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TOXICANT LOSS OF IMMUNE TOLERANCE, NEUROLOGIC DISEASE, AND NUTRITIONAL STRATEGIES

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ABSTRACT

This paper reviews immunology models of chemical tolerance and the role they may play with the pathogenesis of neurological autoimmune and neurodegenerative disease and how we may be able to reduce the impacts of these adverse reactions with various nutritional applications. The immune model of chemical tolerance describes how trace amounts of exposures to various chemicals commonly found within our environment lead to exaggerated immune responses turning on the cascade of immune dysregulation and systemic inflammation leading to neurological disease. Immune chemical tolerance is maintained by healthy integration of various immune cells that can be disrupted from toxicant exposure, chronic stress physiology, blood-brain barrier compromise, intestinal barrier compromise, hormone imbalances, antigenic models, oxidative stress models, and various mechanisms that induce loss of healthy immune integration. These mechanisms themselves have been shown to have the ability to be manipulated and modulated with various nutritional applications. With an increasing epidemic of toxicant load and virtually no conventional or pharmaceutical strategies to decrease their impacts on human systems evidence-based consideration leads us to the potential role of various natural compounds that exhibit activity that can decrease the expression NF-kappaB, optimize glutathione redox systems, improve barrier system impermeability, and support regulatory T-cell activity all which is essential to improve chemical immune tolerance environmental toxicants.

Keywords: Autoimmune, neurodegenerative disease, environment, chemical tolerance, oxidative stress, blood-brain barrier, nutrition

INTRODUCTION

There is no question that environmental pollution and toxins have potential for severe adverse impacts on both developmental brain health and inflammatory and autoimmune mechanisms of neurodegeneration [1]. We are living in a world that has changed dramatically within our lifetimes. We are now exposed to countless chemicals, hybridized foods, and genetically modified foods, all of which are very immune activating. Additionally, the increased use of pharmaceutical drugs is increasing rapidly. This polypharmacy model of various drugs potentially has diverse impacts on human physiology beyond known adverse reactions and iatrogenic causes of death and disability. The U.S. consumption of foods known as the Standard American Diet (SAD) is not only very

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inflammatory but also very immune activating. The combination of chronic exposure to immune triggering pollutants, toxins, and inflammatory foods has potentially contributed to various inflammatory ailments that we as clinicians face today. Many have theorized that the growing development of autoimmunity, autism, and neurodegenerative diseases and other chronic inflammatory conditions may be result of our newly immune reactive environment [2-5].

Chemical Tolerance

Chemical tolerance is our immune system's ability to react proportionately to compounds such as toxins, pollutants, and environmental proteins. The loss of chemical tolerance is a phenomenon both researchers and clinicians have identified as a mechanism leading to disease and inflammatory promoting reactions to commonly exposed pollutants within the environment that then lead to pathophysiological expression leading to chronic illness [6].

Immune chemical tolerance is dependent upon many overlapping physiological factors that include regulatory T-Cell integrity, antioxidant reserves, barrier system integrity, and integrity of hepatic biotransformation pathways. All of these systems can be compromised with various toxins; however these systems can also be compromised unrelated to toxin exposure from various etiologies and also lead to loss of chemical tolerance. Our immune system has some degree of tolerance to our environment however and loss of immune tolerance may lead to neurological autoimmunity involving known autoimmune diseases such as multiple sclerosis, autoimmune neuropathy, etc., but it may also be an underlying autoimmune factor for diseases such as Alzheimer's, Parkinson's, and autism [7-9].

The unprecedented levels of chemicals and heavy metals today, as well as hybridized, genetically modified, and industrially processed foods, all activate the immune system towards a proinflammatory expression. Only a minority of the synthetic compounds introduced to our environment have been researched individually, much less in conjunction with one another. The Environmental Protection Agency (EPA) doesn't require testing on chemicals introduced to market unless evidence of potential harm exists, which means testing seldom happens. The EPA approves about 90 percent of new chemicals and only a quarter of more than 80,000 have been tested for toxicity [10]. Americans are born with increasingly high levels of chemical and toxin burdens. For example, a 2005 study of cord blood from newborns found almost 300 environmental compounds, including mercury and DDT. Another study showed first-time mothers in the United States had levels of flame retardants in their breast milk 75 times higher than in similar European studies. Environmental toxins have been linked with neurodegenerative conditions such as Alzheimer's and Parkinson's disease [13-15].

NF-κB and Chemical Immune Reactivity

Environmental toxicant activations of NF-kappaB is a powerful force capable of igniting relentless inflammatory cascades that play a role in neurological degeneration, autoimmunity, cancer, and loss of chemical tolerance. [16]. NF-κB is a protein inside of cells that acts as a switch to turn inflammation on and off in the body. It responds to whatever may be conceived as a threat to the cell, including environmental toxins, toxic metabolites, pollutants, and xenobiotics [17]. Systemic toxic load increase NF-κB activation promotion inflammation degradation of the barriers of the gut, brain and lungs, further increasing inflammation and loss of chemical tolerance [18]. Chronic activation of NF-κB also impairs cytochrome p45O hepatic biotransformation phase 1 oxidation/reduction reactions yielding compounds that are more immunoreactive and further perpetuating loss of chemical tolerance and perpetuation of inflammatory cascades that have potential to activate environmental hapten-induced neurodegeneration or autoimmunity [19-23].

It has been shown recently that NF-κB is required for activation of autoreactive T-cells, and its hyperactivity in monocytes and dendritic cells results in altered cytokine secretion and antigen presentation, which ultimately contribute to the initiation of autoimmunity [24]. An increasing number of studies indicate that NF-κB plays an important role in controlling the expression of genes relevant to the pathogenesis of autoimmunity. NF-κB is a protein complex that controls the transcription of DNA. It is found in all cell types and is involved in cellular responses to stimuli, such as stress, cytokines, free radicals, and antigens. NF-κB controls the expression of genes encoding the proinflammatory cytokines, chemokines, adhesion molecules, inducible enzymes (COX-2 and iNOS), and growth factors [25].

Once the NF-κB amplifying loop is activated, it may persist as an expression of chronic inflammation and autoimmunity, unless an active NF-κB inhibitor is provided. The two most naturally powerful supporters of a healthy NF-κB suppression are resveratrol and curcumin [26]. In recent studies, both curcumin and resveratrol have supported healthy numbers of T-cell cytokines [27, 28]. These results suggest the potential use of these select phytochemicals for supporting healthy immune responses. Research indicates that curcumin has the potential to support cardiovascular health through the minimization of IL-1beta, TNF-alpha, GATA-4 and NF-κB expression [29]. Curcumin has been shown to support healthy anti-inflammatory response. Studies show both compounds are effective in protecting the body from damage due to environmental toxins and for dampening NF-κB activation and inflammation [30-32].

Glutathione and Chemical Tolerance

Glutathione serves as key antioxidant to protect cells from environmental toxicants and pollutants by converting from reduced glutathione (GSH) to oxidized glutathione (GSSG), but even before the oxidation of glutathione occurs at the cellular level, glutathione is also involved with quenching oxidative stress occurring at our immune barrier to limit external chemical haptens exposure to our internal physiology [33]. Glutathione also supports both Phase I and Phase II hepatic biotransformation systems necessary for hepatic metabolic clearance of toxic metabolites [34]. Each of these mechanisms of glutathione protect us from toxicant induced neurological disease and neurological autoimmune disease to some degree and research has found that loss of chemical tolerance or autoimmunity may be kept in check at various levels by the pleiotropic impacts of glutathione [35,36]. GSH depletion is associated with environmental-induced inflammatory reactions. Researchers are now finding that environmental pollutants do not trigger an immune response until glutathione levels are depleted [37-39].

Continued oxidative stress from chemicals, immune-reactive proteins, and infections all deplete the glutathione protective system at our barriers. However, when glutathione becomes depleted there is no protection for the barrier system and free radicals can readily destroy them leading to exposure of chemicals and large particles to the underlying immune cells of the barrier system. This can lead to exaggerated inflammatory responses and be participating in a vicious cycle in those that suffer from chronic loss of immune tolerance integrity [40-45].

Glutathione doesn't just protect cells from chemical oxidants is also possess natural chelation properties that allow the tripeptide to bind to environmental compounds and help remove them from the body without displacing them into other tissues, such as the brain that occurs with chelator [46-50].

Numerous botanicals have been found to support glutathione levels in our body from various mechanisms. N-acetyl-cysteine is a key compound to glutathione activity. It is rapidly metabolized into intracellular glutathione [51-52]. Alpha-lipoic acid directly recycles and extends the metabolic life spans of vitamin C, glutathione, and coenzyme Q10, and it indirectly renews vitamin E, all of

which support glutathione recycling [53-54]. L-glutamine is important for the generation of glutathione and oral ingestion is transported into the cell, converted to glutamate, and readily available to intracellular glutathione synthesis [55-57]. Selenium is a trace element nutrient that serves as the essential cofactor for the enzyme glutathione peroxidase, which converts GSH to GSSG so glutathione can quench free radicals in order to spare cells [58-60]. Cordyceps has been shown to activate both glutathione and peroxidase synthesis in the body and protect cells by engaging the glutathione enzyme cycle. Cordyceps increases glutathione levels in the cells by 300 percent within minutes [61-62]. Oral ingestion of Centella asiatica rapidly and dramatically increases the activity and amount of glutathione peroxidase and the quantity of glutathione [63]. Milk thistle has been shown to significantly increase glutathione, increase superoxide dismutase activity, and positively influence the ratios of reduced and oxidized glutathione [64,65]. In addition to the Pro-GSH compounds listed above that are useful in supporting glutathione recycling. Glutathione can also be taken directly, but only if it is the S-Acetyl-Glutathione. This form of glutathione has been shown to be efficiently absorbed unlike other versions [66-70].

Toxicants, Chemical Tolerance and Immune Barrier Systems

Many of the top ten Unites States list of hazardous substances, established by the Agency for Toxic Substances and Disease Registry, are found in such high levels that the chemicals themselves are leading to continued oxidative stress and breakdown of the barriers. Polychlorinated biphenyls (PCB), listed #4 on the top 10 list of hazardous substances, has been shown to disrupt the blood-brain barrier [71, 72]. Chronic exposure of arsenic in human water has been shown to alter the lung epithelial barrier and restrict wound repair [73]. Pesticides have also been found in food and drinking water and therefore are now considered a major route of exposure to the general population. The organo-photothionates in pesticides have been found to directly cause intestinal tight junction breakdown [74]. Polychlorniated biphenyls commonly found in the environment have also been found to cause alterations in tight junction integrity [75]. Unfortunately, it now appears that because of the commonly found chemicals in our environment, it itself is contributing to breakdown of our barrier system that is in turn leading to loss of chemical tolerance.

The blood-brain barrier (BBB) maintains central nervous system homeostasis by preventing entry of substances that may alter or harm neuronal function, and also allows chemicals necessary for brain function to cross. The BBB is a membrane structure composed of endothelial cells surrounded by astrocyte cell projections tightly surrounded in brain capillaries. The BBB was first discovered by bacteriologist Ehrlich in the 19th century while he was performing tissue staining. When he injected animals with staining chemicals, all of the structures in the body would be stained except the brain. When he injected into the central nervous system he found that the stain would not penetrate outside of the central nervous system. These observations led him to conclude that there was a barrier between the central nervous system and the rest of the body. When the electron microscope was invented in the 1960s, the actual BBB membrane could be demonstrated.

The structural composition of the BBB easily allows the entry of oxygen, carbon, dioxide, fatty acids, ethanol, and steroid hormones. Certain amino acids and sugars may also cross the BBB necessary for energy metabolism and neurotransmitter synthesis. However, neurotransmitters cannot cross the BBB with the exception of epinephrine and norepinephrine at thin areas of the BBB found in the hypothalamus. The BBB has special sites present with thinner membranes where its permeability is penetrated easier. These are a normal part of the BBB and include three important circumventricular organs, the subfornical organ, the area postrema, and organum vasculosum of the lamina terminalis. These hypothalamic integrative centers are very important for regulating fluid electrolyte balance,

sodium excretion, blood volume, regulation of vasopressin secretion, and detecting toxins in the blood to induce vomiting [76].

The BBB restricts B cell entry and protects the brain from general infections. Therefore, infections rarely occur in the brain, but when they do occur they are very difficult to manage. In cases of extreme infection, the BBB will lose its membrane integrity and immune cells from the peripheral system such as macrophages and bone marrow-derived progenitor cells will cross into the brain. Once the infection has been managed, the BBB membrane is reestablished [77]. Loss of BBB integrity has been proposed for the etiology of numerous disease processes including meningitis, multiple sclerosis, Alzheimer's disease, and Parkinson's disease [78-80]. Loss of BBB integrity may lead to infiltration of environmental compounds (haptens), dietary proteins, or pathogenic organisms (antigens) to expose them to microglia and activate a neuroinflammatory response. The BBB has demonstrated loss of integrity from alcohol exposure [81], stress responses [82], elevated homocysteine [83,84], hyperglycemia [85], prostaglandin imbalances [86], and oxidative stress [87].

Regulatory T-Cells and Chemical Tolerance

Regulatory T cells, are a subpopulation of cells that downregulates the immune system, maintains tolerance to self-antigens, and down-regulates autoimmune disease. Regulatory cells are a component of the immune system that suppresses the immune responses of other cells. This is an important "self-check" built into the immune system to prevent excessive reactions. Regulatory T cells come in many forms, with the most well understood being those that express CD4, CD25, and Foxp3 ($CD4^+CD25^+$ regulatory T cells). These cells are involved in shutting down immune responses after they have successfully eliminated invading organisms and also in preventing autoimmune T_H1 and T_H2 polar shifts. They play a critical role in both the modulation of autoimmunity and loss of chemical tolerance [88-90].

Regulatory T cell function can be supported with glutathione and vitamin D. When nutritionally supporting loss of chemical intolerance, vitamin D levels should always be addressed. Research shows vitamin D plays a critical role in the development of general tolerance, immune system defense, immune balance (regulatory T-cells) and immune barrier integrity [91-92]. On a 25-hydroxy vitamin D test, it is ideal to see a level no lower than 50 ng/mL. Several nutrients have been shown to support the regulatory T cells, such as vitamin D and glutathione support [93-97].

CONCLUSION

Toxicants, environmental pollutants, and inflammatory reactions lead to immune loss of chemical tolerance. Loss of immune chemical tolerance leads to increase oxidative, inflammatory, and immunoreactive responses to vulnerable tissues such as the brain and nervous system thereby promoting neurodevelopment disorders such as autism, neurodegenerative diseases such as Parkinson's and Alzheimer's, and neurological autoimmune disorders such as multiple sclerosis. Physiological depletion of glutathione redox systems, wind-up and amplification of NF-kappaB inflammatory expression, immune barrier system breakdown, and regulator T cell dysregulation all play key roles in maintaining healthy immune chemical tolerance. Nutritional strategies that may impact the integrity and the expression of these physiological systems may provide some potential support to address the growing concerns of environmental induced brain disease and neurological autoimmune disorders.

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