Causes & Prevalence

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Review

Detoxification mechanisms in autism spectrum disorders

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Abstract

Introduction

Xenobiotics are neurotoxins that dramatically alter the health of a child. A three-phase efficient mechanism is involved in detoxifying these toxins. Autism spectrum disorders are neurodevelopmental disorders that result from a combination of genetic or biochemical susceptibilities in the form of a reduced ability to excrete heavy metals and/or increased environmental exposure at early developmental times. This review is an attempt to understand and highlight the impaired detoxification pathways in autistic individuals. Role of glutathione redox imbalance, bacterial toxins, impaired heavy metal detoxification, abnormal levels of metallothionein, thioredoxins, glutaredoxins and peroxiredoxins in the aetiology of autism will be clarified and discussed in detail.

Conclusion

The sulphur redox-related abnormalities indicate that mercury and lead intoxication was associated with increased oxidative stress and decreased detoxification capacity. These mechanisms are circulating with autism-associated abnormal gut microbiota. Understanding these aspects could help in tailoring a combined treatment strategy that could help to reduce the increased prevalence of the disorder.

Introduction

Detoxification, 'Detox', is defined as the capacity to remove any toxic substances from the body. It is one of the major functions of the liver, kidney and gastrointestinal tract. Additionally, it is the biochemical process that transforms non-water-soluble toxins and metabolites into water-soluble compounds that can be excreted in urine, sweat, bile or stool. Endogenous toxins are those that are generated internally as end products of metabolism, bacterial byproducts and other complex molecules. In contrast, external xenobiotics are toxins of external origin such as chemicals and pollutants in the air, water, food additives and drugs.

In recent years, there has been much research directed to understand the remarkable difference of environmental contaminants on children compared with adults. Because children have a smaller body mass than adults, relative exposures to pollutants can be much greater. In addition, children have unique behaviours, diets and physiologic characteristics that put them at higher risk for exposures to environmental toxins. Diets of children are also different from diets of adult because they often eat a limited variety of foods. Adverse health effects can also result from parental exposures before conception, near conception and during pregnancy[1].

Inherited defects or differences in the body's ability to detoxify can contribute to heavy metal accumulation. Deficiencies of certain minerals, vitamins and amino acids reduce the body's ability to excrete toxins following exposure[2,3]. Many studies revealed that prenatal exposures to mercury from mother's amalgams and other mercury sources (thimerosal for RH factor) along with susceptibility factors such as ability to excrete mercury appear to be major aetiological factors in Autism Spectrum Disorders (ASD)[4,5]. While the hair test levels of mercury of infants without autism were positively correlated with the number of the mother's amalgam fillings, vaccination thimerosal exposure and mercury from fish, the hair test levels of those with chronic neurological conditions such as autism were much lower than the levels of controls and those with the most severe effects had the lowest hair test levels concomitant with high body mercury burden.

Understanding factors affecting different aspects of the detoxification mechanisms in autistic patients could encourage the early intervention through supplementation of perfect and safe antioxidants such as *N*-acetyl cysteine, vitamin E, carnosine, melatonin and Coenzyme Q. This could help to reduce the burden of heavy metal toxicity. Of course autistic children, who undergo intensive intervention, can socially and behaviourally do better than children who do not. The aim of this review was to discuss detoxification mechanisms in autism spectrum disorders.

Discussion

The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Phases of detoxification

Detoxification mechanisms occur through three different phases that

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Review

neutralize and solubilize toxins, and transport them to secretory organs (like the liver or kidneys), so that they can be excreted from the body (2). In the first phase, detoxifying enzymes resulting in an intermediary metabolite metabolise the toxin. Although there are several phase I enzymes, the most abundant and important are the cytochrome P-450s (P-450s).

During detoxification, P-450s perform two important functions. First, they make toxins more water soluble and second, convert the toxin into less toxic and, hence, less reactive molecules towards body DNA, proteins and so on. Interestingly, sometimes this phase converts a less toxic molecule into a more toxic molecule. After undergoing phase I detoxification, many toxins are then subject to phase II detoxification.

One of the most important enzymes of phase II is glutathione-*S*-transferases. These enzymes conjugate a reduced glutathione (GSH) molecule with the toxin. Like phase I detoxification, this step also serves to make the toxin water soluble and less toxic to the body. Besides GSH, the body uses several other molecules to bind to the toxin and increase its solubility including sulphates, amino acids and glucuronic acid. However, if we are exposed to excessive amounts of toxins, they could rapidly deplete our GSH reserves resulting in very little GSH available to scavenge free radicals and detoxify toxins.

Finally, phase III of detoxification involves the elimination of toxins from cells. In this step, the products of phase I and II reactions are transported out of cells and into the bloodstream for elimination (Figure 1).

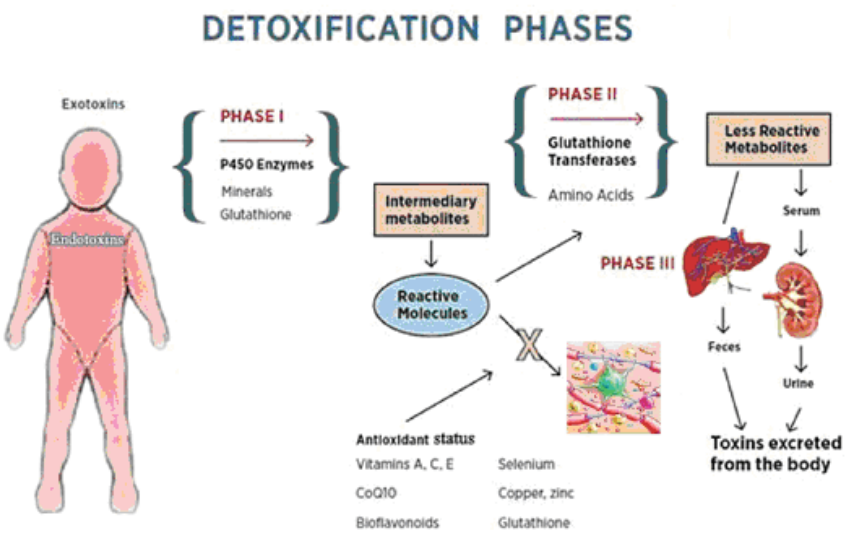

Figure 1: Detoxification phases.

Redox imbalance in autism

A known hypothesis in autism suggests that this disorder is a result of disequilibrium between oxidants and antioxidants in the body, leading to accumulation of reactive oxygen species (ROS). Ordinarily, ROS is removed by superoxide dismutase, catalase and glutathione-related enzymes, as GSH peroxidase and GSH reductase. Accumulation of these reactive species can induce chemical modifications and functional changes of DNA, RNA, protein, lipid and carbohydrate moieties concomitant with cellular dysfunction.

The potential involvement of redox imbalance in the pathogenesis of autism has been suggested by neuropathologic[6], genetic[7] and clinical studies[8]. Differences in allele frequency and/or significant gene interaction between individuals with autism and healthy control subjects were found for relevant genes encoding GSH *S*-transferases, a phase II detoxification enzyme[7].

Peripherally, decreased levels of antioxidant enzymes, such as erythrocyte GSH peroxidase and superoxide dismutase[9], and decreased cellular and mitochondrial GSH were found in several investigations[7–9]. Contradictory evidences reported stimulation of Superoxide dismutase (SOD) in autism indicate increased levels of superoxide radical, which is the first reduction product of molecular oxygen. In contrast, H_2O_2, the product of reaction catalysed by SOD, is a substrate for catalase (CAT) and glutathione peroxidase (GP). Therefore, the higher SOD activity indicates an over production of H_2O_2, which is not apparently compensated by parallel increases in either CAT or GPx activity; the consequent H_2O_2 accumulation may lead to the oxidative stress conditions in the blood of autistic children[11,12]. Decreased plasma *S*-adenosyl-L-homocysteine, as well as *S*-adenosyl-L-methionine, two intermediates in the synthesis of cysteine, which is a key precursor of GSH, had also been reported[8].

Additionally, glutathione status is an excellent indicator of cell integrity and function[13–15]. The ratio of reduced/oxidized glutathione (GSH/GSSG) known as glutathione redox ratio is a sensitive index of oxidative stress, which can lead to and reflect the imbalance between the production and scavenging of ROS. A lower GSH/GSSG may lead to decreased cell proliferation, DNA damage[16] and increased apoptosis[17] that could potentially affect neonatal neurological development. As a decreased glutathione redox ratio has also been reported in many studies of individuals with autistic disorder, it may be hypothesised that a shift in the glutathione redox ratio may play a role in the aetiology of autism[18–21]. Moreover, the remarkable increase of Hg and Pb was reported in autistic patients compared with controls recorded significant increase of both

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toxicants in the hair of autistic compared with non-autistic children[22]. This in turn could reflect the impairment of detoxification mechanism as risk factor greatly contributed in the aetiology of autism since dental amalgams, fish and vaccinations were recorded as sources of mercury vapour, methylmercury and ethylmercury, respectively, to which autistic patients could be exposed during their early childhood[23–25]. Elevation of both metals in autistics could be easily related to and support the previous work of Al-Yafee et al.[21], in which they described autistics as poor detoxifiers, have lower GSH/GSSG ratio and have remarkably less active glutathione-s-transferase (GST) and thioredoxin reductase as markers of detoxification mechanism. It is well known that GSH and GST are critically needed for the detoxification of mercury[26]. While GSH carries Hg through biliary transport for excretion, Hg^{2+} rapidly oxidises glutathione[26]. This could be easily be correlated with the depleted GSH levels repeatedly reported in autistic patients compared with healthy controls[12,27], showing a significant inverse correlation between blood GSH levels and autism severity measured using Childhood Autism Rating Scale (CARS).

Under normal physiologic conditions, glutathione reductase enzyme activity is sufficient to maintain the high GSH/GSSG redox ratio. However, excessive intracellular oxidative stress that exceeds the capacity of glutathione reductase will result in GSSG export to the plasma in attempt to regain intracellular redox homeostasis. Thus, an increase in plasma GSSG is a strong indication of intracellular oxidative stress. Further, GSSG export represents a net loss of glutathione to the cell and increases the requirement for cysteine, the rate-limiting amino acid for glutathione synthesis. Of possible relevance, plasma cysteine levels were significantly reduced in many autistic patients[27]. It is important to note that cysteine is a 'conditionally' essential amino acid that is dependent on adequate methionine status; thus, a decrease in methionine precursor levels effectively increases the requirement for preformed cysteine[28].

Bacterial toxins and autism

It has previously been shown in several studies that the gut microbiota of autistic children contained an overgrowth of *Clostridium* spp., compared with healthy controls[29]. It is possible that chronic diarrhoeal episodes associated with some forms of ASD could be attributed to an overabundance of *Clostridium* spp. and to the accumulation of their uncharacterised neurotoxins, among which is propionic acid (PPA).

Impaired function of gut epithelial is critically involved in the aetiology of autism, so that toxins, bacterial products, lymphocytes, proinflammatory cytokines and neurotransmitters can reach blood circulation and cross the blood–brain barrier[30]. In the system connectivity model, three items lead to leaky gut that includes inflammation, increased zonulin levels such as from an allergic reaction to gluten and cell morphological changes from clostridial toxins. Furthermore, six factors are proposed to contribute in gut inflammation in autism pathogenesis: clostridial toxins, hydrogen sulphide from *Desulfovibrio*, dietary allergens such as gluten, reduced removal of toxic heavy metals such as Hg and Pb, reduced sulphation detoxification of xenobiotic compounds and an inflammatory cytokine imbalance towards proinflammatory cytokines. Another mechanism, through which toxins (e.g. Hg and Pb) could be related to brain dysfunction in autistic patients, is the activation of brain mast cells especially in those areas associated with behaviour and language. This could lead to brain allergies and subsequent focal encephalitis. Of course, this is more likely occur in the subgroup of autistic patients with mast cell activation a susceptible gene[31].

In relation to gut microbiota, a recent study done by Persico and Napolioni[32] shows that exposure to the organic aromatic toxin *p*-cresol (4-methylphenol) was found to contribute in worsening autism severity and gut dysfunction. It is well known that the main source of this compound is represented by some gut bacteria, which expresses *p*-cresol synthesising enzymes not found in human cells. Urinary *p*-cresol and its conjugated derivative *p*-cresylsulphate have been found to be elevated in autistic children below 8 years of age, where it is associated with female sex, clinical severity regardless of sex and history of behavioural regression. Potential sources of *p*-cresol excess in autism could be attributed to gut infection, chronic constipation, antibiotics and leaky gut.

Among other behaviourally active, gut-derived bacterial metabolites related to autism is PPA, a short chain fatty acid produced in the gut by anaerobic bacteria including Clostridia and Propionibacteria, through fermentation of dietary carbohydrates and several amino acids[33]. Intracerebroventricular administration of PPA to young rats yields behavioural abnormalities similar to autism, neuroinflammation in the form of activated microglia and reactive astrogliosis[34], similar to those detected in postmortem autistic brains[35]. Oral administration of PPA was effective in inducing persistent biochemical alteration typical to those seen clinically in autistic patients, for example proinflammation, neurotransmitters alteration, impaired energy metabolism and pro-apoptotic changes[36] (Figure 2).

Metallothionein and metal detoxification in autism

Developmental exposure to transition metals such as mercury causes cognitive impairment[37]. Organic mercury (methyl or ethyl) is a much more potent neurotoxicant than metallic mercury; however, metallic mercury

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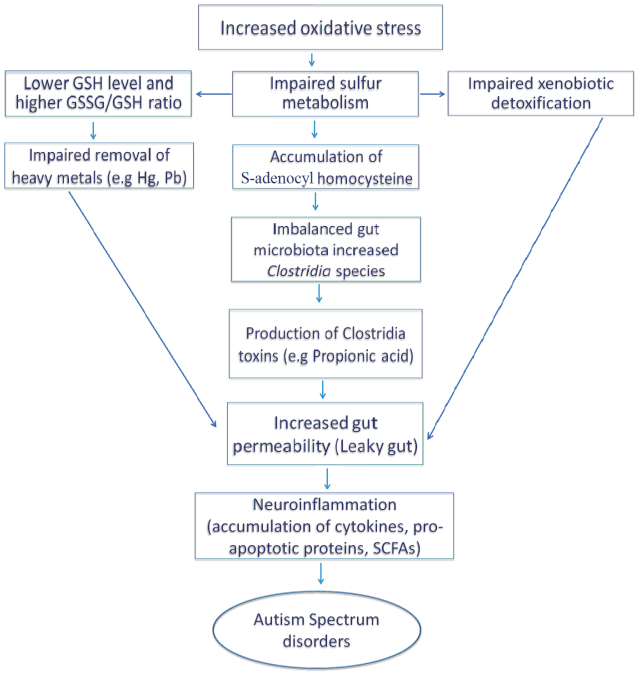

Figure 2: Proposed mechanism of circular relationship among oxidative stress, sulphur metabolic deficiencies and pathogenic alteration of gut microbiota.

($HgCl_2$) has neurotoxic effects as well. With low-level mercury exposure, there is considerable variation in toxic response. This may be due to heterogeneity of control over the distribution and detoxification of mercury.

Metallothionein (MT) is a cysteine-rich protein involved in homeostasis of essential metals, detoxification of toxic metals and scavenging of free radicals[38]. In humans, there are four major MT isoforms: the ubiquitous MT-1 and MT-2[38], the brain-specific MT-3[39] and the squamous epithelium-specific MT-4[40]. Abnormalities in MT level and/or structure, together with the presence of anti-MT antibodies, have been hypothesised to be associated with autism[41]. Again this could support the role of impaired detoxification mechanism in the pathophysiology of autism. The critical role of MT system in detoxifying mercury was investigated by Eddins et al. [42], who proved that MT-1/MT-2-null mice are more susceptible to environmental Hg exposure that in turn could explain the reported higher levels of mercury in autistic patients[43].

Helal et al.[44] reported that MT induction by zinc sulphate inhibits carmustine (BCNU)-induced hippocampus toxicity in rats with subsequent preservation of cognition. MT effects were attributed to its potency in preventing glutathione reductase inhibition, GSH depletion and counteracting the increased levels of tumour necrosis factor-α, lipid peroxides and caspase-3 activity. Based on the neuroprotective role of MT[44], its potency in ameliorating the increased ROS and caspase-3 as markers of oxidative stress and pro-apoptosis, respectively, together with the anti-inflammatory, anti-apoptotic[45] and MT-1/ MT-2 expression-induced effects of gold, implanting gold was suggested as novel hypothesised treatment strategy for autistic patients[46].

Thioredoxins, glutaredoxins and peroxiredoxins in autistic patients

Thioredoxins (Trxs), glutaredoxins (Grxs) and peroxiredoxins (Prxs) have been characterised as electron donors, guards of the intracellular redox state and 'antioxidants'. Today, these redox catalysts are increasingly recognised for their specific role in redox signalling[47]. The role of these proteins in the regulation or removal of ROS and oxidative stress is not well understood in the CNS. In agreement with several reports[48], the Trx1 and Trx2 are present in most regions of the CNS for both neurons and neuroglia. Trxs have been implied in neuroprotection during a hypoxic/ischaemic insult in the CNS Trx1 and Trx2 concentrations are low in the hippocampus, which could explain the vulnerability of this region to oxidative stress[49,50]. Intravenous administration of recombinant human Trx1 in mice was reported to decrease the hippocampal brain damage following transient focal cerebral ischaemia. The administration of Trx1-reduced protein carbonyl content and attenuated the activation of the stress-related Mitogen activated protein kinase (MAP kinase) p38 in response to the ischaemic insult[51]. Trx2 is the mitochondrial Trx and an important factor for cell viability. Fibroblasts of Trx2 knockout embryos undergo extensive apoptosis[52]. Trx2 can interact with mitochondrial respiratory chain components, affecting the mitochondrial membrane potential and apoptosis[53].

In addition to its protective role, the Trx system is involved in many cellular processes, such as cell signalling, transcriptional regulation and DNA synthesis[54]. One of the most important roles of the Trx/TrxR system is to maintain reduced redox status and prevent oxidative stress. This function is holding up mainly by the Prx system. Recently, Drechsel and Patel[55] demonstrated that Trx/Prx is the major contributing enzyme system to respiration-dependent H_2O_2 scavenging in brain mitochondria, while GSH/GPx and non-enzymatic systems show only minor contributions. Overexpression of

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Review

TrxR as a major antioxidant enzyme, recently reported by Al-Yafee et al.[21], again supports the role of oxidative stress in the pathology of autism[12,54]. This pathway could be easily followed in Figure 3. In addition, over expression of both Prx1 and Prx3 as biomarkers of oxidative stress in autistic patients compared with age and gender-matching control subjects could support their roles in the pathology of autism[21]. Besides their protective antioxidant function, Prxs appeared to play an important role in cell proliferation, differentiation, immune response, regulation of cellular H_2O_2 and control of apoptosis[56]. Prx3 overexpression alters the mitochondrial membrane potential, reduces endogenous cellular H_2O_2 levels. The results of Nonn et al.[57] suggested that mitochondrial Prx3 is an important regulator of H_2O_2 in the cell. They reported that at low physiological levels of H_2O_2, Prx3 inhibits the growth-stimulating effects of H_2O_2, while at higher levels of H_2O_2 generation, Prx3 protects cells against apoptosis[58].

Conclusion

A confirmed impaired detoxification mechanism in autistic patients could support the use of GSH/GSSG, GST, Trx, TrxR and Prx together with increased Pb and Hg burden as biomarkers for the early diagnosis of autism.

A circular relationship represented by oxidative stress and sulphur metabolic deficiencies could be related to the pathogenic changes in gut microbiota composition, which in turn could lead to elevated oxidative stress in autistic individuals.

A combined treatment to combat intestinal permeability, pathogenic bacterial overgrowth and sulphur-related metabolic deficiencies could be promising in treating autistic patients.

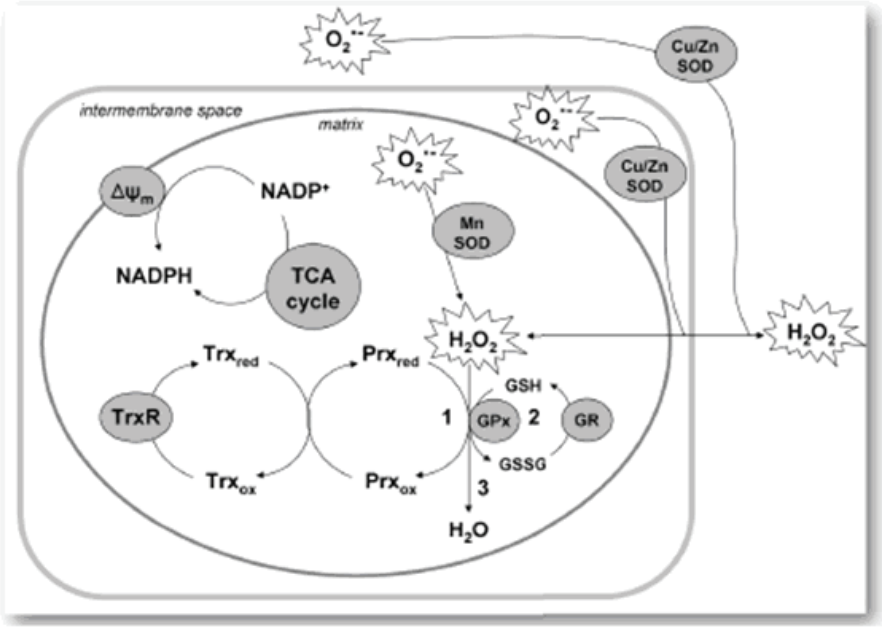

Figure 3: Role of thioredoxinperoxidoxin system and glutathione system in detoxifying brain mitochondrial H_2O_2.

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