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Immunoexcitoxicity as the possible major pathophysiology behind multiple sclerosis and other autoimmune disorders

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ABSTRACT

Autoimmune disorders are destructive processes considered to be an attack on "self" antigens by the immune system CD-+4 T-cells that are directed toward antigens, in the case of multiple sclerosis (MS), particularly myelin antigens. Yet, there is growing evidence that the major destructive events in MS, as well as other non-central nervous system (CNS) autoimmune disorders, are much more than an immune attack on the CNS initiated by a misdirected immune system that attacks a "self" antigen or antigens by a process called molecular mimicry. Extensive evidence suggests that inflammation, in turn, initiates excitotoxicity, which is responsible for the majority of pathological findings in all stages of the disease, especially a loss of oligodendroglia (source of myelin) and axon injury in MS. Excitotoxicity also is a better explanation for progressive MS, in which the immune attack has either slowed or is halted; yet, the destructive pathology continues to progress. It also explains the destructive lesions seen in gray matter, which is essentially devoid of inflammation. It has recently been shown that most of the damage to the oligodendrocytes, as well as axonal injury, is secondary to excitotoxicity. While there is a growing appreciation that excitotoxicity plays a major role, there has been little effort to link the immune changes to the excitotoxic process, recently named immunoexcitotoxicity, even though the role of excitotoxicity has been shown to occur in the inflammatory stage in the beginning and throughout the process of the disease, particularly the chronic progressive stage. It is also known that peripheral glutamate receptors exist throughout the body, thus making the process of immunoexcitotoxicity a possible integral part of all or most autoimmune disorders in which the immune system is intimately linked to enhancing the excitotoxic process. This is of special concern now that peripheral glutamate receptors have been isolated in many peripheral tissues and are known to be fully functional.

Keywords: Autoimmune disorders, Immunoexcitoxicity, Multiple sclerosis

INTRODUCTION

Most research in this area has assumed that the disease is a combination of a genetically dysfunction immune system combined with an infectious trigger.[61] It has been observed that all patients with MS have an antibody to Epstein–Barr (EB) compared with 86–95% of controls. EB virus has been most associated as the infectious trigger for MS. Infections, both viral and bacterial, as well as vaccines, have been associated with a number of autoimmune disorders.[66]

Most treatments are designed to stem or reduce the immunological reactions seen in autoimmune diseases, especially in the early stages of relapsing remitting multiple sclerosis (RRMS making

up 80–90% of cases) and are directed at reducing the immunological reaction as the intended target. Despite these immunologically directed treatments, their effectiveness in stemming the progression of this disease has been modest at best.[67,68] This is especially true for chronic progressive MS, particularly the secondary types, in which the inflammatory role is far less involved and invariably occurs years after the initial stages. Primary progressive MS appears to be destructive and progressive from the start (PPMS). Most such patients die within 1 year. New evidence indicates that even in the early stages of the relapsing-remitting disease, neurodegeneration is occurring, that is, excitotoxicity. It has also been noted that in MS gray matter lesions, considered non-inflammatory, we see evidence of pathological excitotoxicity.[24,54,82] Memory impairments in MS are mostly associated with gray matter lesions.[5] We also see extensive gray matter lesions occurring before substantial white matter demyelination, and this predicts the future progression of the disease and disability.[59,68]

It has been shown that there is a link between the activation of the immune system in the periphery and the initiation of excitotoxicity within the central nervous system (CNS), mainly initiated by microglial activation but also involving astrocytes and macrophages.[7,43,45]

I coined the name immunoexcitotoxicity to describe this linkage.[10] In describing this link, using chronic traumatic encephalopathy as a model, I made a connection to excitotoxic mechanisms initiated when peripheral immune activation was triggered. I demonstrated that some pro-inflammatory cytokines could enhance excitotoxicity by several mechanisms, including the insertion of GuR2 lacking amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which are calcium sensitive. This makes the AMPA receptors more reactive and potentially more destructive. It has been shown that oligodendroglia has only AMPA-type receptors.[64,79] It has also been shown that in the MS lesions, there is an increase in glu2-lacking, calcium permeable AMPA receptors but not Glu2-containing AMPA receptors.[56] The former is significantly more destructive. It has been noted that a loss of myelin (produced by oligodendrocytes) and subsequent axonal injury accounts for most of the clinical signs and symptoms of MS.

Discoveries of excitotoxicity have been described in which significantly elevated glutamate in the cerebrospinal fluid (CSF) of MS patients occurs in the early acute phase.[93] This has been reconfirmed along with the disease state, which has been correlated with elevated glutamate levels with the activity of the disease.[87] In addition, one sees a relation between glutamate levels and the extension of axonal lesions.[32]

It was assumed that the loss of myelin and damage to the axons, including transection, was secondary to an immune attack on oligodendroglia in the lesions. Newer evidence suggests that excitotoxicity accounts for most of the damage with the inflammatory/immune reaction enhancing the excitotoxicity.[81]

This is explained by the interaction of immune cytokines with various enzymes related to glutamate-enhanced excitotoxicity among other linked mechanisms, as shown in Figure 1, mainly involving tumor necrosis factor (TNF)-alpha and less so Interleukin (IL)-1ß. In Figure 1, it appears that activation of the AMPA receptors, especially the calcium sensitive glutamate receptor 2 (GluR2)-lacking AMPA receptors, kills the majority of oligodendrocytes in the lesions and is not a product of immune reactions alone.[68,81] It has been estimated that 60% of the destruction of oligodendrocytes is secondary to excitotoxicity.[81] Inflammation has been shown to enhance the trafficking of Glu2-lacking AMPA receptors to the endoplasmic reticulum so that the synaptic plate contains GLuR2-lacking AMPA receptors that are now calcium sensitive.[56] They also transfer inhibitory gamma amino butyric acid (GABA)receptors into the cytoplasm of the neuron.

This combination (immune activation and excitotoxicity) greatly enhances excitotoxic destruction of neurons, glia, and axons. It is known that TNF-alpha is found in the CSF at high levels in over half of patients with chronic progressive MS not treated with immunosuppressive medications.[88] These levels correlated with the degree of disability and the rate of neurological deterioration over 2 years. Low levels of TNF-alpha actually enhance remyelination (by stimulation tumor necrosis factor receptor @ [TNRF]), and completely blocking TNF-alpha with blocking drugs has been shown to worsen MS.[89]

Subpial lesions represent the most abundant type of lesion in progressive MS but can be seen in RRMS as well.[55,68] These normally extend to cortical layers III and VI but rarely invade subcortical white matter.[15]

Active tissue damages, such as demyelination, oligodendrocyte loss, axon transection, neuronal death, and reduced presynaptic terminals, are accompanied by microglial activation, a major source of glutamate in the CNS. While these reactions have been attributed to inflammation, newer evidence suggests that excitotoxicity is the main pathological event.[23,58,68,81]

Degeneration of axons within the lesions is considered the major cause of disability in MS. In experimental animals with experimental allergic encephalitis (EAE), it is estimated that there is a 30% loss of axons in the lesions and in humans, this can reach 60-70% loss.[23]

It is of note that in the spinal cord, we see global atrophy, which is often independent of focal white matter plaques.[38] This could be another indication of more widespread excitotoxicity.

While T-lymphocytes are considered to be the hallmark of the disease process during the early stages, they become

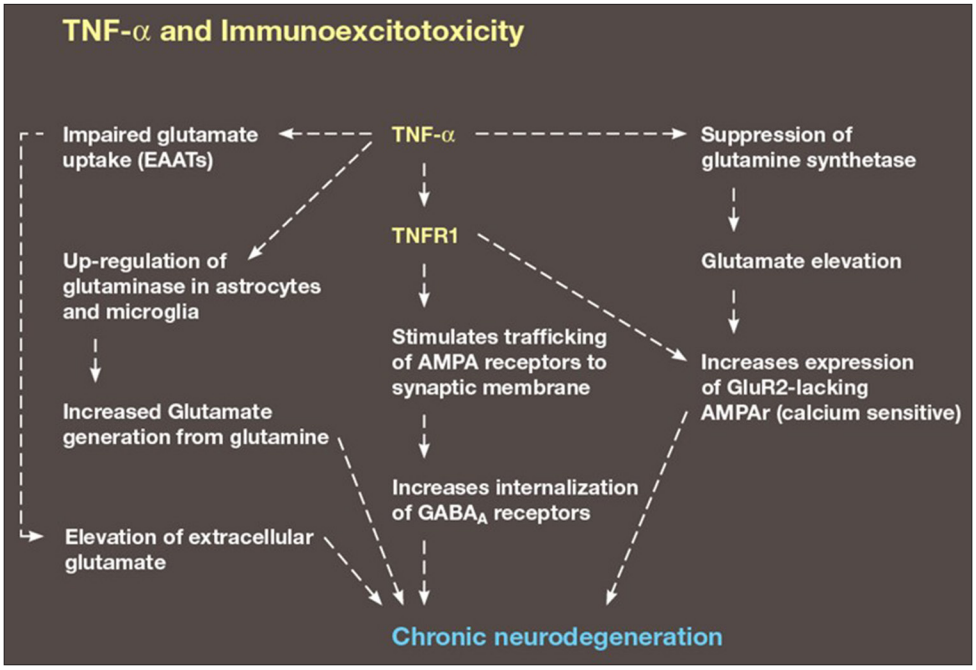

Figure 1: Demonstrating interaction of tumor necrosis factor-alpha with excitotoxic mechanisms and enzymes. AMPA: Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, TNF: Tumor necrosis factor, TNFR: Tumor necrosis factor receptor, GABA: Gamma amino butyric acid, EAAT: Excitatory amino acid transporters

less important and involved with chronic progressive disease.[59]

As with many neurological diseases, with progressive destruction, we see a number of other factors come into play, such as mitochondrial dysfunction, initiation of immune reactions to excitotoxic damaged tissues, reactive oxygen species (ROS), and reactive nitrogen species (RNS) generation and other pathological mechanisms occurring in the damaged tissue. Many of these mechanisms are seen with excitotoxicity. Important to this discussion is that most of the damage in MS is not immunological/inflammation in origin but rather excitotoxic. Immunologically induced inflammation enhances the damaging effects of excitotoxicity. Likewise, excitotoxicity can induce inflammation, and immune reactions directed toward glutamate receptors can initiate excitotoxicity.[75]

It has also been proposed that the immune reaction we see in the lesions may be an epiphenomenon. That is, a secondary attack initiated by the excitotoxic reaction and the presence of damaged tissue caused primarily by excitotoxicity.[68,81]

In progressive MS with active demyelination, we see microglial activation as an early event.[40] Microglia play both neurodestructive and reparative roles. They represent an important removal system for extracellular glutamate utilizing a series of five glutamate transport proteins [excitatory amino acid transporters (EAATs)]. ROS, RNS, and inflammatory cytokines inhibit these transport proteins, resulting in a rapid buildup of excitotoxins and ultimate excitotoxicity. Some of these proinflammatory cytokines, such as TNF-alpha and IL-1ß, can enhance excitotoxicity.

Blood-brain barrier (BBB) damage can be the result of both lymphocyte infiltration and excitotoxicity.[30] Glutamate exclusion from the brain depends on an intact BBB. Certain areas of the brain, such as the circumventricular organs, have a very poor BBB.[4] It has been shown that acutely, the brain can prevent excess glutamate from entering the brain, but chronic elevations of blood glutamate will penetrate an intact BBB. Humans are several times more sensitive to elevated blood glutamate than any other examined species of animal, especially the neonate.[72] It is important to appreciate that only the brain and spinal cord have barriers to glutamate entry, and then only under normal conditions.

While several peripheral tissues have fully functional glutamate receptors, there is no barrier to blood levels of glutamate or other excitotoxins entering these tissues. With aging, it has been shown that microglia are primed to become more reactive, and this priming also occurs in many other situations, including vaccination and repeated infections.[69]

THE PATHOPHYSIOLOGY OF IMMUNOEXCITOXICITY

The process of excitotoxicity was discovered by Olney and Sharpe in 1969 while studying the toxicity of monosodium

glutamate.[72] Since that original discovery, scientists have uncovered a number of glutamate receptor types and subtypes. They have also discovered several systems to reduce extracellular glutamate, where it is harmful. Other excitotoxins, such as aspartate, quinolinic acid (QUIN), and metabolites of homocysteine (homocysteine, cysteine sulfonic acid, and homocysteic acid), have also been discovered.

Glutamate is one of the major neurotransmitters and its level is over 1000-fold higher than the other neurotransmitters.[92] The main source of glutamate in the CNS is the microglia. Astrocytes, along with microglia, utilize a group of 5 glutamate transporters (EAAT 1–5) to keep extracellular levels of glutamate low, as high concentrations in the extracellular space (ECS) can be quite destructive. Activated microglia secrete considerably more glutamate than resting microglia (microglia never rest, as they are constantly sampling the ECS for glutamate levels.). Within the microglia, the enzyme glutaminase converts glutamine into glutamate. There are several systems the microglia use to regulate glutamate production and control its concentration, such as the enzyme glutamine synthase, which converts glutamate into the non-destructive molecule glutamine. This enzyme is redox sensitive to some oxidants and reactive nitrogen radicals, such as peroxynitrite. Inhibiting this enzyme by free radicals prevents the conversion of excess glutamate into glutamine and, in addition, has been shown to enhance microglial immune responses.[14,33,75]

Glutamate receptors are divided into two basic groups – ionic glutamate receptors, such as n-methyl-d-aspartate receptor (NMDAR), AMPA, and kainate type ionotropic glutamate receptors (iGluRs), which control ion entry into the cell and are named according to their main agonist and metabotropic glutamate receptors (mGluRs), which are divided into three groups. The latter receptors control a cell-signaling system through G-proteins (G-protein-coupled receptors).

The metabotropic receptors are found both pre-synaptically and post-synaptically. Group I (mGluR1 and 5) enhances glutamate receptor activity. Group II (mGluR 2 and 3) has primarily inhibitory effects on iGluRs. Group III (mGluRs 4, 7, and 8) are mainly inhibitory of iGluRs.[80]

Certain immune cytokines, such as tumor necrosis-alpha and IL-1ß, have been shown to enhance excitotoxicity by their effects on glutamate receptors when found in excess.[2,56,85] The pro-inflammatory cytokine TNF-alpha can either enhance neurodegeneration or suppress neurodegeneration, depending on the concentration, which determines which TNFR is activated, with TNFR1 being neurodestructive and TNFR2 protective.[44]

A number of processes are activated by the immune system that make this link to excitotoxicity. For example, macrophages, neutrophils, and lymphocytes secrete glutamate at high levels when activated, increasing local levels of glutamate at the site of neurodestructive reaction, leading to excitotoxicity. Excitotoxicity, in addition dramatically increases free radical generation that damages the local mitochondria in both neurons and axons.[60] Nitric oxide, which is dramatically elevated in excitotoxic reactions and is seen in multiple sclerosis (MS), suppresses mitochondrial energy production.[1,21]

Low-energy production has been shown to dramatically increase excitotoxicity, so much so that even normal levels of glutamate can become excitotoxic.[70] With the immune reaction, nitric oxide, and free radicals impairing energy production, we see increased sensitivity of the ionic glutamate receptors to excitotoxicity.

Free radicals also impair the glutamate transport proteins, the most important being EAAT1 and EAAT2 (glutamate transporter-1 (GLT- 1) and glutamate-aspartate transporter (GLAST) in the animal models).[90] In addition, the transporters can reverse the transport, thus raising the extracellular fluid (ECF) levels of glutamate.[46] This results in the accumulation of glutamate in the ECF and excitotoxicity. The free radicals are being produced both by the immune reaction and excitotoxicity itself. As a result, we see the process being self-generated.

Being that the AMPA receptor is the main glutamate receptor on oligodendrocytes, trafficking of the calcium sensitive AMPA receptor in the face of immune-induced inflammation triggers worsens the pathologic effect.

TNF-alpha, which is markedly elevated in MS, also impairs glutamate uptake, increases glutaminase enzymes, impairs glutamine synthetase, and induces movement of GABA into the cell.[8,88] Figure 1. It was also found that the CSF level of TNF-alpha correlated with the increase in neurological disability at 24 months of observation. All these immune processes worsen excitotoxicity. Destruction of the oligodendrocytes by excitotoxicity, in turn, impairs myelin formation. Oligodendrocyte death with subsequent demyelination and axon destruction represents the major pathophysiological event in MS, especially in its progressive form.[6]

The enhancement of the excitotoxic mechanism by the immune system explains the resulting pathology as well as the clinical response to the immune attack. In total, this represents immunoexcitotoxicity.

MICROGLIAL ACTIVATION

Microglial activation is ubiquitous in MS, especially in gray matter. The cortical lesions have few macrophages, no inflammatory infiltrates, and abundant activated

microglia.[41] It has been proposed that leptomeningeal inflammation is driving microglial activation especially in secondary progressive MS.[34,84]

Activated microglia, especially when primed, are the main source of glutamate and other excitotoxins.[16] Microglia can react to damage damage-associated molecular patterns (DAMPs), produce other destructive compounds, and also act as antibody presenting cells. These cells contain toll-like receptors and receptors to advance glycation products (receptor for advanced glycation end products [RAGE] receptors). They also have receptors for purines released from dying cells.

While intact functional astrocytes can remove glutamate from the ECS, when they die within lesions, they release their store of glutamate and purines as well, both acting as sources of excitotoxicity activation. In the cortex, subpial inflammation activates the microglia in the sulci, leading to demyelination in the deeper layers.[52]

RELEASE OF GLUTAMATE BY SYSTEM X_C^- ANTI-PORTER

The major source of glutamate from the microglia is the cystine-glutamate anti-porter or system X_c^-.[57] This anti-porter system is designed to allow the amino acid cystine to enter the cell in exchange for glutamate, which is extruded from the cell. To prevent accumulation in the ECS, the glutamate transporter proteins move the glutamate inside the cell to be used again. The cystine is used to manufacture glutathione, a major cell protectant. Impairment of the glutamate transporters, as we see with high proinflammatory cytokine levels (TNF-alpha, IL-1ß, or ROS accumulation), inhibits these transport proteins, allowing glutamate to accumulate in the ECF rapidly. This results in excitotoxicity.

This again connects inflammation to excitotoxicity. Researchers have noticed a progression to disability in the absence of active inflammatory disease despite the treatment of these patients with highly effective anti-inflammatory medications, suggesting excitotoxicity as the major pathological process.[22,68,81]

Using a mouse model of MS, researchers found that drugs used to block the system X_c^- anti-porter-attenuated autoimmune inflammatory-enhanced neurodegenerative demyelination.[39] To eliminate the possibility that what was being altered was immune cell infiltration into the CNS, the researchers allowed immune cell infiltration for 7 days before they initiated treatment with the inhibiting drug. They also demonstrated that mice lacking a functional system X_c^- were resistant to the induction of EAE.

At least in this model, we see that even with immune initiation in such mice, it was impossible to induce the lesions as well as demyelination seen in animals possessing this glutamate extrusion system. This points clearly to excitotoxicity being the main destructive process, with immune activation being an enhancer (immunoexcitoxicity).

The system X_c^- anti-porter is recognized as the main site of extrusion of glutamate from the microglia when it is activated.[20]

More evidence is the use of [2,3-dioxo-6-nitro-7-sulfamoyl-benzo [f]quinoxaline (NBQX)] to block the AMPA receptor, the primary glutamate receptor on the oligodendrocytes, which was shown to significantly reduce these mouse models of EAE from pathological lesions as well as clinical symptoms and signs of MS.[97,98] This anti-porter also has been shown to stimulate T-cell infiltration into the lesions.[39]

Blockade of the enzyme glutamine synthetase, which reduces excitotoxicity by converting glutamate to glutamine, has been shown to enhance the inflammatory response of the microglia and would also be expected to enhance excitotoxicity.[75]

RELEASE OF GLUTAMATE FROM IMMUNE CELLS

Several studies have shown that T-cells release glutamate when activated, and when infiltrating the CNS can result in excitotoxic levels of glutamate, especially when the mitochondria are producing insufficient energy.[53] Pacheco *et al*. found that T-cells interact with dendritic cells to release significant amounts of glutamate.[74] There appears to be an interaction between microglial released glutamate and immune signaling, producing damage to oligodendroglia.[63] He also demonstrated that lower concentrations of glutamate sensitized oligodendrocytes to attack by complement. Kainate receptors, closely related to AMPA receptors, also play a role in these glial cells.

There is also evidence that both neutrophils and macrophages release neurotoxic levels of glutamate when these immune cells are activated.[36,62,78]

INFLAMMATION EFFECTS ON KYNURENINE METABOLISM

Under basal conditions, tryptophan metabolism results in the formation of various products, the majority of which are glutamate receptor suppressors, such as kynurenic acid. During inflammation, this excitotoxic suppressor is reduced and the metabolism is shifted toward the production of QUIN, which can stimulate the NMDA receptor. We see elevated QUIN in a number of neurodegenerative diseases, such as major depression, autism spectrum disorders, ulcerative colitis, rheumatoid arthritis, and even metabolic syndrome.[26,47,25,71,76,86]

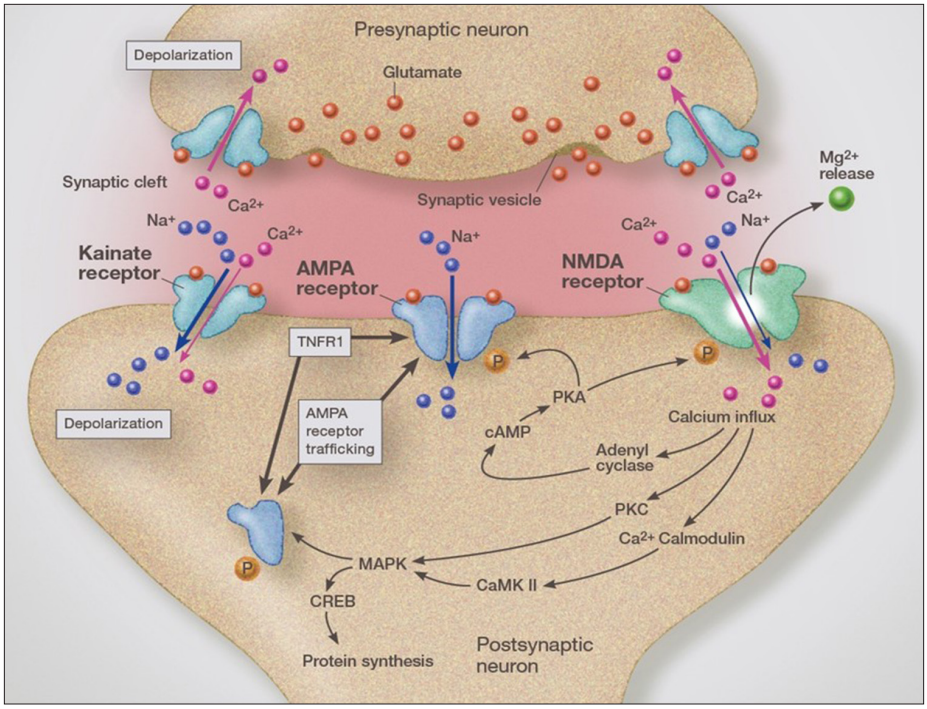

Figure 2: Diagram demonstrating the release of glutamate from pre-synaptic site to receptors of post synaptic site. We also see the trafficking of GluR2-lacking AMPA receptors to the synaptic site, which makes the AMPAR calcium permeable. NMDA: N-methyl-D-aspartate, MAPK: Mitogen-activated protein kinases, CREB: Cyclic adenosine monophosphate response element binding protein, PKA: Protein kinase A, Na: Sodium, K: Potassium, MG:Magnesium, AMPA: Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, TNFR: Tumor necrosis factor receptor, Ca: Calcium

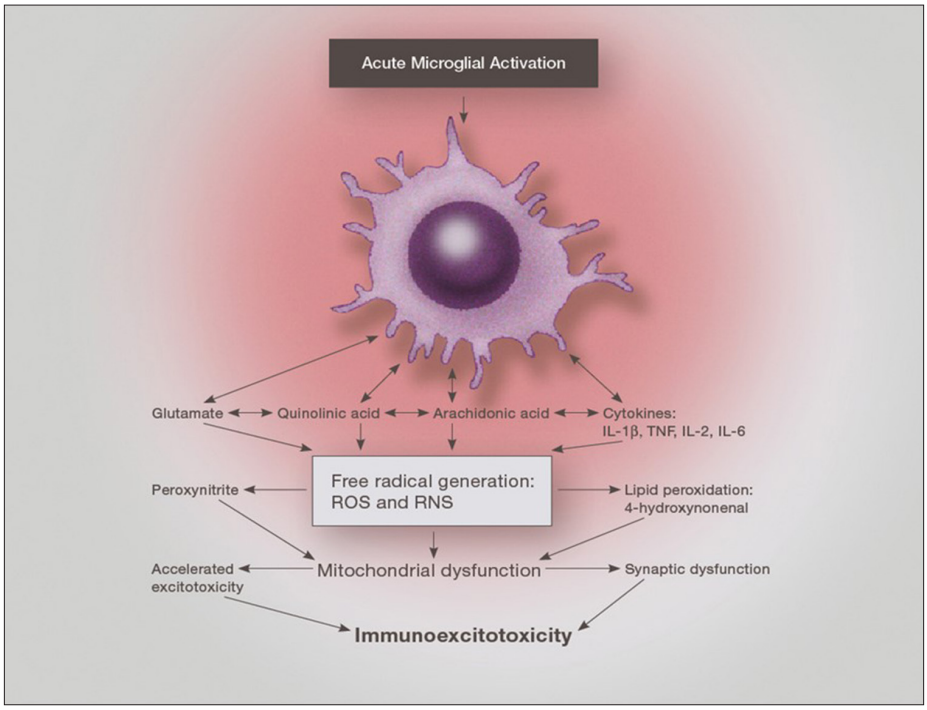

Figure 3: Demonstrating the destructive elements released by excitotoxic stimulation resulting in immunoexcitotoxicity. IL: Interleukin, TNF: Tumor necrosis factor-alpha, RNS: Reactive nitrogen species, LPP: Lipopolysacchride, NMDAR:NMDA receptor, ROS: Reactive oxygen species

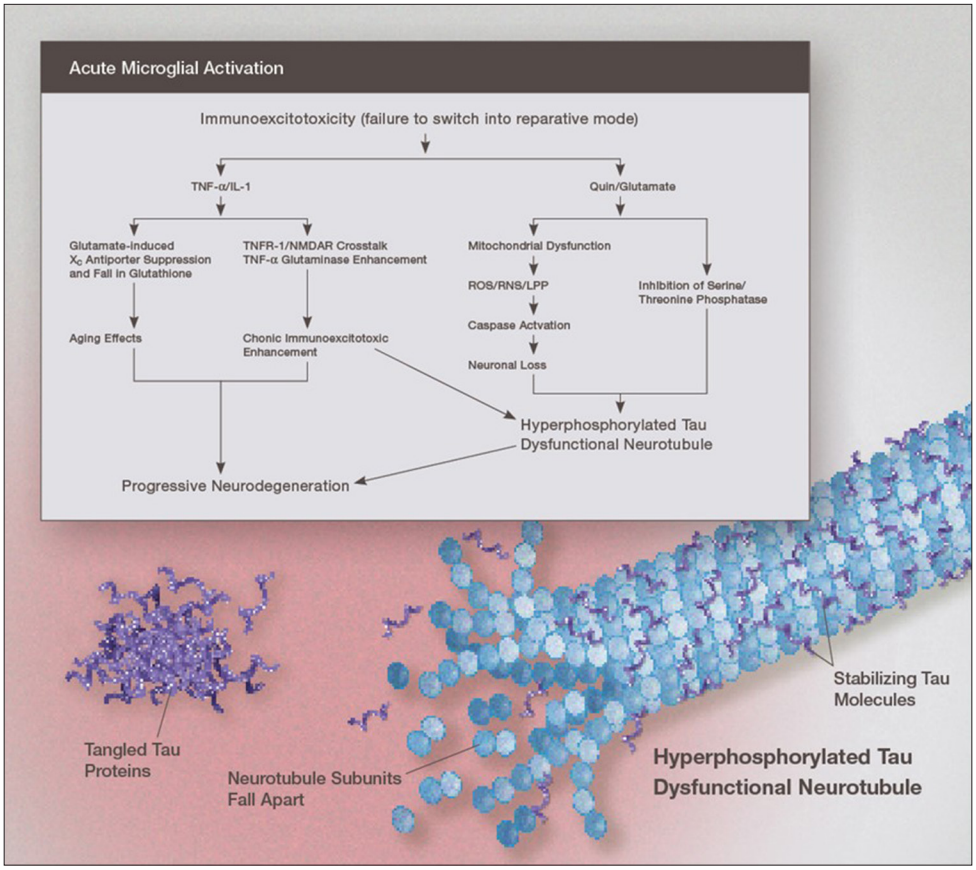

Figure 4: Diagram demonstrating the mechanism by which excitotoxicity results in hyperphosphorylated tau accumulation. IL: Interleukin, TNF: Tumor necrosis factor-alpha, RNS: Reactive nitrogen species, LPP: Lipopolysacchride, NMDAR:NMDA receptor, ROS: Reactive oxygen species

As an autoimmune disease, as well as elevated glutamate, both increase inflammation one would expect elevation of QUIN in all cases of systemic and CNS inflammation. QUIN acts as an excitotoxin through the NMDA receptors.[77] QUIN also inhibits glutamate uptake by astrocytes as well as stimulating glutamate release from synapses, making it a very toxic molecule.[94]

OTHER AUTOIMMUNE DISORDERS AND IMMUNOEXCITOTOXICITY

It is known that many cells and tissues within the body, other than those in the CNS, also contain functional glutamate receptors resembling those within the CNS.[49] This makes other cell types susceptible to excitotoxic damage, just as within the CNS. For example, glutamate receptors have been discovered within the islets of the pancreas and appear to play a role in diabetes.[51,73] Glutamate receptors appear to be present in all endocrine cells and neuroendocrine cell nuclei.[19]

There is also evidence of excitotoxicity in systemic lupus erythematosus with auto antibodies to the NR2 subunit of NMDA receptors, which makes these receptors hyperactive.[35] The spinal fluid of these patients contains these antibodies and can activate the NR2 subunit as well.

We also see glutamate receptors playing a major role in joint destruction in rheumatoid arthritis.[42] These researchers found glutamate receptors on a number of joint tissues, and glutamate levels were very high in the synovial fluid of affected joints. Others have disclosed similar findings.[50] It was also found that the degree of resorptive changes in the tempomandibular joint of rheumatoid patients was related to high levels of glutamate within the joint.[17,48]

McNearney *et al.* found elevated glutamate levels as well as TNF-alpha within the joints of patients with active rheumatoid arthritis and the level of TNF-alpha was increased as the glutamate levels rose.[65]

Autoimmune diseases associated with epilepsy from such conditions as thyroiditis are associated with excitotoxicity within the brain induced by the immune reaction and elevated levels of glutamate.[31,83] Acute colon inflammation has also been shown to induce immunoexcitoxicity within the CNS.[25,96]

According to several immunologists, autism spectrum disorders represent a group of autoimmune disorders.[3,37] Yet, considerable evidence suggests that it represents a series of immunoexcitotoxic disorders.[9,10,11,13]

CONCLUSION

There is growing evidence that autoimmunity represents a complex of pathological disorders triggered by an immune reaction involving certain "self" tissues. While it has been considered a purely immunological disease resulting from this attack on "self" antigens by immune cells, recent evidence indicates that glutamate toxicity plays a major role in these disorders and that the immune system acts as an enhancer of the excitotoxic reaction by a number of mechanisms, such as suppression of glutamate uptake, enhancement of the cystine/glutamate anti-porter, enhancement of excitability of specific subtypes of receptor subunits, glutaminase enhancement, glutamine synthetase suppression, ROS, RNS activation, and especially trafficking of GluR2-lacking AMPA receptors Figure 2. We also see that inflammation itself shifts kynurenine metabolism toward the production of QUIN, itself an excitotoxin as well as having other toxic effects.

While glutamate receptors have been identified within the CNS, there is now evidence that many peripheral tissues, immune cells, and other organs also contain fully functional glutamate receptors and several release high levels of glutamate when inflamed. Immune cells are known to secrete large amounts of glutamate when activated, as do microglia and astrocytes within the CNS and peripheral nerves. This released glutamate can result in tissue destruction by generating RNS, ROS, and lipid peroxidation products, as well as nitric oxide, as shown in Figure 3. Damage to mitochondria, with a reduction of energy production, results in excitotoxic damage to these tissues, as low mitochondrial energy production, in addition to massive free radical production and changes in the metabolism of substrates, also enhances glutamate sensitivity to excitotoxicity. Immunoexcitoxicity can also result in tau protein accumulation Figure 4.

Glutamate is considered to be an immunotransmitter in the immune cell, altering the function of immune cells' behavior. In combination, the pathophysiological changes result in definable lesions to the tissues involved, resulting in specific clinical syndromes, depending on the area or areas involved.

While in the beginning, glutamate receptors were considered functional only in the CNS, recent evidence demonstrates that glutamate receptors exist in a great number of tissues and resemble those seen in the CNS.[29,49] Within the CNS, the BBB protects the CNS from excess dietary glutamate acutely, but chronic exposure can breach the barrier as well as the circumventricular organs, which have either no or a poorly functional barrier. The BBB is poorly functional soon after birth and matures as the child matures.

This would expose these glutamate receptors to elevations of the blood glutamate, caused either by dietary habits or caused by systemic disease, as we see with infections.[27,28,91,95,99]

A low glutamate diet has improved symptoms of both the autism spectrum disorder and the Gulf War Syndrome.[18]

A combination of a low glutamate diet and compounds that reduce excess glutamate elevations by inhibiting microglia activation may offer better treatment of autoimmune disorders of various kinds than immune reduction alone.

One of the questions confronting this mechanism in MS is the various presentations of the disease, such as a relapsing/remitting course (the most common) versus progressive forms. This might depend on the ability of the immune system to activate natural immune suppression initially. If the immune attack is continuous during the early stages, the disease will be unrelenting, possibly unaccompanied by sufficient physiological immune suppression. If full physiologic immune suppression (Tregs, for example, or activation of the 7 alpha-nicotine acetylcholine system) occurs, we will have a relapsing/remitting course. The other possibility is that the immune system is unable to clear the triggering infection, and either its recurrence or new infection will cause the disease to relapse, resulting in the RRMS pattern. Once the immune reaction has been eliminated (during the later course of the disease – unexplained by the autoimmune explanation), excitotoxicity continues, accounting for the terminal (previously unexplained) course of the disease, often leading to death. Only a handful of researchers have seen the role played by excitotoxicity, but to date, there has been no explanation as to its mechanism linking immune activation with excitotoxicity.

Most "autoimmune diseases" are discussed by immunologists, and it was assumed the major damage was immunological – but now these disorders have been shown to have major excitotoxic mechanisms. Together, we have a much better picture; that is, an immunoexcitotoxic pathophysiology is linking the two processes.

Several natural products reduce glutamate excitotoxicity, either by suppressing glutamate release, inhibiting microglial activation or reducing multiple mechanisms seen in immunoexcitotoxicity.[12]

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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