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Editorial

Why immunoexcitoxicity is the basis of most neurodegenerative diseases and systemic immune activation: An analysis

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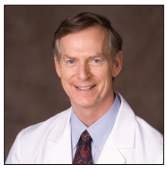

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Immunoexcitotoxicity simply means a connection between immune activation in the body and enhancement of excitotoxicity in tissues containing glutamate receptors. This series of reactions occurs principally by the number of systems at play. It has been demonstrated, for example, that the glutamate transporters are inhibited by reactive oxygen species (ROS) as well as activation of cell systems that make up the various glutamate (excitotoxic) receptors, basically their subunits.[17,19]

In the first instance, ROS are known to inactivate the main glutamate transporters, GLT1, and GLAST.[17,19] As a result glutamate and other excitotoxins, rapidly build up outside the neuron where the danger lies. Glutamate inside the neuron or cell is basically harmless. Extracellular glutamate, if allowed to reach high levels, becomes very harmful and can kill many cell types, including neurons.

In most cases, the most destructive excitotoxic reaction occurs by opening a cell membrane calcium pore.[9,14] Calcium is the most common cell-signaling chemical and is responsible for a great deal of destructive reactions if not controlled.[12] As we age, cells have greater difficulty controlling calcium entry.[4,5] Normally, cells use the mitochondria as a calcium sink. With excitotoxicity and inflammation, we have injury to mitochondria, thus impairing this protective system. Excess calcium is not only responsible for this cell injury but also promotes the progression of cancer.

In the immunoexcitotoxic reaction, ROS are massively generated and consequently the transporters are inactivated [Figure 1]. The main cells for controlling extraneuronal glutamate are astrocytes and microglia. As the neurodegenerative process progresses, astrocytes undergo apoptosis and necrosis, both of which release not only stored glutamate but also DNA products, pyridines.[10] These products activate receptors on the surface of the microglia that are excitotoxic. Ionic mercury triggers this very efficiently, a major problem with previous childhood vaccines (ethyl mercury, used previously in vaccines, is metabolized to ionic mercury in the central nervous system [CNS] progressively destroying the astrocytes).[1]

Inflammatory cytokines generate several free radicals (especially interleukin-1 beta [IL-1ß] and tumor necrosis factor-alpha [TNF-alpha]). A second reaction that has been recently recognized is the ability of some inflammatory cytokines (IL-1ß and TNF-alpha) to enhance particular excitotoxic subunits, for example, the NR1 subunit of the N-methyl-D-aspartate (NMDA) receptor

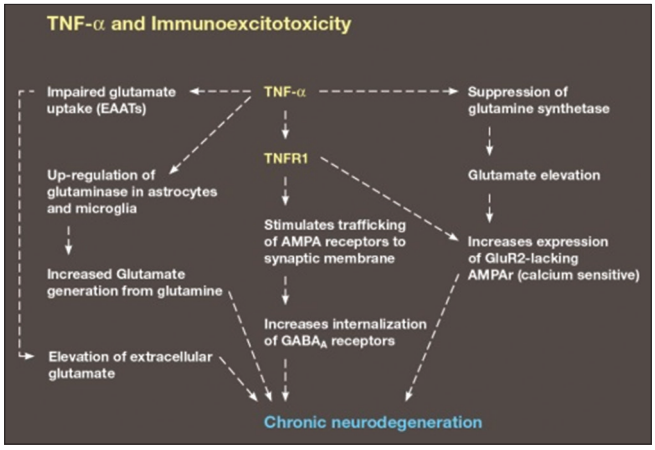

Figure 1: Demonstration of various mechanisms used by the immune system to enhance excitotoxicity. EAATs: Excitatory Amino Acid Transporters, TNFα:Tumor Necrosis Factor alpha, TNFR1:Tumor necrosis factor receptor 1, AMPA:α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, (GABAA):γ-Aminobutyric acid type A (GABAA).

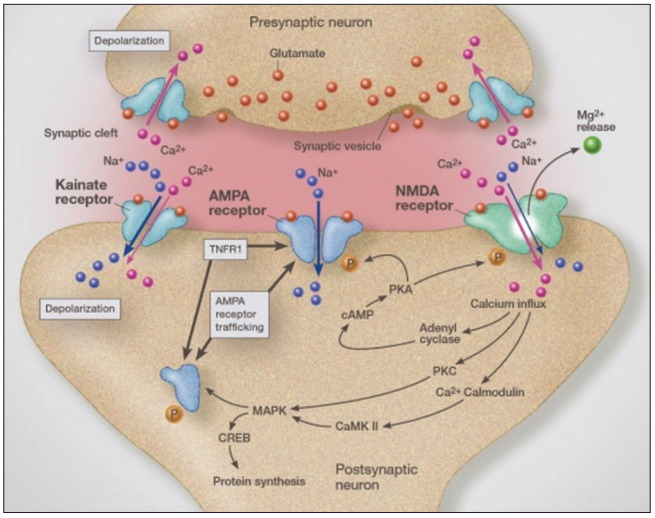

Figure 2: Illustration demonstrating the various glutamate receptors and the effect of activating TNFR1 and well as calcium channels in this process. NMDA: N-methyl-D-aspartate, PKA: cAMP-dependent protein kinase A, PKC: Protein kinase C, cAMP: Cyclic adenosine monophosphate, MAPK:Mitogen-activated protein kinase, CREB: cAMP-response element binding protein, CaMkII: Ca2+/calmodulin-dependent protein kinase-II.

[Figures 1 and 2].[20] Lupus inflammation enhances antiNR2 subunit activation, making the receptor more destructive than normal.[7] A more common reaction associated with inflammation is the conversion of noncalcium permeable AMPA receptors to calcium permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.[6] It occurs in the endoplasmic reticulum, which stores these special receptors. Under inflammatory conditions, they are transferred to the neuron membrane and inserted into the synaptic plate.

Like NMDA receptors, they are calcium permeable and are responsible for greatly enhanced excitotoxicity. The AMPA receptor normally makes up the fast transmission system. With inflammation, anywhere in the body, they become more destructive within the CNS. Unlike NMDA receptors, they are not controlled by magnesium.[8]

The metabotropic receptors control the sensitivity of the main glutamate receptors, (NMDAR, AMPAR, and kainate receptors). By enhancing the sensitivity of metabotropic receptor 1 (an activator), the inflammatory cytokines can enhance the sensitivity of the main receptors, especially NMDA receptors [Figure 2].[3] The metabotropic receptors operate through the G-protein system. Several other metabotrophic receptors do the opposite. That is, they down-regulate the glutamate receptors.

There are other systems at play in excitotoxicity, such as the X_c system, which exchanges external cystine for internal glutamate.[2] The glutamate is expelled and is quickly and safely placed in the astrocyte or microglia by the transport proteins, mainly GLT-1 and GLAST. Inside the cell, the cystine is utilized biochemically to make glutathione, a powerful cell protectant. If the glutamate transporters are paralyzed by ROS and/or inflammatory cytokines, the externally exchanged glutamate remains elevated and builds up in the extraneuronal space where it is destructive.

Recent research indicates that there are hemichannels that move glutamate out of the cell in massive amounts and that inflammatory cytokines can activate these hemichannels worsening excitotoxicity.[15] Normally, in the CNS, the cytokines are in very low concentrations. TNF-alpha and IL-6 at these concentrations are neuroprotective but at high concentration, as seen with infarction and trauma, make excitotoxicity worse. Repeated bouts of inflammation prime all immune cells, especially the macrophages and the microglia. On top of this, we have inflammatory cytokines switching the calcium impermeable AMPA receptors into calcium-permeable, highly destructive AMPA receptors. TNF-alpha does this by activating one of its two receptors, TNFR1. As we have seen in the case of the autoimmune disease, such as multiple sclerosis, we have this switch in AMPA receptors occurring in the oligodendroglia, responsible for myelin production.[16]

In addition, TNF-alpha suppresses glutamine synthetase, an enzyme which protects the neuron by converting glutamate to glutamine [Figure 1]. To make matters worse, TNF-alpha increases the internalization of protective GABAa receptors and enhances the enzyme glutaminase within astrocytes and microglia, which converts glutamine to glutamate. This greatly enhances excitotoxicity [Figure 1].

In essence, we see a very intimate connection between glutamate receptors and the immune system mediators. It has been shown that this enhancement is present even with minor surgical operations systemically. The length of this enhancement varies

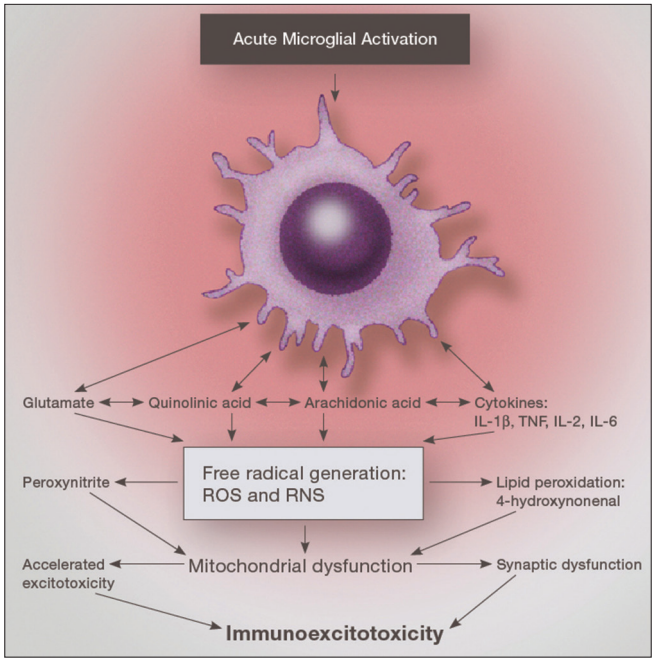

Figure 3: Illustration of the immunoexcitotoxic process. ROS: Reactive oxygen species, RNS: Reactive nitrogen species, IL: Interleukin, TNF: Tumor necrosis factor.

from a few days to decades (in the case of head trauma and autism).[13,18,21] In addition, it has been noted that pathology within the brain greatly enhances immunoexcitoxicity triggered by systemic immune activation[11] [Figure 3].

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