



Neurometabolic Cascading, Glutamate Efflux and Neuronal Excitability: the Essential Process Responsible for Delayed Concussion Recovery

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Received Date: February 19, 2026; Accepted Date: March 03, 2026 Published Date: March 06, 2026

Abstract

Multiple mechanisms have been found to be involved in the delayed recovery from mild-to- severe traumatic brain injuries (msTBI), including neurometabolic cascading, glutamate efflux, sympathetic hyperreactivity and neuronal excitability. Research has determined that adrenergic receptors on sensory neurons provides a coupling mechanism that translates sympathetic hyperactivation into glutamatergic output. Autonomic rehabilitation represents a methodology where the aberrant neuroplasticity that underlies glutamatergic dysregulation can be modified through targeted training.

Introduction

Post-concussion syndrome (PCS) refers to a cluster of symptoms that are associated with the delayed recovery from mild traumatic brain injuries (mTBI). These impairments generally fall into cognitive, emotional, somatic and sleep categories [1]. The cognitive issues emerging from PCS include lack of concentration, memory deficits, difficulty paying attention, slow speech, impaired judgement and comprehension challenges. Emotional features can include mood disturbances, anxiety, irritability and depression. Physical symptoms may consist of headache, sensitivity to light, dizziness, nausea, vomiting, numbness, problems with balance and vestibular dysfunction. Sleep impairments include challenges falling asleep, daytime fatigue and impaired sleep quality.

Although normally these symptoms resolve in anywhere from 10-14 days [2]. An estimated 30% of the population experience persistent post concussive symptoms [3]. Delayed mTBI recovery in these instances is reported to take anywhere from 2 weeks to 3 months [4]. While the causes for these pathophysiological disturbances aren't entirely accounted for [5]. It is recognized that the neurobiology underlying concussive injuries involves a neurometabolic cascade that includes massive ionic flux, glutamate release, impaired neurotransmission and chronic neuronal dysfunction [6]. The ionic flux produces indiscriminate

glutamate release, which is responsible for triggering neuronal depolarization. These synaptic alterations are associated with the widespread neural dysfunction that contributes to attentional deficits, dizziness and memory impairments.

Glutamate Release and Ionic Flux

The pathophysiological cascade that is generated by traumatic brain injuries is initiated by the hyperacute release of the excitatory amino acid (EAA) glutamate, which leads to the production of the ionic fluxes responsible for inducing alterations in cellular physiology [7]. These changes are triggered by the outflow or *efflux* of intracellular potassium ions, and the *influx* of sodium and calcium ions. The resulting changes in cellular membrane polarity then triggers the activation of sodium-potassium ($\text{Na}^+\text{-K}^+$) membrane ionic pumps in an attempt to revive cellular homeostasis.

The effort required to restore the impaired membrane potential causes ionic pumps to increase their activation level, and their elevated output rapidly decreases intracellular energy stores. When this disruption takes place, adenosine triphosphate (ATP), the "energy currency" of the cell, becomes depleted; and cellular energy production diminishes as a result. The ensuing energy breakdown results in further neuronal depolarization, and massive calcium influx [8]. This process unleashes a secondary cascade

responsible for upsetting the homeostatic balance of cellular fluids, which can lead to fluid build-up and cellular body swelling [9].

This secondary biochemical cascade impairs cerebral blood flow, and can lead to cerebral perfusion pressure and blood vessel damage. The resulting vascular constriction is associated with oxidative stress, ischemia and toxic levels of reactive oxygen species (ROS). The indiscriminate glutamate release instigated by sudden depolarization initiates a cortical ‘spreading depression-like’ condition originally associated with migraine symptom generation [10]. The excessive concentration of glutamate that emerges as a result is associated with glutamate-mediated excitotoxicity, a condition related to neuronal damage, neural toxicity and neurodegenerative disorders [11]. Under these circumstances, the abnormal expression of glutamate increases sensitivity to glutamate; and the ensuing sensitivity then sets off the release of more glutamate, initiating a depolarization/ hyperexcitability feedback loop. This self- amplifying loop is exacerbated by the failure of energy dependent glial cells to sufficiently clear and metabolize glutamate from the synaptic cleft as a result of cellular energy depletion [12].

Glutamate induced excitotoxicity plays a prominent role in

facilitating the neuronal damage characteristic of neurodegenerative conditions including Huntington’s disease, Parkinson’s, ALS and Alzheimer’s [13]. Impaired glutamate uptake leads to the hyperactivation of neuronal glutamate (NMDA) receptors, which can then induce oxidative stress [14]. When excitotoxicity- based alterations in glutamate receptor composition produces oxidative stress, it can trigger excessive calcium ion (Ca²⁺) influx [15]. The resulting Ca²⁺ homeostatic imbalance correspondingly exacerbates the excitotoxic cascade, which disrupts neuronal mitochondrial functioning and, in some instances, leads to neuronal death.

To the extent that glutamate initiates reactive oxygen species (ROS) production upon binding to its NMDA receptors, and ROS serves as a mediator of oxidative stress, research has suggested that glutamate serves as a prominent source of the oxidative stress that activates excitotoxicity, which studies show lends itself to neurodegeneration. Chronic hypoxia is similarly linked with cognitive impairment as a result of the increased expression of NMDA receptors, serving to elevate oxidative stress. Finally, as circumstances seem to have it, increased NMDA receptor activation resulting from glutamate excitotoxicity is reported to contribute to neuronal inflammation [16].

Table 1 : Neurometabolic Cascade Progression

1. Initial Ionic Flux	13. Cortical Spreading Depression
2. Neuronal Depolarization	14. Glutamate Mediated Excitotoxicity
3. Indiscriminate Glutamate Release	15. Increased Glutamate Sensitivity
4. Cellular Homeostasis Disruption	16. More Glutamate Release
5. Cellular Energy Depletion	17. Glutamate / Hyperexcitability Feedback Loop
6. Further Neuronal Depolarization	18. Excessive Calcium Influx
7. Secondary Biochemical Cascade	19. Chronic Hypoxia
8. Cellular Fluid Imbalance	20. Neuronal Inflammation
9. Vascular Constriction	21. Disrupted ANS Functioning
10. Oxidative Stress	22. Pro-Inflammatory Cytokine Release
11. Ischemia	23. Increased Sympathetic Outflow
12. Reactive Oxygen Species (ROS)	24. Concurrent Sympathetic Hyperactivity

In fact, hypoxic damage resulting from TBIs has been determined to disrupt autonomic functioning relative to the release of pro-inflammatory cytokines [17]. Studies report TBIs to be responsible for increasing sympathetic outflow and instigating hyperadrenergic activity. Concurrent sympathetic hyperactivity is reported to extend into the chronic phase of post-TBI injury, and its impact is said to encompass emotional and cognitive consequences that contribute to psychological morbidity [18].

As noted, the autoregulatory compromise that accompanies mild-to-severe traumatic brain injury (msTBI) has historically

been associated with the cortical spreading depression originally observed in migraine [19]. The extent to which a history of pre-existing migraine assumes a role in delayed or prolonged concussion recovery is an area that has generated interest among researchers [20]. Noteworthy within this arena is the neuroplasticity responsible for the transition from episodic to chronic migraine, which includes peripheral and central sensitization [21]. As it turns out, the disturbed neuroplasticity that defines central sensitization is said to play a central role in the pathophysiology of migraine; specific to the episodic migraine-chronic migraine (EM-CM)

transition, which is reported to be bi-directional [22].

It's the bi-directionality of the EM-CM transition relative to its maladaptive neuroplasticity that provides an opportunity for migraine to be successfully ameliorated through the autonomic modulation process known as biofeedback [23]. As a clinical modality employed to moderate sympathetic hyperactivation, biofeedback has been demonstrated to mediate an array of autonomic nervous system-based disorders over the years, including chronic pain [24]. Like migraine, chronic pain is fundamentally influenced by abnormalities in glutamate transmission and alterations in neuroplasticity that lead to peripheral and centralized sensitization. The subsequent increase in neuronal excitability and pain sensitivity assumes a significant role in the transition from acute to chronic pain (AP-CP). The AP-CP transition is recognized for its relationship with neuroinflammation, and prolonged inflammatory responses [25].

While the synaptic changes that accompany pain chronification are known to induce inflammation-mediated sensitization and spontaneous nociceptor activation, to date the applicable processes haven't been entirely accounted for [26]. Apart from reductions in synaptic signalling thresholds, it isn't completely clear which additional influences instigate the persistent neuroinflammatory cascading that characterize chronic pain, chronic migraine and delayed concussion recovery. One way of attempting to account for the ongoing production of inflammatory mediators in these instances involves the background impact of sustained synaptic activation.

Synaptic Transmission and Sustained Glutamate Release

Clinical myotonia is an example of a neurologic condition that consists of the impaired ability of muscle fibers to lengthen and relax following activation [27]. Classically, myotonic disorders are separated into dystrophic myotonias, and non-dystrophic myotonias (NDMs); with the NDMs that are associated with ion channel variations being responsible for the generation of skeletal muscle action potentials [28]. NDM disorders are often described as neuromuscular transmission disorders, and they frequently display muscular hyperexcitability at rest [29]. The features associated with clinical myotonia include rigidity, pain and stiffness.

Non-hereditary, or acquired myotonias represent a sub-category of clinical myotonias: a late-onset condition unrelated to genetic mutations that emerges as a result of continuous motor activity. This represents an example of a condition that is predicated on background action potential generation associated with autonomic nervous system dysregulation [30].

Functional neurologic disorder (FND) is a condition that refers to persistent and disabling irregularities in homeostatic balance, abnormal motor movements and in some cases, seizure activity.

Formerly referred to as conversion disorder, the constellation of symptoms characteristic of this condition may at times contain cognitive impairment, abnormal sensory functioning and disordered emotional processing [31]. The diverse functional motor disturbances in these instances can consist of gait disorders, tics, tremors, and dystonic movements. The functional movement components are often accompanied by pain, and provide a basis for surreptitious action potential generation assuming a back-channel presence in stimulating long term homeostatic dysregulation [32].

Non-dystrophic myotonias and FND are two conditions where ongoing synaptic transmission is stimulating the glutamate-mediated release associated with sympathetic hyperactivity, central sensitization and the pathophysiology of migraine development. Pre-existing migraine as it turns out is considered to be a risk factor relative to the changes in vestibular and oculomotor functioning that are linked to both FND and delayed concussion recovery [33]. Perhaps unsurprisingly, glutamatergic dysfunction has also been reported to be a potential factor in the pathophysiology of FND [34].

While excitatory glutamatergic synapses are credited for generating excitotoxicity, it seems surprising that sympathetic hyperreactivity hasn't received greater consideration as a mechanism critical to the initiation of impaired glutamatergic neurotransmission [35]. Yet the placement of alpha-adrenergic receptors on sensory neurons provides a basis for nociceptor-sympathetic interaction, where norepinephrine release in sympathetic terminals results in nociceptor activation [36]. To the extent that adrenergic mediators have been recognized to moderate nociceptive excitability in dorsal root ganglion (DRG) neurons, this relationship would seem to represent the operant lynchpin of the process responsible for making chronic pain chronic, and has been tied to the development of sympathetic neuropathy [37].

Conclusion

The adrenergic coupling on sensory neurons results in action potential generation and induced glutamate release; where the sympathetic activation has been found to mediate neuronal sensitization and neurogenic inflammation [38]. This sensory-sympathetic reflex is associated with pain generation [39], and reported to induce mechanoreceptor firing [40].

Cellular mechanotransduction refers to the conversion of mechanical impulses into biological signals [41]. Research has determined that stretch-activated ionic channels orchestrate an array of concerted responses [42]. Inasmuch as the associations between mechanical signaling and cellular homeostasis have been investigated, prolonged or excessive mechanical stimulation has been found to lead to pathological conditions [43]. The degree that ion channels convert mechanical energy from muscle spindles

into the production of glutamate helps account for the cycling glutamate dysregulation that is linked to FND, migraine, chronic pain and post concussive syndrome [44].

Evidence suggests that if there is a ‘smoking gun’ responsible for generating the disrupted ion homeostasis and glutamatergic efflux linked with delayed concussion recovery, than the conversion of mechanical impulses into the production of glutamate represents just such a mechanism; and chronic sympathetic hyperactivation accounts for the cycling trigger. The changes in synaptic plasticity underlying glutamate dysregulation represent a cascading systems failure that is responsible for the disordered autonomic regulation that accompanies mTBIs and induces pain chronification. Gratefully, the resulting depolarization/ hyperexcitability ‘doom loop’ has been found to be amenable to targeted autonomic regulation [45].

When applied strategically, autonomic rehabilitation has been demonstrated to successfully moderate the sympathetic hyperreactivity, biochemical cascade and sudden depolarization that has been found to be associated with migraine generation and pain chronicity [46]. The implications of targeted autonomic mediation are potentially far-reaching, and include the prospect of arresting the glutamate excitotoxicity associated with post concussion syndrome (PCS), as well as the pathogenesis of neurodegenerative disorders, psychiatric conditions [47] schizophrenia [48], and substance use disorders [49]. Additional research will help determine whether moderating neurometabolic cascading provides a practical means of mediating dysregulated neuroplasticity in these emerging application areas.

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