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Research Article,

Neurologic Disease Caused By Toxic Followed By Immune Tolerance

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Abstract:

It's a research which discusses immunological models of chemical tolerance, the potential role they may play in the aetiology of neurological autoimmune and neurodegenerative disease, and possible dietary approaches to mitigate the effects of these unfavourable responses. According to the immune model of chemical tolerance, small amounts of exposure to a variety of chemicals that are frequently present in our environment trigger exaggerated immune reactions that set off a chain reaction of immune dysregulation and systemic inflammation that results in neurological disease. Immune chemical tolerance is maintained by the healthy integration of different immune cells. This integration can be lost due to toxicant exposure, chronic stress physiology, blood-brain barrier compromise, intestinal barrier compromise, hormone imbalances, antigenic models, oxidative stress models, and other mechanisms. These pathways may be changed and controlled by a variety of dietary applications, it has been shown. Evidence-based consideration points to the potential role of various natural compounds with activity that can reduce the expression of NF-kappaB, optimise glutathione redox systems, improve barrier system impermeability, and support regulatory T-cell activity, all of which are crucial to improve chemical immune tolerance. There is an epidemic of toxicant load, and there are essentially no conventional or pharmaceutical strategies to decrease their impacts on human systems.

Keywords: Autoimmune Conditions, Blood-Brain Barrier, Oxidative Stress, Neurodegenerative Conditions, Cytotoxins

Introduction:

There is little doubt that environmental pollutants and pollution have the potential to have serious negative effects on the health of the developing brain as well as the inflammatory and autoimmune systems that cause neurodegeneration [1]. Within our lives, the world in which we now reside has undergone significant transformation. The many chemicals, hybridised foods, and genetically engineered foods to which we are currently exposed all have a strong immune-stimulating effect. In addition, the usage of pharmacological medications is expanding quickly. Beyond established adverse responses and iatrogenic causes of mortality and disability, this polypharmacy model of numerous medications may have varied effects on human physiology. The Standard American Diet (SAD), which is what most Americans eat, is extremely immune-activating and inflammatory. The variety of inflammatory illnesses that we as doctors deal with today may have been influenced by the interaction of long-term exposure to immune-stimulating pollutants, poisons, and inflammatory diets. Numerous people have hypothesised that our environment's increased immunological

reactivity may be the cause of the rise in autoimmunity, autism, neurodegenerative illnesses, and other chronic inflammatory problems [2–5].

Immune system and toxins:

m's capacity to respond appropriately to substances like poisons, pollutants, and environmental proteins is known as chemical tolerance. Researchers and clinicians have recognised the phenomena of loss of chemical tolerance as a mechanism causing sickness and inflammatory responses to frequently exposed environmental contaminants, which in turn causes pathophysiological expression resulting in chronic illness [6]. Immune chemical tolerance depends on a number of interrelated physiological parameters, including the health of the barrier system, antioxidant reserves, regulatory T-cells, and hepatic biotransformation pathways. All of these systems are susceptible to being compromised by a variety of toxins, but they may also become affected for reasons unrelated to toxin exposure and result in the loss of chemical tolerance. The loss of immune tolerance, however, can cause neurological autoimmunity, including autoimmune diseases like multiple sclerosis, autoimmune neuropathy, etc. It may also be an underlying autoimmune factor for conditions like Alzheimer's, Parkinson's, and autism [7-9]. Our immune systems are somewhat tolerant to our environment. Hybrid, genetically modified, and industrially processed foods, as well as the unprecedented quantities of chemicals and heavy metals present today, all stimulate the immune system to express itself in a proinflammatory manner. Few, if any, of the synthetic substances that have been added to our environment have been studied alone, much less in combination. The Environmental Protection Agency (EPA) accepts around 90% of new compounds, and only 25% of more than 80,000 have been evaluated for toxicity [10]. The EPA does not mandate testing on chemicals brought to the market until proof of potential damage emerges. Increased chemical and toxic loads are present at birth in Americans. For instance, a 2005 study of babies' cord blood discovered over 300 environmental substances, including mercury and DDT. According to a different research, American first-time moms had levels of flame retardants in their breast milk that were 75 times greater than those in comparable trials conducted in Europe. Neurodegenerative diseases including Alzheimer's and Parkinson's disease have been related to environmental pollutants [13–15]. The activation of NF-kappaB by environmental toxins is a potent catalyst for protracted inflammatory cascades that contribute to neurological decline, autoimmune disease, cancer, and decreased chemical tolerance. [16]. An internal protein called NF-B functions as a switch to turn on and off inflammation in the body. It reacts to everything that may be considered a danger to the cell, such as xenobiotics, toxic metabolites, contaminants, and environmental toxins [17]. The barriers of the stomach, brain, and lungs are degraded as a result of systemic toxic load rise, NF-B activation, inflammatory promotion, and loss of chemical tolerance [18]. Chronic NF-B activation also impairs phase 1 oxidation/reduction reactions of the cytochrome p45O hepatic biotransformation, which results in compounds that are more immunoreactive and further prolongs loss of chemical tolerance as well as inflammatory cascades that have the potential to trigger environmental hapten-induced neurodegeneration or autoimmune disease [19–23]. The recent discovery that NF-B is essential for the activation of autoreactive T-cells leads to increased cytokine production and antigen presentation in monocytes and dendritic cells, which eventually aid in the onset of autoimmunity [24]. Numerous studies suggest that NF-B is crucial for regulating the expression of genes involved in the aetiology of autoimmunity. A protein complex called NF-B regulates DNA transcription. Involved in cellular reactions to stimuli including stress, cytokines, free radicals, and antigens, it is present in all cell types. Proinflammatory cytokines, chemokines, adhesion molecules, inducible enzymes (COX-2 and iNOS), and growth factors are all under the control of NF-B [25]. If an active NF-B inhibitor is not present, the NF-B amplification loop may continue to produce chronic inflammation and autoimmune disease. Resveratrol and curcumin are the two naturally occurring substances that assist a healthy NF-B suppression the most [26]. Both curcumin and resveratrol have been shown

in recent research to promote healthy levels of T-cell cytokines [27, 28]. These findings point to a possible application of these particular phytochemicals for promoting healthy immune responses. Curcumin may promote cardiovascular health by reducing the expression of IL-1beta, TNF-alpha, GATA-4, and NF-B, according to research [29]. It has been shown that curcumin supports a healthy anti-inflammatory response. Both substances are efficient in preventing NF-B activation and inflammation, according to studies [30–32]. They also protect the body from harm caused by environmental pollutants.

By converting from reduced glutathione (GSH) to oxidised glutathione (GSSG), glutathione acts as a critical antioxidant to protect cells from environmental toxins and pollutants. However, even before glutathione is oxidised at the cellular level, glutathione is also involved in quenching oxidative stress at our immune barrier to limit the exposure of external chemical haptens to our internal physiology [33]. The hepatic metabolic clearance of hazardous compounds requires both Phase I and Phase II hepatic biotransformation systems, both of which are supported by glutathione [34]. Each of these mechanisms of glutathione protects us to some extent from toxicant-induced neurological disease and neurological autoimmune disease, and research has discovered that the pleiotropic effects of glutathione may be used to regulate chemical intolerance or autoimmunity at different levels [35,36]. Inflammatory responses brought on by the environment are linked to GSH depletion. According to recent findings, environmental toxins do not start an immune response until glutathione levels are low [37–39]. The glutathione protection mechanism at our barriers is continuously depleted by oxidative stress brought on by chemicals, immune-reactive proteins, and viruses. However, as glutathione levels drop, the barrier system is no longer protected and free radicals may easily damage them, exposing chemicals and big particles to the barrier system's underlying immune cells. In those who have a persistent loss of immunological tolerance integrity, this may trigger heightened inflammatory reactions and contribute to a vicious loop [40–45]. Glutathione has natural chelation properties that enable the tripeptide to bind to environmental compounds and aid in their removal from the body without displacing them into other tissues, such as the brain, as is the case with chelators [46–50]. As a result, it does more than just protect cells from chemical oxidants. Numerous plants have been discovered to boost the body's glutathione levels via a variety of processes. A crucial component for glutathione function is N-acetyl-cysteine. It converts quickly to intracellular glutathione [51–52]. Vitamin C, glutathione, and coenzyme Q10's metabolic life spans are directly recycled and prolonged by alpha-lipoic acid, while vitamin E is indirectly renewed. which aid in the recycling of glutathione [53–54]. Oral consumption of L-glutamine is immediately accessible for intracellular glutathione production and is taken into the cell where it is converted to glutamate [55–57]. An crucial cofactor for the enzyme glutathione peroxidase, which changes GSH into GSSG so glutathione may scavenge free radicals in order to protect cells, is selenium, a trace element vitamin [58-60]. It has been shown that cordyceps stimulates the body's production of glutathione and peroxidase and protects cells by triggering the glutathione enzyme cycle. Within minutes, cordyceps causes a 300 percent rise in glutathione levels in cells [61–62]. Glutathione peroxidase activity and glutathione levels are both markedly and quickly increased by oral administration of Centella asiatica [63]. It has been shown that milk thistle dramatically raises glutathione levels, boosts superoxide dismutase activity, and has a favourable impact on the ratios of reduced and oxidised glutathione [64,65]. In addition to the above-mentioned Pro-GSH molecules, there are other substances that may help glutathione recycling. The S-Acetyl-Glutathione form of glutathione is the only one that may be consumed directly. Contrary to other forms, this glutathione has been found to be well absorbed [66–70].

Many of the top 10 dangerous compounds in the United States, according to the Agency for Toxic Substances and Disease Registry, are present in such high concentrations that the chemicals themselves are causing oxidative stress and barrier collapse. Blood-brain barrier disruption has been linked to polychlorinated biphenyls (PCB), which

is ranked #4 on the list of the top 10 dangerous compounds [71, 72]. It has been shown that long-term exposure to arsenic in human water alters the lung epithelial barrier and prevents wound healing [73]. Since pesticides have been discovered in both food and drinking water, they are now recognised as a significant source of exposure for the general public. It has been discovered that the organo-photothionates present in pesticides directly contribute to intestinal tight junction disintegration [74]. Tight junction integrity has also been reported to change as a result of polychlorinated biphenyls, which are often present in the environment [75]. Sadly, it now seems that the prevalent chemicals in our environment are itself contributing to the breakdown of our barrier system, which is in turn causing us to lose our ability to tolerate chemicals. The blood-brain barrier (BBB) permits chemicals required for brain function to pass while blocking substances that might change or impair neuronal function from entering and maintaining the homeostasis of the central nervous system. The BBB is a membrane made up of endothelial cells that are firmly encircled by astrocyte cell projections in the brain capillaries. Ehrlich, a bacteriologist, made the first discovery of the BBB in the 19th century while staining tissue. All the bodily organs would be discoloured when he administered chemical stains to animals, except the brain. He discovered that the stain would not pass outside of the central nervous system when he injected into it. He came to the conclusion that the central nervous system and the rest of the body were separated by a wall as a result of his observations. The BBB membrane could be seen in person when the electron microscope was created in the 1960s. The BBB's structural makeup makes it simple for substances including oxygen, carbon dioxide, fatty acids, ethanol, and steroid hormones to enter. For the creation of neurotransmitters and the metabolism of energy, some carbohydrates and amino acids may also pass across the BBB. Neurotransmitters, with the exception of epinephrine and norepinephrine in thin sections of the BBB located in the hypothalamus, cannot cross the BBB, however. Special locations inside the BBB with thinner membranes allow for better penetration of its permeability. The subfornical organ, the region postrema, and the organum vasculosum of the lamina terminalis are three significant circumventricular organs that are included in this typical component of the BBB. These integrative regions of the hypothalamus play a crucial role in maintaining fluid electrolyte homeostasis. Blood volume, control of vasopressin production, salt excretion, and finding poisons in the blood to cause vomiting are all factors [76]. The BBB limits B cell entrance and guards against general infections in the brain. Because of this, infections in the brain are uncommon but very challenging to treat when they happen. Extreme infections may cause the BBB to lose its integrity, allowing immune cells from the peripheral system to enter the brain, including macrophages and progenitor cells produced from bone marrow. The BBB membrane is restored when the infection has been controlled [77]. Numerous disease processes, including meningitis, multiple sclerosis, Alzheimer's disease, and Parkinson's disease, have been linked to a loss of BBB integrity [78–80]. When the BBB is compromised, environmental substances (haptens), food proteins, or pathogenic organisms (antigens) may infiltrate the body and be exposed to the microglia, triggering a neuroinflammatory response. Alcohol exposure [81], stress reactions [82], increased homocysteine [83,84], hyperglycemia [85], prostaglandin imbalances [86], and oxidative stress [87] have all been shown to cause the BBB to lose its integrity. A cell subset known as regulatory T cells is responsible for suppressing the immune system, maintaining tolerance to self-antigens, and suppressing autoimmune disease. An element of the immune system known as regulatory cells inhibits other cells' immunological reactions. The immune system has an essential "self-check" built in to avoid overreacting. There are many different types of regulatory T cells, but those that express CD4, CD25, and Foxp3 (CD4+CD25+ regulatory T cells) are the best studied. These cells help avoid autoimmune TH1 and TH2 polar shifts as well as the shutting down of immune responses after they have effectively destroyed foreign invaders. Both the regulation of autoimmunity and the loss of chemical tolerance depend on them [88–90]. Glutathione and vitamin D may boost the

activity of regulatory T cells. Vitamin D levels should always be taken into consideration while nutritionally supporting reduction of chemical sensitivity. According to research, vitamin D is essential for the growth of immunological defence, immune balance (regulatory T-cells), and immune barrier integrity [91–92]. It is preferable to have a level of 25-hydroxyvitamin D that is no lower than 50 ng/mL. Vitamin D and glutathione support are two nutrients that have been demonstrated to promote regulatory T cells [93–97].

Conclusion:

Immune tolerance to chemicals decreases as a result of toxins, environmental contaminants, and inflammatory responses. Increased oxidative, inflammatory, and immunoreactive responses to delicate tissues, such as the brain and nervous system, are brought on by a loss of immune chemical tolerance. These responses support neurodevelopmental disorders like autism, neurodegenerative diseases like Parkinson's and Alzheimer's, and neurological autoimmune disorders like multiple sclerosis. Healthy immune chemical tolerance is maintained in part by physiological depletion of glutathione redox systems, wind-up and amplification of NF-kappaB inflammatory expression, immune barrier system breakdown, and regulator T cell dysregulation. The integrity and expression of these physiological systems may be impacted by nutritional measures, which might provide some assistance in addressing the rising concerns about environmental-caused brain illness and neurological autoimmune diseases.

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