuronal uptake may alter the communication between these interdependent cell types. Morphological changes in cortex astrocytes, including significantly decreased branching processes, total branching length and cell body sizes [141], suggest a significant role for altered astrocyte regulation of neuronal activity and oxidant status in ASD.

As well as decreased antioxidants, there is also a decrease in the major antioxidant serum proteins, including transferrin (iron-binding protein) and ceruloplasmin (copper-binding protein), in ASD children, which correlate with reduced levels of acquired language skills [142,143].

Regulators of O&NS and Antioxidants

As well as anti-oxidant susceptibility genes, a number of environmental and dietary factors contribute to the etiology and course of ASD. The short chain fatty acid, propionic acid, is a cellular metabolism intermediate, with a number of beneficial effects. However, when it accumulates it is neurotoxic [144], decreasing GSH and GSH/GSSG ratio in brain homogenates of treated animals [144], coupled to increased pro-inflammatory cytokines and neuronal apoptotic pathways. Similarly mercury intoxication parallels ASD central and peripheral changes, and is an environmental contributor to ASD etiology [145]. Mercury exposure may also be *via* thimerosal, which is present in vaccines as a preservative. Some of the effects of thimerosal are mediated *via* alterations in dopaminergic signalling [146], and therefore in co-ordinating amygdala interactions with the cortex and sensory processing [81]. Thimerosal derived ethylmercury is also a mitochondrial toxin in astrocytes [147], increasing astrocyte superoxide, hydrogen peroxide, and Fenton/Haber-Weiss generated hydroxyl radical, which drive astrocyte mitochondrial DNA damage. This may contribute to the altered astrocyte morphology and function in ASD [141]. Mercury concentration in hair positively correlates with ASD symptom severity [148]. Interestingly mercury induced toxicity centrally is mediated *via* the activation of the NMDAr [149], suggesting overlaps to astrocyte dysregulation of glutamatergic activity, as well as to stress induced amygdala QUIN [150]. As such dysregulation of dopamine and O&NS by environmental risk factors drives the association of early developmental risk factors in the etiology of ASD.

Valproate administered prenatally is an animal model thought to parallel the development of ASD. Prenatal valproate increases lipid peroxidation, 4HNE and wider O&NS, as well as inducing stereotypies and macrocephaly, coupled to learning and memory deficits in the offspring [151]. Valproate effects are mediated in part by increased excitatory activity in the lateral amygdala [114]. As with mercury this suggests an impact on O&NS in driving changes in amygdala co-ordination of early developmental process in ASD etiology.

Causally modelling the effects of O&NS in the etiology and course of ASD is still controversial, with some arguing that it may produce symptoms and changes not relevant to core ASD symptoms. However, when placed in the outlined developmental model above, O&NS and immuno-inflammatory processes are major drivers of the patterned development by co-ordinating factors such as epigenetic processes, miRNA and dopamine influenced amygdala activity. Genetic and epigenetic regulation of redox status are relevant to the effects of viral infection, both in the mother prenatally, and in the response of offspring. Many viruses utilize cellular ROS for viral entry, genomic replication and survival within host cells, with decreased anti-oxidants and increased oxidants thereby enhancing viral entry, replication and effects [152]. The GSH inducer, N-acetylcsyteine, decreases the entry and effects of some viruses, whilst the addition of H2O2 increases entry and levels of infection [152]. As such O&NS will be an important determinant of the effects of viral infection in ASD, including the role of viral infection in regression induced changes.

Wider Consequences to O&NS Dysregulation

Increased O&NS has a number of consequences, including increased vascular activation [153]. Decreased

GSH potentiates the effects of TNF-α, which is increased in lymphocytes, CSF and brain in ASD [154]. An important consequence of raised O&NS is the lipid peroxidation driven increase in autoimmunity, including from newly exposed lipid membrane epitopes. O&NS, as indicated by increases in the lipid peroxidation marker F2-isoprostane and decreased glutathione peroxidase, is highly associated with autoimmunity in ASD [155], as in many other psychiatric and neuro-degenerative conditions [156,157]. Raised O&NS is strongly linked to wider changes in ASD. Work by Adams and colleagues in ASD children shows increased O&NS correlating with changes in biotin, red blood cell (RBC) S-adenosyl-l-methionine, plasma uridine, plasma ATP, RBC NADH, RBC NADPH, plasma sulfate (free and total), plasma tryptophan and plasma glutamate [158]. Many of these factors, especially levels of vitamins, minerals and plasma amino acids show significant associations with ASD symptom severity [158]. Such O&NS associations with changes in metabolic status and levels of plasma amino acids, including tryptophan, link to decreased serotonin and melatonin. Increased O&NS and immuno-inflammatory cytokines mediate these changes *via* indoleamine 2,3-dioxygenase (IDO) and perhaps tryptophan 2,3-dioxygenase (TDO) activation, driving tryptophan down the TRYCAT pathways and away from serotonin and melatonin production. TRYCATs, including KYNA QUIN, are significant neuro-modulators. Such interactions of O&NS with immuno-inflammation, metabolism and TRYCAT pathways, places O&NS in a powerful position to modulate major processes thought to drive ASD.

AUTOIMMUNITY

Increased frequency of autoimmune disorders occurs in ASD families [51,159]. A family history of allergy and autoimmune disorders, especially in mothers, is associated with offspring ASD [160]. This suggests genetic susceptibility to autoimmune manifestations in ASD, including genetic susceptibility to O&NS driven autoimmune processes.

O&NS driven damage to lipid membranes is a major contributor to autoimmunity *via* the exposure to the immune system of previously unseen neo-epitopes. Increased circulating autoantibodies to neuronal and glia filaments occur in ASD [161]. Other changes indicative of autoimmunity, including increased albumin, globulin, IgG2 and IgG4 are also evident [162]. For a subgroup of ASD, autoimmunity is likely to modulate the course of ASD and may contribute to a neuroprogressive process, whereby autoimmune driven changes alter the course of presenting ASD symptomatology over time. With CNS cell specific autoantibodies evident in ASD children, such impacts of O&NS on ASD autoimmunity is not something necessarily only linked to later adult life presentations [161,163].

Although increased O&NS and lipid peroxidation damage to membranes is important to the induction of autoimmune responses, other factors may also be involved, including the major histocompatibility complex genes and their products [164]. Also SNPs of the human leukocyte antigen gene associate with the susceptibility to ASD [165]. As well as correlating with symptom severity, decreased vitamin D also associates with increased anti-myelin-associated glycoprotein (anti-MAG) autoantibodies [166]. Such changes in anti-MAG autoantibodies and immune alleles highlight the importance of immune changes in ASD. The role of autoimmunity in the etiology and/or course of ASD will be important to determine, including as to whether there is a staging or neuroprogressive aspect, which may have treatment implications.

PTEN is a susceptibility gene for ASD, where its decreased function increases PI3K/Akt signaling, linking PTEN to macrocephaly. Decreased PTEN function in mature T-cells leads to multi-organ autoimmunity [167], suggesting that PTEN driven macrocephaly will associate with autoimmunity and wider immune alterations in ASD.

CELL MEDIATED IMMUNITY

As well as increased autoimmunity in ASD, there is a wider dysregulation of cell-mediated immunity (CMI) and consequent pro-inflammatory cytokine levels and patterning. Whole blood levels of IFN-γ and IL-1 receptor antagonist (IL-1RA) are increased in ASD children, coupled to a trend increase in IL-6 and TNF-α [168]. Stimulated and unstimulated ASD peripheral blood mononuclear cells show a dramatic increase in cytokine production, including TNF-α, IL-1b and IL-6 [169], linked to decreased GSH and increased GSSG [131]. Such changes in oxidant status of T-cells alter the responsivity of the adaptive immune system, which is evident in ASD [170]. This highlights the importance of altered redox regulation to crucial immuno-inflammatory facets of ASD.

High functioning ASD similarly show changes in cytokine profiles, with increased plasma concentrations of IL-1β, IL-1RA, IL-5, IL-8, IL-12(p70), IL-13, IL-17 and GRO-α versus matched controls [171]. Similarly increased Th1 cytokines, IFN-γ, TNF-α and IL-6 are evident centrally in ASD [172,173], along with raised levels of granulocyte/ macrophage colony-stimulating factor, monocyte chemo-attractant protein (MCP)-1, transforming growth factor-B1 and IL-8 [174]. In ASD children, raised levels of IFN-γ positively correlate with levels of NO metabolites, nitrite and nitrate (NOx) [175], suggesting a co-ordination of immuno-inflammation with levels of NO, NOx and nitrosative stress.

CMI and cytokine changes correlate with core behavioral features of human ASD. Elevated plasma IL-4 associates with communication deficits, whilst stereotypy in ASD children associates with increased plasma IL-8, IL-12p40, IL-6, and IL-1β [176]. Alterations in TGF-β1, macrophage migration inhibitory factor and CD31, associate with the ASD symptom severity [177], as do lowered levels of plasma IgG and IgM [178]. Not all cytokine alterations are increases. In a study of 29 plasma cytokines and chemokines in ASD children, eight were significantly decreased: IL-1α, IL-6, granulocyte colony stimulating factor, epidermal growth factor-2, fractalkine and monocyte chemotactic protein-3, as well as macrophage inflammatory proteins 1α and 1β [179].

A small subset of ASD children shows significant fluctuations in behavioural symptoms and cognitive skills following immune activations. A proportion of these children

also have specific polysaccharide antibody deficiency (SPAD), leading to frequent infections driven by encapsulated organisms [180]. Children with ASD and SPAD have significant alterations in the patterning of gene responses in immune cells, including monocytes [180], which contribute to their behavioural and cognitive fluctuations, highlighting the role of altered immuno-inflammatory responses in the course of ASD. In ASD/SPAD children supplemental intravenous immuno-globulin provides effective treatment.

Monocyte counts are increased in ASD children [181] and show significantly increased cytokine production to different toll-like receptor (TLR) stimulations. TLR2 stimulation significantly increases pro-inflammatory IL-1beta, IL-6, and TNF-α, whilst TLR 4 stimulation relatively increases IL-1b [182]. In contrast TLR 9 stimulation results in relatively decreased IL-1β, IL-6, granulocyte/macrophage colony stimulating factor and TNF-α responses in ASD monocytes versus controls, suggesting an altered viral response. Such altered innate immune cytokine production will contribute to IDO induction, with differential TRYCATs production at different sites consequently regulating neuronal activity and specific patterning. Increased TLR-2 activity will interact with decreased vit D in ASD, given that vit D is required for TLR-2 induction of the endogenous antimicrobial, cathelicidin [183]. Decreased GSH in ASD monocytes will heighten inflammatory response to TLR-2 and TLR-4 [131]. As to whether such anti-oxidant dysregulation modulates sphingosine-1-phosphate (S1P) receptor subtype levels and activity is unknown. S1P1r and S1P3r have opposing effects on TLR-4 induced NF-κB and pro-inflammatory cytokines in macrophages and epithelial cells, with S1Pr activation being important to immune cell movement and morphological changes [184,185]. Overall redox regulation of immunity is altered, with consequences for immuno-inflammatory responses, which may be important to both etiology and course of ASD.

In animal models of ASD, maternal infection decreases regulatory T-cells and increasing IL-6 and IL-17 producing CD4+ T-cells in the offspring [22]. The fact that irradiation, followed by normal replacement bone marrow prevents the stereotypies and anxiety changes evident in offspring following maternal infection, suggests a powerful role for immune driven changes in the etiology and course of ASD-like symptoms. The relevance of this in subsets of ASD with a history of maternal infection, and in other ASD models, requires investigation. Similar data in Rett syndrome shows microglia to be the determinant immune cell driving the course of this ASD associated disorder [186]. Increased IL-17, which correlates with symptom severity [187], also suggests an association of maternal infection linked ASD symptoms with autoimmunity. IL-6 is increased in the frontal cortex and cerebellum in ASD, with IL-6 overexpression in rodents mimicking many ASD symptoms, including increased brain volume and social interaction deficits, as well as dendritic and synaptic changes [188]. Overall the changes in immune responses, and their interaction with O&NS, are more than epiphenomenal to ASD presentations, being intimately involved in driving changes centrally.

WIDER IMMUNE CHANGES

As well as increased CMI and autoimmune responses, wider immune changes occur in ASD, including increased B-cells and natural killer (NK) cells [189]. The activating types of killer-cell immunoglobulin-like receptors and their cognate human leukocyte antigen ligands are significantly increased in ASD, which will modulate both innate and adaptive immunity [190]. A high percentage of ASD children show decreased NK cell cytotoxicity, driven by decreased intracellular levels of GSH, IL-2 and IL-15 [191]. Basally perforin, granzyme B, and IFN-γ production are increased in ASD NK cells, but coupled to a decrease in cytotoxicity upon activation [192], contributing to increased cancer prevalence in ASD. A number of genes showing altered expression peripherally in ASD are regulators of NK cytotoxicity [193]. The increased opioidergic activity in ASD will also have consequences for NK cell regulation and wider immunity. Naltrexone's beneficial effects in ASD children are putatively *via* immune modulation [194].

Influenza virus associated death is usually a result of secondary bacterial superinfection, with viral induced type I IFN inhibiting γδ T cell induced IL-17 [195]. As to whether such viral-bacterial interactions are relevant to the etiology and course of ASD is unknown. However, it does highlight the significant role that γδ T cells can have in regulating the consequences of viral infection. γδ T cells are present in the thymus prenatally. It is unknown as to whether they are significantly modulated by maternal prenatal infection. Maternal repeat memory viral infection, but not a naive infection, increases IL-17 and Th17 cells in the offspring [196], suggesting differential effects of repeat versus naïve infection. Vit D, known to decrease Th17 development [197], is decreased in ASD. Vit D also regulates the activity and level of γδ T cells [198]. γδ T cells develop as subsets, expressing predominantly either IFN-γ or IL-17 [199]. Other factors altered in ASD, including IL-18 and Notch [200], also modulate γδ T cells, increasing IFN-γ and IL-17 producing subsets respectively [201,202]. Overall, given the influence of viral infection on γδ T cells and the influence of these cells to the consequences to subsequent infection, it will be important to clarify how relevant γδ T cells are in the etiology and course of ASD, including as to whether prenatal modulation of γδ T cells is relevant to the consequences of postnatal viral infection as a "second hit", often in the second year of life.

Increased myeloid dendritic cells are also evident in ASD children [203]. Dendritic cells are major regulators of T cell subtype activation and proliferation, immune tolerance and innate immunity *via* the phagocytosis of pathogens and debris. Increased myeloid dendritic cells correlate positively with amygdala volume, gastrointestinal symptom severity and repetitive behaviours [203]. Plasmacytoid dendritic cell levels in ASD positively correlate with amygdala volume and developmental regression, suggesting a role for dendritic cell levels and their regulation of immune functioning in the etiology and course of ASD.

Allergy and Mast Cells

Allergy levels are increased in ASD, often without raised serum IgE and chronic urticaria, suggestive of non-allergic

mast cell activation [204]. A number of factors can stimulate mast cells in the absence of IgE, including B-endorphin, substance P and neurotensin, with only the latter being shown to be increased in the serum of ASD children [205]. Mercury's role in the inflammatory etiology to ASD includes increasing mast cell VEGF and IL-6 release; thereby contributing to BBBp, gut permeability and leukocyte extravasation [206]. Similar effects will arise from stress induced CRH and raised levels of circulating mitochondrial DNA, which also increase mast cell activation [207, 208]. The tenfold ASD incidence increase in mastocytosis, suggests a role for mast cell activation in the etiology and course of ASD [209].

Such data highlights the potential importance of permeability regulation, centrally and peripherally, in modulating the influence of the immune system. Factors that modulate mast cell, astrocyte and pericyte activation and reactivity threshold will regulate leukocyte infiltration into the CNS and therefore central immune influence. Many factors can increase BBBp, including IL-1b, TNF-α, MMP2, MMP9, VEGF and C-reactive protein. How such factors are regulated, including in early development, will modulate the influence of BBBp in ASD, consequently impacting on local O&NS, immuno-inflammation and TRYCAT driven neuronal regulation. Activation of the α7nAChr increases the activation threshold of both mast cells and astrocytes [210,211], suggesting that epigenetic, melatoninergic and KYNA regulation of the α7nAChr, will impact on the reactivity of these cells and their role in BBBp and ASD more widely.

SEROTONIN AND TRYCATS

Serotonin

Altered serotonin levels have long been associated with ASD [212]. Prior to foetal endogenous serotonin production placental stores provide serotonin to the developing brain [213]. Factors acting to modulate placental serotonin provision to the foetus require investigation in the etiology of ASD. Maternal platelet serotonin, important in preeclampsia, may also be relevant prenatally. The use of SSRIs in pregnancy, especially in the first trimester, increases the risk of offspring ASD [214]. Such data suggests that serotonin may be relevant to the etiology of ASD.

Early work suggested hyperserotonemia in ASD [212]. However, later work showed decreased central serotonin in ASD, but increased platelet and blood serotonin [215]. Decreasing serotonin by tryptophan depletion exacerbates ASD symptoms, including stereotypies and repetitive behaviours [216], paralleling the effects of serotonin depletion in rodents by tryptophan hydroxylase-2 depletion [217]. This led to treatment with SSRIs [218], not always with positive results [219].

A number of factors can influence serotonin regulation, many of which are susceptibility genes for, or show alterations in, ASD, including genetic variations in tryptophan hydroxylase-2 [220], monoamine oxidase [221] and serotonin transporter alleles [222], suggesting that many factors influencing serotonin regulation are relevant to ASD's etiology and course. The administration of L-5-hydroxytryptophan to ASD teenagers increases levels of blood serotonin, but not in matched controls [223]. Increased plasma cortisol/ dehydroepiandrosterone-sulphate ratio is evident in ASD, and is significantly decreased by serotonin precursor administration [224,225], showing serotonin to modulate wider biological systems in ASD. Serotonin transporter alleles with heightened uptake associate with decreased central serotonin, as indicated by decreased CSF 5-hydroxyindolacetic acid [226]. In a 4-year-old ASD child with high uptake serotonin transporter alleles, the administration of serotonin alleviated symptoms, highlighting the role of decreased serotonin for some people with ASD [226]. In a postmortem ASD sample from 2 to 29 years of age increased serotonin axons levels to the cortex are evident [227], suggesting that a serotonin deficit arises from levels of production and/or release rather than serotonin neuron numbers. Decreased central serotonin also associates with increased aggression [228], linked to altered amygdala-cortex interactions [81]. Overall serotonin is relevant to ASD etiology and course and for some may be an important treatment target.

TRYCATs

Such changes in serotonin are part of wider dysregulation in factors that require tryptophan for synthesis, including IDO and TDO induced neuromodulatory TRYCATs, such as kynurenine (kyn), KYNA and QUIN. Central TDO2 is predominantly expressed in astrocytes and is located at a susceptibility locus for ASD [229]. In rodents the loss of CNS TDO increases levels of serotonin twenty fold, coupled to increased neurogenesis and decreased anxiety [230]. Such data emphasizes the importance of TDO and IDO driven TRYCAT in the regulation of central serotonin and wider processes.

Raised levels of IFN-γ and TNF-α, as well as IL-1β, IL-6 and IL-18, will activate microglia IDO, increasing the range of TRYCATs produced compared to astrocyte TDO activation. IDO driven TRYCATs include picolinic acid the excitotoxic QUIN, both excitatory at the NMDAr. These TRYCATs may contribute to increased levels of epilepsy in ASD, where microglia levels/density are raised in many brain regions [232, 233], although not all studies show increased QUIN and neopterin, an indicant of IFN-γ activation, in the CSF of children with ASD versus other neurological disorders [234]. However, CSF measures are not sensitive enough to show clinically relevant but local and restricted IDO and IFN-γ variations. Astrocyte and neuronal TDO versus microglia IDO will have differential consequences for neuronal regulation *via* differential TRYCAT inductions, as highlighted in rodent stress models [150].

Recent ASD conceptualizations emphasize synaptic dysfunction, including genetic synaptic protein variations [235,236], contributing to seizures in ASD [237]. This may a neuroncentric bias, given the powerful neuromodulatory role of glia and glia TRYCATs, including on NMDAr function [186,238]. In a comparison of gene transcription differences in ASD brains versus controls, two main categories emerged: the first showing suppressed transcription at the synapse; the second showing increased glia and immune activation [239]. These two categories are intimately linked [11]. Rett

syndrome, strongly associated with ASD symptoms, is driven by mutations in MeCP2. Classically the effects of MeCP2 mutations are attributed to synaptic dysregulation. However, recent data shows that MeCP2 in astrocytes and microglia are the major drivers of Rett syndrome, with wild-type microglia in the MeCP2 KO rodent preventing neuronal damage and substantially increasing lifespan [186]. Such data suggests a powerful role for glia in determining the etiology and course of disorders classically linked to synaptic dysfunction. Changes in glia activity and TRYCAT production will significantly modulate synaptic and wider neuronal function in ASD.

Stress, Cortisol and HPA axis

In the rodent chronic unpredictable mild stress model, the shift to depression is driven by increased QUIN in the amygdala and striatum, co-ordinated with increased cortex KYNA [150,240]. Mutations in astrocyte TDO2 in ASD, would suggest that chronic stress effects will be altered, including as to how interarea activity is patterned by TRYCATs in response to stress. As to how increased amygdala volume and activity in ASD would interact with such chronic unpredictable mild stress induced TRYCAT changes are unknown, including as to the relevance of this to the distress associated with eye aversion. Cortisol is a significant inducer of astrocyte TDO. However, raised levels of pro-inflammatory cytokines such as IL-1β can induce astrocyte μ-opioid receptors and enkephalin release. Raised opioid levels are found in ASD, which can negatively feedback on cortisol levels and HPA axis activity. As such wider changes in stress regulation may be relevant in ASD, intimately linked with differential glia and TRYCAT regulation in different CNS areas. With the amygdala being activated under conditions of uncertainty, danger and stress it is likely to be intimately involved in the developmental and interarea patterning changes driving stereotypies and the search for sameness. The differential local regulation of TRYCATs is likely to be intimately associated with alterations in inter-area patterning.

Serotonin, cortisol and TRYCATs are important in stress regulation. Stress driven cortisol induces TDO, increasing kyn and KYNA [241]. Cortisol and HPA axis activation in ASD have produced mixed results [242-244], perhaps reflective of altered processing of social cues and adaptation to change. Decreased sensitivity to adrenocorticotropic hormone (ACTH) induced cortisol may contribute to this, with ACTH positively correlating with ASD symptoms [243, 245]. Lowered diurnal salivary cortisol response occurs in an ASD subgroup with increased repetitive behaviours [246]. As to whether this reflects a dampening of the HPA axis by repetitive behaviours as seen in animals [247] and/or is driven by increased opioidergic regulation of stress responses, with opioids negatively feeding back on the HPA axis requires investigation. Increased central opioidergic activation of the μ-opioid receptor is evident in depression [248], which correlates with circulating IL-18 levels, and could suggest that repetitive behaviours act to dampen chronic stress induced depression. In altering cortisol responses, repetitive behaviours will then impact on levels of cortisol induced TDO and neuron regulating TRYCATs, kyn and KYNA, as well as cortisol impacts on neurogenesis, suggesting that repetitive behaviours will act to modulate wider CNS and peripheral measures, including possibly the shift to depression that is linked to cortex arousal suppression by KYNA.

Early measures of attachment using the Strange Situations Test shows an insecure and often disorganized type of attachment in young ASD children [249]. This is accompanied by a relatively decreased cortisol response, which correlated with the severity of ASD symptoms. This suggests that variations in cortisol response may be relevant early in ASD, linked to repetitive stereotypies, whilst concurrently impacting on TRYCAT regulated neuronal activity and patterning. The role of altered opioidergic regulation in changing early cortisol responses requires investigation, including when driven by maternal high fat diet prenatally.

It should be noted that increased O&NS, immuno-inflammatory processes and decreased central serotonin in ASD are also intimately associated with a number of other disorders, particularly depression [250]. As noted above, and as commonly believed for compulsive behaviours in obsessional compulsive disorder, repetitive behaviours may afford protection against stress-induced depression. As well as alterations in stress regulation, wider aspects of the immune response may be relevant to anxiety and depressive responses, including changes in the microbiome and gut permeability. In contributing to O&NS and immuno-inflammation, the microbiome and gut permeability will modulate both depression and ASD per se. Gastrointestinal dysregulation is common in ASD and has been a significant target for treatment interventions.

MITOCHONDRIA AND ASD

A recent systematic review of the role of mitochondria in ASD found that all included studies showed disruption of the electron transport chain [251]. The prevalence of formal mitochondrial disorder in ASD is around 5%, about 500 times higher than in the general population [252]. The prevalence of abnormal mitochondrial dysfunction biomarkers is much higher than formal mitochondrial disorder in ASD, being estimated to be evident in about 80% of ASD diagnoses [253]. Mitochondrial dysfunction will crucially contribute to, and be modulated by, redox dysregulation. When formal mitochondrial disorder associates with ASD, there is a significantly increased prevalence of developmental regression (52%), seizures (41%), motor delay (51%), gastrointestinal abnormalities (74%), female gender (39%), and elevated lactate (78%) and pyruvate (45%) versus the general ASD population. Mitochondrial dysfunction is suggested to connect the diverse range of symptoms associated with ASD, partly driven by O&NS and decreased anti-oxidants [254]. Mitochondrial dysfunction associates with dysregulation in multiple high-energy consuming organs, including the CNS, gastrointestinal system and muscles. This would suggest that ASD when comorbid with formal mitochondrial disorder, perhaps especially when inhibitory variations in mitochondrial genes are evident, may form a significant subgroup with higher levels of CNS and wider organ dysfunction. For such people targeting mitochondrial

function with CoQ10, B-vitamins, melatonin and carnitine may provide relatively heightened benefit. A downregulation of genes driving mitochondrial oxidative phosphorylation is more widely evident in ASD [255], although the extent of mitochondrial dysfunction may vary across brain regions [256]. As to how this links to differential glia TRYCAT production requires investigation.

Given the increased O&NS and mitochondrial dysfunction in ASD, coupled to the efficacy of CoQ10 in preventing some ASD symptoms [251], it is surprising that no data on the longevity modulating sirtuins is evident in ASD. Sirtuin-3 is present at mitochondria and is a significant regulator of mitochondrial function. Sirtuin-1 regulates peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1α), the master mitochondria regulator, and also contributes to sirtuin-3 maintenance [257]. Sirtuin-1 is also a significant circadian and neurogenesis regulator [258], both altered in ASD [259]. Also increased lipid peroxidation in ASD will induce DNA damage, leading to the induction of poly(ADP-ribose) polymerase-1, which depletes NAD+, driving down sirtuin-1 and PGC-1α, decreasing sirtuin-3 and further contributing to mitochondrial dysregulation, O&NS and autoimmunity. The relevance of this is further suggested by decreased NAD+ in ASD [127].

Although dysregulated mitochondrial function is important in ASD, SNPs in mitochondrial DNA are not strongly associated with ASD [260], suggesting other aspects to mitochondrial regulation are relevant in ASD, including from variations in mitochondria Ca2+ regulation by the aspartate/glutamate carrier-1 [261]. Local mitochondrial dysregulation as a consequence of non-mitochondrial gene variations in specific cell types, such as in synapse Ca2+ regulation [262], will contribute to more local mitochondrial dysregulation and influence on cell functioning [263]. As emphasized above, the impact of such synaptic changes may be strongly determined by glia response.

Local Melatonin, Glia and Inflammation

Pineal circadian melatonin is generally decreased in ASD [264], with mutations in melatonin synthesis genes being ASD susceptibility genes [265,266]. However, melatonin is also produced by astrocytes [267] and many other immune cells, and not unlikely by microglia. In macrophages, NF-κB activation induces melatonin efflux, with autocrine effects that increase phagocytosis, whilst decreasing pro-inflammatory TNF-α and IL-1β [268]. Melatonin generally increases the more beneficial phagocytic and anti-inflammatory response in immune cells, and it is this response that seems crucial to the prevention of Rett syndrome progression in MeCP2 KO rodents with wild-type microglia [269]. As to whether MeCP2 wild-type restores melatonin production in microglia or whether astrocyte melatonin drives microglia phagocytosis and anti-inflammatory activity, including *via* increased MeCP2, is unknown. However, with genetically decreased melatonin in ASD coupled to a decrease in its central precursor serotonin and increased IDO/TDO driving tryptophan to TRYCAT production, there will be an altered local melatonin and NAS response to inflammation, changing the nature of the inflammatory response. With MAO being a susceptibility gene in ASD and MAO being a significant regulator of astrocyte melatonin production [267], coupled to genetically decreased melatonin synthesis, there may be a couple of melatonin regulating susceptibility genes that will alter local glia, and wider immune cells, melatonin production. If decreased glia and immune cell melatonin production occurs locally then a number of consequences may arise: decreased melatonin's antioxidant, anti-inflammatory and beneficial effects on mitochondrial functioning in immune, glia and neuronal cells; altered levels of phagocytosis and microglia/immune cell inflammatory activity; decreased miR-7 induction, leading to increased Kruppel-like factor-4 [270], in turn increasing oxidants, including 4HNE, which can change the conformation and activity of mitochondria associated sirtuin-3 [271]; any decrease in sirtuin-3 will increase mitochondrial oxidants and decrease anti-oxidant SOD levels [272]; loss of NAS activation of the BDNF receptor TrkB [273]. Kruppel-like factor-4 will also increase the excitotoxicity driven by glutamate at the NMDAr [274], increasing Ca2+ influx and mitochondrial dysfunction. As such alterations in local melatonin and NAS production may be significant modulators of O&NS, phagocytosis, inflammatory responses and mitochondrial changes as well as neuronal functioning and survival.

O&NS Treatments

The treatment of ASD is out with the focus of this article. However, as a proof of principle, many studies have shown efficacy of antioxidant and anti-inflammatory treatments, as well as treatment targeted to amygdala functioning, including hydrogen [275], oxytocin and NAD+ [276], vitamin and mineral supplementation [277], naltrexone [278], DSMA metal detoxification [279], GSH and N-acetylcysteine [280]. It should be noted that many of the pharmaceutical used to treat ASD [281] are also powerful antioxidants and anti-inflammatories, including antidepressants [282].

In principle melatonin should be beneficial in many aspects of ASD and data supports this [283]. Many of the prenatal risk factors for ASD involve hypoxia [284], for which melatonin would be expected to be beneficial [285]. Melatonin, in the brain and other organs, is protective against mercury [286-288], attenuating mercury induced lipid peroxidation and antioxidant changes. However, regulators of astrocyte NAS and melatonin production may be of particular value and will be important to determine. Local melatonin can increase MeCP2 [289], leading to many epigenetic effects, including the suppression of the pro-inflammatory cytokine IL-6 [290], and therefore of IL-6 induced IDO and neuroregulatory TRYCATs. With its anti-oxidant, anti-inflammatory and beneficial mitochondrial effects, glia melatonin production may be an important ASD treatment target.

CONCLUSIONS

ASD is a multi-faceted set of disorders with significant genetic, epigenetic and environmental determinants. O&NS, immuno-inflammation, TRYCATs and mitochondrial dysfunction play a significant role in driving the early developmental etiology and course of ASD. Many biological processes are still to be investigated, which may be necessary before a clear conceptualization of ASD, and

possibly early biological markers, can be achieved. A role for decreased local melatonin production by immune and glia cells may be a significant investigative and treatment target.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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