

# Immunoexcitotoxicity offers new insight in brain injury related research, care

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Approximately 1.5 million people in the United States annually experience a traumatic brain injury (TBI). The number of unreported head injuries is much higher. Of these, a great number occur in sports-related events, professional and nonprofessional. There are approximately 100,000 to 300,000 concussions occurring in the game of football alone each year. Most sports-related head injuries are minor concussions and a significant number are repeated injuries over a relatively short period of time. It is known that football players and boxers experience thousands of subconcussive blows during a career.

Until recently, it was assumed that minor injuries resulted in few long-term neurological problems and were, in fact, characterized by a lack of neuropathological damage to the brain. Although it was recognized that a small percentage of these individuals could suffer from an array of neurological and constitutional complaints, called the post-concussion syndrome, there was little evidence of anatomical damage to explain these symptoms.

Post-concussion syndrome (PCS), post-traumatic stress disorder (PTSD), and chronic traumatic encephalopathy (CTE) are devastating neurological conditions, not completely understood in terms of their pathogenesis. There is, however, accumulating scientific evidence that physical injury as in football or other contact sports as well as some psychiatric disorders (e.g., depression and PTSD) produce a neuroinflammatory and excitotoxic response in the brain. In the case of concussions, cumulative injury

may lead to progressive neurodegeneration of the brain (CTE). This process has been termed “immunoexcitotoxicity,” first observed in the “Gulf war syndrome.”

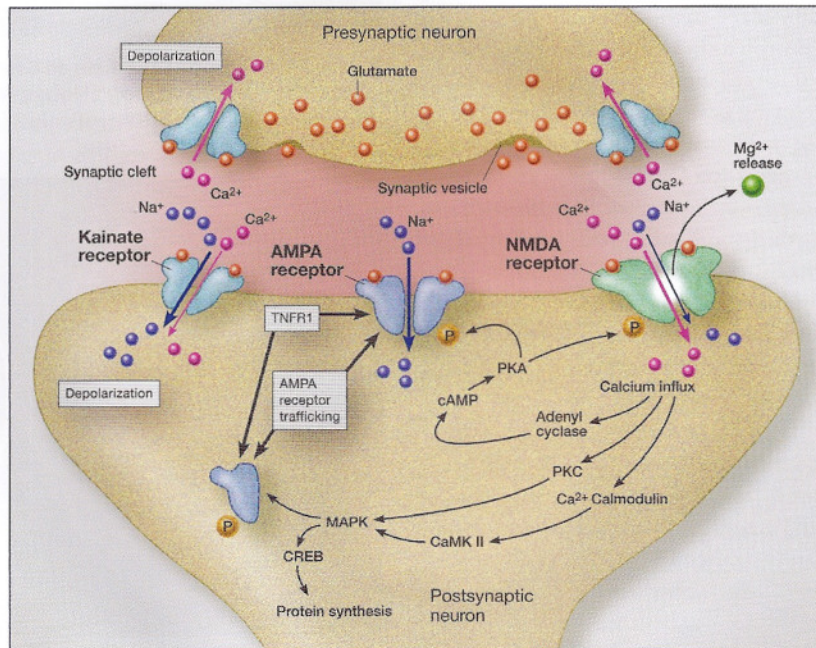
Immunoexcitotoxicity relates to an over-reaction of the resident macrophage immune protective cells in the brain (microglia). When stimulated by trauma, viruses, or other toxic substances, they normally release chemicals (cytokines and excitotoxic amino acids) that initiate a cascade of effects that, if failing to “switch off,” further leads to a series of molecular chain reactions called “excitotoxicity.” This can result in the eventual death of nerve cells. It is akin to a smoldering brush fire (inflammation) in the brain that with repeated trauma burns out of control. This process also occurs in other neurological diseases like Alzheimer’s disease, multiple sclerosis, and Parkinson’s.

Immunoexcitotoxicity represents a new concept in medicine in the development of brain diseases and can explain the original observations of subsequent progressive brain injury (pugilistica dementia) in fighters, in other contact sports, and in injury suffered in military combat. This immunoexcitotoxic response may be enhanced by prior “priming” of the microglia by exposure to neurotoxic metals (Pb, Al, Hg, Cd, Fe), neurotoxic chemicals, (pesticides/herbicides), prior or occult infections, and brain trauma (concussions). With subsequent concussions, as in a previously primed immune allergic reaction (e.g., peanut allergy), there is an outpouring of cytotoxic chemicals that is associated with memory loss, personality changes, depression, and more—all common findings in PCS, PTSD, and CTE.

Elevated levels of the same immunoexcitotoxic chemicals

(IL-1, interleukin-6, tumor necrosis factor, and excitotoxins) seen in brain trauma have now been observed in depression, obsessive compulsive disorder, and other psychiatric disorders—unrelated to physical trauma to the brain. Thus, there appears to be a continuum from traumatic concussion to PTSD to CTE—all with the underlying substrate of immunoexcitotoxicity.

We are of the opinion that there exists abundant evidence that mild, repetitive concussions can trigger immunoexcitotoxicity that in some cases can result in a progressive degeneration in a pattern seen with CTE. A number of studies have shown immune proinflammatory cytokine responses in the traumatized brain that are widespread, with more intense localization within areas of the brain also affected in Alzheimer’s disease.



**Illustration of glutamatergic synapse demonstrating AMPA receptor trafficking from the endoplasmic reticulum, which is driven by activation of tumor necrosis factor receptor-1. Crosstalk between the 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor and tumor necrosis factor receptor-1 increase synaptic insertion of GluR2-lacking (calcium permeable) 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptors, thus increasing synaptic glutamate-related sensitivity. tumor necrosis factor receptor-1 activation also increases GABA receptor endocytosis, which increases synaptic sensitivity to excitotoxicity even further.**

Most such studies have examined acute immune effects in moderate to severe TBI, but a few are concerned with chronic immune responses as well. Likewise, there are a number of studies, both in human beings and experimental animals, demonstrating a massive acute accumulation of glutamate, aspartate, and other excitotoxins in the central nervous system (CNS) following TBI.

With neuroinflammation linked with excitotoxicity as a possible common genesis to all, preventive and therapeutic strategies with anti-inflammatory agents and glutamate receptor modulators, both pharmacologic (non-steroidal anti-inflammatory drugs (NSAIDs), tetracycline’s, etc.) and natural (Omega 3 fatty acids, vitamin D3, resveratrol, curcumin, quercetin, magnesium, luteolin, and hyperbaric O<sub>2</sub>, etc.) should be thoroughly investigated. •