REVIEW ARTICLE

Neurotoxicity Associated with Traumatic Brain Injury, Blast, Chemical, Heavy Metal and Quinoline Drug Exposure

Timothy M. Marshall, PhD; Geoffrey P. Dardia; Kathryn L. Colvin, PhD; Remington Nevin, MD, MPH, DrPH; James Macrellis, MAJ(R)

ABSTRACT

Chronic, excessive exposure, and accumulation of neurotoxic agents such as heavy metals (lead, mercury, cadmium), mefloquine (Lariam), and food additives such as monosodium glutamate and aspartame cause neurotoxicity and brain damage. This chemical-induced brain damage closely resembles the pathophysiology of classical traumatic brain injury with decreased cognitive function, neurodegeneration, and increased psychiatric manifestations (depression, anxiety, sleep disturbances, and irritability). Current evidence supports a strong causal relationship between military-related exposure to specific neurotoxins, and the development of serious medical conditions and higher rates of suicide among service members. To address this current deficit in military health care, it is recommended that efficacious, nontoxic, neuroprotective, and neuroregenerative agents such as highly bioavailable magnesium, nutritional lithium, zinc, selenium, boron, ascorbate, tocopherols, heavy metal chelators, and glutathione precursors such as *N*-acetyl-cysteine be immediately used as a "protective shield" and to support critical healing processes in the brain and nervous system. (*Altern Ther Health Med.* 2018;25(1):28-34.)

Timothy M. Marshall, PhD, is a neuropharmacologist, nutritional biochemist in Tucson, Arizona. SFC Geoffrey P. Dardia is an Army Green Beret, special forces weapons sergeant, certified recovery care coordinator, and the founding director of the SOF Health Initiatives for Task Force Dagger Foundation. Additional contributing authors: Kathryn L. Colvin, PhD; Remington Nevin, MD, MPH, DrPH; James Macrellis, MAJ(R).

Corresponding author: Timothy M. Marshall, PhD
E-mail address: office@dr-marshall.com

INTRODUCTION

Neurotoxicity is a term used to describe the neurochemical and neurophysiological changes caused by specific toxic agents. These changes can include negative effects on cognition, memory, mood, and sleep along with increased sensitivity to emotional and physiological stress. In today's world, we are continuously exposed to toxins from multiple sources: the environment, diet, certain drugs, heavy metals, oxidative stress, and occupational hazards. Although all people are at risk of toxicity, military service members are a population with some of the highest rates of occupational exposure to neurotoxic agents such as heavy metals (eg, lead, mercury, cadmium), prescription drugs (eg, mefloquine), blast waves, and dietary neurotoxins such as aspartame from food sources commonly consumed by military service members.

In addition to chemical toxins and physical injuries that induce brain trauma, nutritional deficiencies play a fundamental role in the progression and severity of the injury and directly influence healing. A 2014 study published in *Nutritional Neuroscience* found that important brain nutrients (eg, magnesium, vitamin C, folate) were frequently deficient in the diets of patients being treated for traumatic brain injury (TBI), which resulted in the "worst mean neurobehavioral scores for those patients not meeting the estimated average requirements."[1]

Particulate pollution is also a major concern. Dust and air quality studies in both Iraq and Afghanistan have shown unsafe levels of lead, other heavy metals, industrial pollutants, and depleted uranium.[2] Other countries where service

members are deployed such as Pakistan, Yemen, Saudi Arabia, and central African countries are known for being some of the most polluted areas in the world. Many service members are suffering from unexplained illness, also known as "Gulf War Syndrome," and health care providers repeatedly fail to perform the proper tests for these well-known toxic influences.

Service members are frequently exposed to unsafe levels of toxic substances from constant immersion into highly polluted, austere environments under extreme stress conditions with inadequate sleep, poor nutrition, along with chronic and continual use of antibiotics putting the service member at a higher risk of toxin exposure.

Another source of heavy metal exposure is the dirt and dust at firing ranges and shoot houses. Service members who explosively breach in these highly contaminated areas are at greater risk of heavy metal poisoning, neurotoxicity, and cancer.[3] These toxins build up on equipment and uniforms, which soldiers take home and wash with their family members' clothing, potentially contaminating the home and affecting the entire family. The human body was not designed to protect itself from the extremely high lead levels service members are routinely exposed to in their occupational environment. Heavy metals such as lead, cadmium, and mercury induce oxidative stress and deposit in the brain and nervous system where they promote tissue injury, and increased systemic and neural inflammation. In addition, medications, such as quinolines, fluoroquinolones, or antifungals may put a soldier at increased risk for renal failure when exposed to heavy metals.[4]

HEAVY METAL TOXICITY

Service members who conduct training in "live-fire" shoot houses and dirt flat ranges are at an increased risk of exposure to high levels of lead, tin, and copper.[5] These environments cause excess particle amounts of heavy metals to be inhaled, ingested, and absorbed into soldiers while they conduct training. Excessive exposure to toxic metals leads to acute and chronic cellular dysfunction and classical symptoms of toxicity. The kidneys are the first target organ of heavy metal toxicity due to their ability to reabsorb and accumulate divalent metals (eg, lead, mercury, cadmium). The degree of damage by heavy metals depends on the nature, the dose, and the route and duration of exposure.[6] Due to toxin uptake and partitioning to more metabolically active tissues, routine blood tests are not a reliable measure. Such tests are incapable of providing an accurate assessment of the body burden due to chronic exposure to heavy metals because these metals are sequestered and stored in fat, tissues, organs, and bones.[5]

It has been known for centuries that lead has detrimental effects on the brain and nervous system. Today, we know that lead (Pb^{2+}) displaces calcium (Ca^{2+}) in essential metabolic functions, crosses the blood-brain barrier, and preferentially accumulates in specialized glial cells known as astrocytes, which serve a myriad of vital homeostatic functions in the brain, including regulation of neurotransmitter (eg, glutamate) and extracellular potassium concentrations—both of which are essential for the propagation of actions potentials and neuronal firing.[7]

There are approximately 1 trillion neurons in the central nervous system, with glial cells such as astrocytes accounting for approximately 90% of the total cells. Four main types of glia exist: astrocytes, oligodendrocytes, ependymal cells, and microglia. The astrocytes—the "guardian angels" of the neurons and synapses—are the most common and are so named because of their abundant long, thin projections, which give them a starry look. Astrocytes perform critical housekeeping functions such as supplying neurons with nutrients, energy-rich molecules, and neurotransmitter precursors essential for healthy neuronal function, and remove excess neurotransmitters (eg, glutamate or GABA) from the synapse, so the next signal will be properly received and transmitted.[7] Astrocyte processes surround all synapses and perform essential functions in maintaining the fluid, ion, pH, and neurotransmitter homeostasis of the synaptic interstitial fluid, critical for healthy synaptic transmission. Astrocytes also play a major role in controlling where and when our brain's all-important synapses will form.[8]

LEAD, CALCIUM, AND VITAMIN D

Lead exposure is one of the greatest exposures to combat arms service members next to prescription drugs and explosive blasts. Lead is a well-described, neurotoxic heavy metal that increases oxidative stress, tissue inflammation, and damages sensitive cellular structures such as cell membranes and DNA. When deposited into the bones, brain, or other tissues, it can cause cancer and in some cases encephalopathy. According to a 2009 Veterans Affairs study, elevated bone lead concentrations were associated with 2.5-fold increase in mortality, a 6-fold increase in cardiovascular mortality, and an 8-fold increase in ischemic heart disease.[9]

Vitamin D plays a crucial role in the absorption of lead because the body thinks lead is calcium. Because lead and calcium share the same 2+ charge, the body does not recognize the difference between the 2 ions and absorbs and stores lead in the place of calcium in bone and throughout the body. Calcium channels control the nervous system and conductivity of transmissions across nerves. If lead is in the system, it can negatively affect the function of calcium channels and the resulting conductivity.[9] As a well-known cognitive suppressing agent, lead exposure by altering this conductivity can slow the service member's mental and physical processes.

If a service member is on an intensive repletion protocol to correct a vitamin D deficiency and is consuming 10 to 50 000 IU of vitamin D_3 per day while working at a firing range and exposed to high levels of lead, the following protocol is recommended. Because vitamin D greatly enhances Ca^{2+} absorption, Pb^{2+} absorption will also increase[10] unless calcium (eg, citrate or carbonate) is supplemented to competitively inhibit lead absorption[11-14] via their common uptake channel—the divalent metal transporter.[15,16]

Considering that many service members are vitamin D deficient, careful consideration should be given to service members who work or train at firing ranges regularly. To prevent both acute and chronic lead poisoning, vitamin D supplementation should always be accompanied with supplemental calcium and magnesium (for calcium balance) to decrease gastrointestinal lead absorption.

TESTS FOR HEAVY METAL EXPOSURE

A complete metabolic analysis, male hormone panel, and dimercaptosuccinic acid (DMSA) challenge test, via urinalysis, will show the effects of recent exposure to heavy metals, which invariably correlate with the clinical symptoms and degree of neurotoxicity. The absorption and accumulation of heavy metals can block vital metabolic functions such as the body's primary energy producing pathway (ie, Krebs cycle) and also interferes with endocrine functions throughout the body, especially the hypothalamus, pituitary, adrenal (HPA) axis and hypothalamus, pituitary, thyroid axis.[17] The HPA axis controls every function in the nervous system. If this system is damaged, the inevitable consequence is a multitude of symptoms (eg, chronic fatigue, brain fog, depression, anxiety, sleep disturbances, hormone imbalance) and chronic illness.

The biological half-life of lead in blood is 28 to 36 days in the blood and approximately 10 to 30+ years in bone. Lead has a preferential affinity for bone tissue, where it is sequestered and hidden from detection. Therefore, unless the soldier was exposed to high levels of lead within 36 days, its presence would not be revealed in serum tests. The National Institutes of Health use the DMSA challenge test for chronic heavy metal exposure and X-ray fluorescence, a nondestructive analytical technique to scan bone for chronic lead exposure. Free erythrocyte protoporphyrin level may be useful in demonstrating the degree of biological abnormalities that exist from chronic lead exposure. Elevated blood lead levels are associated with the development of microcytic anemia, and low serum iron and ferritin.[18]

LEAD POISONING AND INCREASED CANCER INCIDENCE IN THE MILITARY

Military personnel are experiencing increased rates of various forms of cancer. A 2009 study found that prostate cancer rates are twice those of the general population, and breast cancer rates are 20% to 40% higher among service members.[19] A 2006 study found that rates for cervical, prostate, and vulvar cancers were significantly higher for US Air Force active duty personnel than the general population.[20] The incidence of thyroid cancer is also significantly higher among active duty US military personnel.[21]

A close inspection of the toxins service members are commonly exposed to offers substantial insight into this growing problem. Military personnel are often exposed to a wide variety of environmental toxins including dangerous levels of lead (a probable human carcinogen) and are deployed to countries that have high amounts of environmental pollutants in the air and soil. Lead and other heavy metals are inhaled and ingested into the lungs where lead is released into the blood and distributed throughout the body and can be absorbed through the skin when conducting training. These metals are found in the primers, propellants, the rounds, and even the barrels of the weapons that the bullets travel through. The cloud of smoke that comes out of the barrel every time a weapon is fired contains particles of these metals. Heavy metals are widely known to disrupt the central nervous system and metabolism, and cause renal failure.[22]

Many of lead's toxic properties are due to its ability to mimic or compete with calcium. Lead has a dual effect on the release of neurotransmitters by increasing spontaneous neurotransmitter release (nonproductive neuronal firing), while decreasing stimulated release. Lead also negatively affects the synthesis of heme for red blood cell production.[22] Lead inhibits DNA repair and acts synergistically with other mutagens, potentiating their negative effects in the body.[23] The symptoms of lead poisoning include renal failure, limb weakness or numbness, hypertension, loss of memory, vision, headache, decreased cognitive function, and behavioral problems and sexual dysfunction.[22] These symptoms are consistent with TBI because both TBI and lead toxicity involve neurotoxicity.

Service members may more successfully detox at home because the foods they need to assist the body are widely available. Soldiers cannot detox when they are deployed outside the continental United States because the foods they eat are missing the necessary building blocks needed for normal detoxification processes. Fresh whole foods (preferably organic, pesticide, and chemical free) rich in antioxidants and glutathione precursors are an absolute requirement for proper detoxification (ie, elimination) of heavy metals and other exogenous toxins.

Soldiers do not receive adequate antioxidants in the processed foods they consume on deployments. Processed foods are often full of preservatives (eg, benzoates) and neurotoxic agents such as synthetic food colors (eg, Red No. 40) and excitotoxic sweeteners (eg, aspartame) and flavoring agents.[24] The human body has a very limited reserve of the body's primary antioxidant, glutathione, which requires a constant intake of adequate sulfurous amino acids (eg, cysteine) to maintain sufficient levels for necessary antioxidant defenses. Once glutathione and other supporting antioxidants are depleted (eg, vitamins C and E, and polyphenolic antioxidants), the body loses its primary antioxidant and heavy metal defense shield—making it much more susceptible to cancer and chronic disease.[25]

TRAUMATIC BRAIN INJURY

TBI, either physically or chemically induced, increases oxidative stress, inflammation, and brain injury. When a service member experiences a TBI, their glutamatergic system becomes upregulated for up to 60 minutes. Excitatory amino acids exceed healthy limits and become toxic. The first 10 days following a

TBI, known as the "acute phase," the following excitotoxic events occur: terminal membrane depolarization along with excessive release of excitatory neurotransmitters (ie, glutamate, aspartate) leading to overactivation of *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolpropionate, and voltage-dependent Ca^{2+} and Na^{+} channels. Subsequent Ca^{2+} and Na^{+} influx leads to an increase in catabolic intracellular processes and a high level of oxidative stress.[26]

The next stage, known as the "subacute phase" (>10 d; <1 y postinjury) is characterized by tissue damage and the beginning of Wallerian degenerative processes if healing is not progressing. The axon response to injury and secondary insults is followed by the process of Wallerian degeneration, which begins as a potentially reversible phase of intra-axonal damage, and proceeds to further axon fragmentation and demyelination of intact axons. These elements of axon and myelin pathology present opportunities for repair, though if no healing techniques are used (eg, biochemical restoration, nutrient therapeutics, hyperbaric oxygen), cell death is often the result.[27] The "chronic phase" of postconcussion is diagnosed as persistent (>1 y and ongoing) and by the severity of the trauma with symptoms such as chronic and progressive cognitive impairment, depression, anxiety, sleep disturbances, and progressive neurodegeneration and decline occurring years after the injury.[28,29] At this point, cell death has occurred, and cognitive function and processing speed are invariably compromised.

An individual who has more exposure to blasts, blows to the head, or hard landings with a parachute is at greater risk for neurodegenerative brain disease. This mechanism of injury is apparent in National Football League players and boxers and is known as encephalopathy. Encephalopathy is well known and found in dead soldiers and athletes who commit suicide.[30] This form of degenerative brain disease is caused by repetitive blows to the head. This is something to be considered with heavy breaching and static line jumping. Every jarring motion of the brain inside of the skull can turn on the glutamate and calcium activating neural circuitry. The severity of the acceleration and deceleration of the brain inside the skull determines the length of time these systems remain activated.

MEFLOQUINE NEUROTOXICITY

The quinoline antimalarial, mefloquine used prophylactically for soldiers abroad is another neurotoxic agent soldiers are having to contend with. When levels in the brain exceed a certain threshold, mefloquine becomes an insidious and damaging neurotoxin. The reason that effects differ is most likely due to genetic and metabolic differences among soldiers, along with body composition and mass differences.[31] Mefloquine accumulates in tissue, rather than in the circulation, and as a result may only be effective if taken 7 to 9 weeks prior to entering a country with high malaria threat.[32] Mefloquine neurotoxicity affects the brainstem and limbic system and may induce long-term or sometimes permanent mental health and neurological symptoms, including personality change, irritability, cognitive deficits, disequilibrium and visual disturbances. Due to its ability to cause neurological injury (ie, brain trauma), mefloquine neurotoxicity has a very similar clinical picture to that of classical TBI and posttraumatic stress disorder.[31-35]

EXCITOTOXINS

One of the principles axioms in the field of toxicology is, "It's the dose that makes the poison." Though, with that said, some substances have greater potential to create toxicity than others. Mercury is one such substance. There are 3 forms of mercury that we are exposed to in our diet and environment: elemental (eg, liquid or vapor), inorganic (eg, $HgCl_2$), and organic (eg, methylmercury). Each has its own profile of toxicity.

Symptoms of methylmercury poisoning include detrimental effects on cognitive thinking, memory, attention, language, fine motor skills, impairment of speech, hearing, walking, muscle weakness, loss of peripheral vision, and "pins and needles" feelings, usually in the hands, feet, and around the mouth. Symptoms of prolonged or acute exposure to elemental mercury include tremors, emotional changes (eg, mood swings, irritability, nervousness, excessive shyness), insomnia, neuromuscular changes (eg, weakness, muscle atrophy, twitching), headaches, disturbances in sensations, changes in nerve responses, and poor performance on tests of mental function.

Another form of organic mercury, ethyl-mercury, found exclusively in the synthetic preservative, thimerosal, has been shown to be 50 times more toxic than methylmercury and contains 49.55% mercury by mass.[36]

Two of the most insidious excitotoxins (ie, neurotoxins) in our food supply today are aspartame and monosodium glutamate (MSG).[24,37-42] There are currently more than 6000 consumer products containing aspartame, and thousands that contain MSG in its many forms (eg, autolyzed yeast, glutamate, glutamic acid, hydrolyzed protein, monopotassium glutamate, MSG, textured protein, yeast extract, yeast food, yeast nutrient, flavors, and flavorings). The mechanism of toxicity of MSG is a very straight forward one: elevation of extracellular glutamate and excitotoxicity from overstimulation of the body's primary excitatory glutamate receptor, the NMDA-R.[38-42]

Aspartame's mechanism of toxicity is a bit more complex and is driven by the following 6 components: phenylalanine, aspartic acid, methanol, formaldehyde, formic acid, and diketopiperazine, and the list of adverse effects associated with its use is truly staggering and include fatigue, depression, anxiety, seizures, headaches, migraines, tachycardia, breathing difficulties, irritability, weight gain, metabolic syndrome, tinnitus, numbness, dizziness, endocrine disruption (ie, Graves' disease), development of phobias, vision problems, night terrors, sleep apnea, and sleep disturbances.[41,42]

From a biological and toxicological perspective, all of these adverse effects make perfect sense given the fact that

aspartame is 10% methanol by weight, which is quickly converted (ie, oxidized) to formaldehyde, and then to formic acid in the liver. Both formaldehyde and formic acid are "neuro-irritants," disruptive to normal cellular function, and display biological toxicity at relatively low levels. Much like lead, formaldehyde is a carcinogen and neurotoxin that binds to proteins and receptors in the brain and nervous system interfering with their function. Both are reactive chemical species, promoting cellular dysfunction, oxidative stress, and neuroinflammation.

Chemically speaking, aspartame is a dipeptide composed of the 2 amino acids, phenylalanine and aspartic acid, with a conspicuous *O*-methyl group at one end of the molecule. It is this latter component that makes it especially toxic to the brain, eyes, and all nervous tissue. When consumed or heated to 85° F (29.4° C), aspartame quickly breaks down (ie, hydrolyzes) into the 2 excitatory amino acids, phenylalanine and aspartic acid,[34] and methyl alcohol (methanol). In a 1980 study published in *Neurobehavioral Toxicology*, Olney et al[38] reported "conspicuous hypothalamic damage" (ie, brain damage) in mice from the voluntary ingestion of glutamate and aspartate, similar to the feeding behavior of many consumers today. This study further substantiated previous studies demonstrating the ability of glutamate and aspartate to destroy neurons in the brains of various animal species.[39,40]

One can of diet soda contains approximately 180 mg of aspartame, which is equivalent to 8.2 packets of aspartame sweetener (eg, Nutrasweet, Equal). Each packet contains 22 mg of aspartame and releases 2.2 mg of methanol per packet. The US Environmental Protection Agency (EPA) classifies methanol as a "cumulative poison due to the low rate of excretion once it is absorbed" and recommends an upper allowable limit of consumption for methanol of 7.8 mg per day. Heavy users of aspartame-containing products can consume as much as 250 mg of methanol daily or approximately 32 times the EPA limit.[41]

Chewing gum is perhaps one of the most unsuspecting, and insidious, sources and "delivery systems" of this neurotoxic poison. When an individual chews gum containing aspartame—the highly vascularized oral mucosa (ie, lingual, sublingual, buccal tissues) in the mouth becomes saturated with this chemical, which is absorbed directly into the bloodstream and carried within seconds to the brain.

Processed foods containing MSG and aspartame are harmful to people who have TBI, nervous system disorders, or metabolic disorders. These toxins cause overactivation of the body's primary excitatory receptor system (NMDA-R), producing neuronal degeneration, excitotoxicity, and eventual cell death. Two of the body's natural neurotransmitters are aspartate and glutamate. MSG and aspartame contain highly potent, synthetic forms of these natural neurotransmitters and cause excitotoxicity and neuronal damage when consumed in large amounts.[20,39-42] Individuals with acute or chronic mercury or lead poisoning, or a predisposition for depression, anxiety, or mood disorders, will experience greater adverse effects to these chemicals than those without a pre-existing health condition. These foods or chemicals should not be consumed by an individual having any type of neurological condition or brain-related injury because they can increase the effects of the initial injury. Metabolism, genetics, size (ie, body mass), and body composition will cause people to have greater or lesser effects.[40-42]

NUTRIENT DEFICIENCIES IN TBI

Magnesium is rapidly depleted following brain trauma,[43,44] which further contributes to the pathophysiology of the trauma (eg, increased oxidative stress, inflammation, excitotoxicity, cell death). Replenishing levels to normal values have been shown to prevent and reverse neurological injury.[45] A 2004 review article titled, "Magnesium Therapy and Recovery of Function in Experimental Models of Brain Injury and Neurodegenerative Disease," reported that magnesium therapy was "effective in facilitating recovery of function and exhibits very robust and unique effects."[46]

Magnesium deficiency promotes inflammation, increasing levels of several proinflammatory mediators such as substance P, tumor necrosis factor-α, interleukin (IL)-1, and IL-6, and has also been shown to promote insulin resistance, type 2 diabetes, and metabolic syndrome.[47,48] Magnesium acts as the brain's primary inhibitory ion, functioning as the "brakes," whereas calcium (influx) serves as the "accelerator" or activator. However, magnesium is not the only nutrient that is depleted during trauma or the chronic stress that precedes and follows injury. Trauma and stress increase the body's requirement for all essential nutrients especially those required in neurorepair and healing. These include the full range of vitamins (eg, A, B-complex, C, D, E, essential fatty acids, docosahexaenoic acid, eicosapentaenoic acid), and trace minerals that reduce oxidative stress and promote neuroregeneration and the formation of new neurons (ie, neurogenesis) such as lithium and zinc.

Lithium is another critically important nutrient in neuroprotection, neurogenesis, and healing processes in the brain and nervous system. Lithium works as a companion nutrient with magnesium and zinc and is needed for vitamin B_{12} and folate utilization. Lithium, magnesium and zinc increase the body's natural antioxidant defense systems (eg, SOD, GPx, catalase) and are essential in preventing NMDA receptor overactivation (ie, hyperactivity). In the 2014 review article, "Lithium to the Rescue," the authors state, "There is now a substantial understanding of how lithium can strengthen and protect the brain."[49] A portion of its beneficial effects reside in its ability to modulate the NMDA receptor, but in large part it is lithium's inhibition of an enzyme called glycogen synthase kinase-3 (GSK3) that is governing its wide-ranging activity.[50,51] Inhibition of GSK3 protects brain cells from a wide range of assaults, including oxidative stress, DNA damage, impairment of mitochondrial function, and excitotoxicity.[52,53]

Along with magnesium and lithium, zinc is needed in higher amounts for healing and repair and to counteract losses by injury and chronic stress. Zinc has been shown to have antidepressive, anxiolytic activity (ie, stress reducing) and works alongside magnesium and lithium in various body systems.[54-46,57] Like magnesium and lithium deficiency, zinc deficiency increases oxidative stress and NMDA receptor dysfunction (overactivity), and contributes to general inflammation,[56] whereas zinc supplementation can reverse this. Symptoms of zinc deficiency include delayed wound healing, frequent infections, mental fatigue, learning difficulties, low testosterone, and neurosensory disorders.[54,56]

The human body requires a broad spectrum of macro- and micronutrients that support a multitude of essential processes and protective functions. Thanks to the invaluable contributions of Gerhard N. Schrauzer, PhD; Linus Pauling, PhD; Jonathan V. Wright, MD; John A. Myers, MD; and many others, we now have strong scientific and clinical evidence identifying more than 31 macro- and micronutrients essential for human health and well-being. Though not complete – these include, vitamins A, B_1, B_2, B_3, B_5, B_6, B_{12}, folate, C, D, E, F (essential fatty acids), K_1, K_2, calcium, magnesium, phosphorus, potassium, sodium, and trace minerals boron, chromium, cobalt (B_{12}), copper, iodine, iron, lithium, nickel, manganese, molybdenum, selenium, silicon, strontium, vanadium, and zinc.[58-68] Evidence also exists for the essentiality of arsenic in the metabolism of the amino acid, methionine, and in the synthesis of spermidine and spermine, and *S*-adenosylmethionine decarboxylase[69] and the trace element, silver in eye function and visual acuity.[70]

Comprising only 3% of the body's total mass, the brain has the highest energy requirement of all human tissues, up to 20% of the body's total energy consumption, and contains 25% of the body's neuroprotective, hormone-precursor, cholesterol—a direct reflection of the brain's enormous metabolic demands.[71,72]

SUMMARY

To address the current deficit in military health care, in addition to an emphasis on proper testing (eg, tox-screens, MRI/DTI, SPECT scans), it is recommended that strategies using optimized levels of neuroprotective, neuroregenerative nutrients such as highly bioavailable magnesium, lithium, zinc, selenium, boron, ascorbate, tocopherols, omega-3 fatty acids, heavy metal chelators, and glutathione precursors such as *N*-acetyl-cysteine be immediately used for their detoxifying and healing benefits on the brain and nervous system.[73]

AUTHOR DISCLOSURE STATEMENT

Dr Marshall's company, NeuroLith Nutraceuticals, LLC, has developed nutritional supplements designed to enhance brain healing, based on research cited here; patents pending.

REFERENCES

1. Vattanasit U, Navasumrit P, Khadka MB, et al. Oxidative DNA damage and inflammatory responses in cultured human cells and in humans exposed to traffic-related particles. *Int J Hygiene and Environ Health*. 2013 pii: S1438-4639(13)00040-0.
2. Hyerim R, Han JK, Jung JW, Bae B, Nam K. Human health risk assessment of explosives and heavy metals at a military gunnery range. *Environ Geochem Health*. 2007;29(4):259-269.
3. Patterson D. Quinolone toxicity: Methods of assessment. *Am J Medicine*. 1991:30(91):35S-37S.
4. Dorman DC, National Research Council; Division on Earth and Life Studies; Board on Environmental Studies and Toxicology; Committee on Potential Health Risks from Recurrent Lead Exposure of DOD Firing Range Personnel; Committee on Toxicology. Potential health risks to DOD firing-range personnel from recurrent lead exposure. National Academies Press Web site. https://www.nap.edu/read/18249/chapter/1. Published 2013. Accessed August 9, 2018.
5. Barbier O, Jacquillet G, Tauc M, Cougnon M, Poujeol P. Effect of heavy metals on, and handling by, the kidney. *Nephron Physiol*. 2005;99(4):105-110.
6. Goldman B. The brain's silent majority: How the other 90% of your brain works. Stanford Medicine Web site. http://sm.stanford.edu/archive/stanmed/2009fall/article6.html. Published 2009. Accessed August 9, 2018.
7. Sofroniewc MV, Vinters HV. Astrocytes: Biology and pathology. *Acta Neuropathol*. 2010 Jan;119(1):7-35.
8. Weisskopf MG, Jain N, Nie H, et al. A prospective study of bone lead concentration and death from all causes, cardiovascular diseases, and cancer in the Department of Veterans Affairs Normative Aging Study. *Circulation*. 2009;120(12):1056-1064.
9. Babarykin DA, Bauman VK. The metabolism of heavy metals depends on the vitamin-D status of the body. *Fiziol Zh Im I M Sechenova*. 1994;80(7):88-98.
10. Bruening K, Kemp FW, Simone N, Holding Y, Louria DB, Bogden JD. Dietary calcium intakes of urban children at risk of lead poisoning. *Environ Health Perspect*. 1999;107(6):431-435.
11. Ettinger AS, Hu H, Hernandez-Avila M. Dietary calcium supplementation to lower blood lead levels in pregnancy and lactation. *J Nutr Biochem*. 2007;18(3):172-178.
12. Ettinger AS, Lamadrid-Figueroa H, Téllez-Rojo MM, et al. Effect of calcium supplementation on blood lead levels in pregnancy: A randomized placebo-controlled trial. *Environ Health Perspect*. 2009;117(1):26-31.
13. Conceicao E, Machado AA, Izumi C, Freitas O. Calcium carbonate reduces iron absorption from iron sulfate, but not when iron is presented as an organic complex. *Alim Nutr Araraquara*. 2005;16(1):1-4.
14. Kayaaltı Z, Akyüzlü DK, Söylemezoğlu T. Evaluation of the effect of divalent metal transporter 1 gene polymorphism on blood iron, lead and cadmium levels. *Environ Res*. 2015;137:8-13.
15. Bressler JP, Olivi L, Cheong JH, Kim Y, Bannona D. Divalent metal transporter 1 in lead and cadmium transport. *Ann N Y Acad Sci*, 2004;1012:142-152.
16. Hegazy AA, Zaher MM, Abd el -hafez MA, Morsy AA, Saleh RA. Relation between anemia and blood levels of lead, copper, zinc and iron among children. *BMC Res Notes*. 2010;3:133.
17. Zhu K, Devesa SS, Wu H, et al. Cancer incidence in the U.S. military population: Comparison with rates from the SEER program. *Cancer Epidemiol Biomark Prevent*. 2009;18(6):1740-1745.
18. Yamane GK. Cancer incidence in the U.S. Air Force: 1989-2002. *Aviat Space Environ Med*. 2006;77(8):789-794.
19. Wade MG, Parent S, Finnson KW, et al. Thyroid toxicity due to subchronic exposure to a complex mixture of 16 organochlorines, lead, and cadmium. *Toxicol Sci*. 2002;67(2):207-218.
20. Enewold LR, Zhou J, Devesa SS, et al. Thyroid cancer incidence among active duty U.S. military personnel, 1990-2004. *Cancer Epidemiol Biomark Prevent*. 2011;20(11):2369-2376.
21. Assi MA, Hezmee MNM, Haron AW, Sabri MYM, Rajion MA. The detrimental effects of lead on human and animal health. *Vet World*. 2016;9(6):660-671.
22. Steenland, K, Boffetta, P. Lead and cancer in humans: Where are we now? *Am J Indust Med*. 2000:38(3):295-299.
23. Olney, JW. Excitotoxins in foods. *Neurotoxicology*. 1994;15(3):535-544.
24. Wu G, Fang YZ, Yang S, Lupton JR, Turner ND. Glutathione metabolism and its implications for health. *J Nutr*. 2004;134(3):489-492.
25. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *Brit J Anaesthesiol*. 2007;99(1):4-9.
26. Armstrong RC, Mierzwa AJ, Marion CM, Sullivan GM. White matter involvement after TBI: Clues to axon and myelin repair capacity. *Exp Neurol*. 2016;275(3):328-333.
27. Fehily B, Fitzgerald M. Repeated mild traumatic brain injury: potential mechanisms of damage. *Cell Transplant*. 2017;26(7):1131-1155.
28. Gardner RC, Yaffe K. Epidemiology of mild traumatic brain injury and neurodegenerative disease. *Mol Cell Neurosci*. 2015;66(Pt B):75-80.
29. Goldstein LE, Fisher AM, Tagge CA, et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Sci Transl Med*. 2012;4(134):134ra60.
30. Ritchie, EC, Block J, Nevin, RL. Psychiatric side effects of mefloquine: Applications to forensic psychiatry. *J Am Acad Psychiatry Law*. 2013:41(2);224-223.
31. Stahlmann R, Lode H. Toxicity of quinolones. *Drugs*. 1999;58(supplement 2):37-42.
32. Nevin R. Limbic encephalopathy and central vestibulopathy caused by mefloquine: A case report. *Travel Med Infect Dis*. 2012;10(3):144-151.
33. Toovey S. Mefloquine neurotoxicity: A literature review. *Travel Med Infect Dis*. 2009;7(1):2-6.

34. Dow G, Hudson T, Vahey M, Koenig M. The acute neurotoxicity of mefloquine may be mediated through a disruption of calcium homeostasis and ER function in vitro. *Malaria J*. 2003:12(2):14.
35. Guzzi G, Pigatto PD, Spadari F, et al. Effect of thimerosal, methylmercury, and mercuric chloride in Jurkat t cell line: Mitochondrial dysfunction, impaired oxidative-reduction activity, degeneration, and death in human neuronal and fetal cells induced by low-level exposure to thimerosal and other metal compounds. *Toxicol Environ Chem*. 2009;91(3-4):735-749.
36. Dingledine R, McBain CJ. Glutamate and aspartate are the major excitatory transmitters in the brain. In: Siegel GJ, Agranoff BW, Albers RW, et al, es. *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*. 6th ed. Philadelphia, PA: Lippincott-Raven; 1999.
37. Olney JW, Labruyere J, de Gubareff T. Brain damage in mice from voluntary ingestion of glutamate and aspartate. *Neurobehav Toxicol*. 1980;2(2):125-129.
38. Olney JW, Ho OL. Brain damage in infant mice following oral intake of glutamate, aspartate or cysteine. *Nature*. 1970;227(5258):609-611.
39. Olney JW. Brain damage and oral intake of certain amino acids. *Adv Exp Med Biol*. 1976;69:497-506.
40. Mercola J. MSG: Is this silent killer lurking in your kitchen cabinets? Mercola Web site. http://articles.mercola.com/sites/articles/archive/2009/04/21/msg-is-this-silent-killer-lurking-in-your-kitchen-cabinets.aspx. Published April 21, 2009. Accessed August 9, 2018.
41. Blaylock RL. Lithium. In: *Excitotoxins—The Taste That Kills*. Abington, UK: Health Press; 1997.
42. Wahls T, Rubenstein L, Hall M, Snetselaar L. Assessment of dietary adequacy for important brain micronutrients in patients presenting to a traumatic brain injury clinic for evaluation. *Nutr Neurosci*. 2014;17(6):252-259.
43. Vink R. Magnesium and brain trauma. *Magnes Trace Elem*. 1991;10(1):1-10.
44. Vink R, McIntosh TK, Demediuk P, Weiner MW, Faden AI. Decline in intracellular free Mg2+ is associated with irreversible tissue injury after brain trauma. *J Biol Chem*. 1988;263(2):757-261.
45. Hoane MR, Knotts AA, Akstulewicz SL, Aquilano M, Means LW. The behavioral effects of magnesium therapy on recovery of function following bilateral anterior medial cortex lesions in the rat. *Brain Res Bull.* 2003;60(1-2):105-114.
46. Hoane MR. Magnesium therapy and recovery of function in experimental models of brain injury and neurodegenerative disease. *Clin Calcium* 2004;14(8):65-70.
47. Rayssiguier Y, Libako P, Nowacki W, Rock E. Magnesium deficiency and metabolic syndrome: Stress and inflammation may reflect calcium activation. *Magnes Res*. 2010;23(2):73-80.
48. Zheltova AA, Kharitonova MV, Iezhitsa IN, Spasov AA. Magnesium deficiency and oxidative stress: An update. *BioMed*. 2016;6(4):20.
49. Jope RS, Nemeroff CB. Lithium to the rescue. *Cerebrum*;2016. pii: cer-02-16.
50. Jope RS, Bijur GN. Mood stabilizers, glycogen synthase kinase-3β and cell survival. *Molec Psychiatry.* 2002;7(supplement 1):S35-S45
51. Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci U S A*. 1996;93:8455-8459.
52. Beurel E, Jope RS. The paradoxical pro- and anti-apoptotic actions of GSK3 in the intrinsic and extrinsic apoptosis signaling pathways. 2006;79:173-189.
53. Hanson ND, Nemeroff CB, Owens MJ. Lithium, but not fluoxetine or the corticotropin-releasing factor receptor 1 receptor antagonist R121919, increases cell proliferation in the adult dentate gyrus. *J Pharmacol Experiment Ther.* 2011;337:180-186.
54. Greenblatt JM, Grossman G. *Nutritional Lithium: A Cinderella Story. The Untold Tale of the Mineral That Transforms Lives and Heals the Brain*. Scotts Valley, CA: CreateSpace; 2016.
55. Greenblatt J. The top 5 minerals for cognition, memory and mood. magnesium, lithium, zinc, chromium, and copper discussed. YouTube Web site. https://www.youtube.com/watch?v=cXv9vI3vxm. Accessed July 25, 2016.
56. Prasad AS. Zinc: An overview. *Nutrition.* 1995;11(suppl 1):93-99.
57. Młyniec K, Davies CL, de Agüero Sánchez IG, et al. Essential elements in depression and anxiety. Part I. *Pharmacol Rep* 2014;66(4):534-544.
58. Krebs NF, Miller LV, Hambidge KM. Zinc deficiency in infants and children: A review of its complex and synergistic interactions. *Paediatr Int Child Health* 2014;34(4):279-288.
59. Huang HY, Caballero B, Chang S, et al. The efficacy and safety of multivitamin and mineral supplement use to prevent cancer and chronic disease in adults: A systematic review for a National Institutes of Health state-of-the-science conference. *Ann Intern Med*. 2006;145(5):372-385.
60. McGarel C, Pentieva K, Strain JJ, McNulty H. Emerging roles for folate and related B-vitamins in brain health across the lifecycle. *Proc Nutr Soc*. 2015;74(1):46-55.
61. Nielsen FH. Nutritional requirements for boron, silicon, vanadium, nickel, and arsenic: Current knowledge and speculation. *FASEB J*. 1991;5(12):2661-2667.
62. Młyniec K, Davies CL, de Agüero Sánchez IG, Pytka K, Budziszewska B, Nowak G. Essential elements in depression and anxiety. Part I. *Pharmacol Rep*. 2014;66(4):534-544.
63. Młyniec K, Gaweł M, Doboszewska U, et al. Essential elements in depression and anxiety. Part II. *Pharmacol Rep*. 2015;67(2):187-94.
64. Bai Y, Feng W, Wang S, et al. Essential metals zinc, selenium, and strontium protect against chromosome damage caused by polycyclic aromatic hydrocarbons exposure. *Environ Sci Technol*. 2016;50(2):951-960.
65. Schrauzer GN. Nutritional selenium supplements: Product types, quality, and safety. *J Am Coll Nutr*. 2001;20(1):1-4.
66. Schrauzer GN, Shrestha KP, Flores-Arce MF. Lithium in scalp hair of adults, students, and violent criminals: Effects of supplementation and evidence for interactions of lithium with vitamin B12 and with other trace elements. *Biol Trace Elem Res*. 1992;34(2):161-176.
67. Schrauzer GN, de Vroey E. Effects of nutritional lithium supplementation on mood: A placebo-controlled study with former drug users. *Biol Trace Elem Res*. 1994;40(1):89-101.
68. Schrauzer GN. Lithium: Occurrence, dietary intakes, nutritional essentiality. *J Am Coll Nutr*. 2002;21(1):14-21.
69. Uthus EO. Evidence for arsenic essentiality. *Environ Geochem Health*. 1992;14(2):55-58.
70. Schutte KH, Myers, JA. *Metabolic Aspects of Health: Nutritional Elements In Health And Disease*. New York, NY: Discovery Press; 1979.
71. Swaminathan N. Why does the brain need so much power? New study shows why the brain drains so much of the body's energy. Scientific American Web site. https://www.scientificamerican.com/article/why-does-the-brain-need-s/. Published April 29, 2008. Accessed August 9, 2018.
72. Iuliano L, Crick PJ, Zerbinati C, et al. Cholesterol metabolites exported from human brain. *Steroids*. 2015;99(Pt B):189-193.
73. Marshall T, Henricks C. The next generation in brain recovery and neuroregeneration. *J Am Physic Surg*. 2017;1(2):1.