The Molecular Pathophysiology of Concussive Brain Injury

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- Concussion
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- Molecular mechanisms

Concussion (or mild traumatic brain injury, mTBI) is a biomechanically induced neurological injury, resulting in an alteration of mental status, such as confusion or amnesia, which may or may not involve a loss of consciousness.\textsuperscript{1} Concussion affects about 1.6 million to 3.8 million athletes yearly, most commonly in contact sports such as American football and boxing.\textsuperscript{2,3} Early clinical effects of concussion include but are

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not limited to behavioral changes, impairments of memory and attention, headache, unsteadiness, and rarely, catastrophic severe brain injury (sometimes described as second impact syndrome). More recently, the consequences of repetitive mTBI from multiple concussions in a sports setting are becoming evident. Repeated concussions have been associated with greater severity of symptoms, with longer recovery time, and chronically with earlier onset of age-related memory disturbances and dementia. As a result and in contradistinction to the decades-earlier perception that these injuries were benign, sports medicine professionals are now increasingly being instructed to recognize and manage concussions as soon as they occur.

Over a decade ago, the American Association of Neurology developed a grading system to help diagnose and treat concussions. Early symptoms (minutes to hours) include headaches, dizziness, nausea, vomiting, and lack of awareness. Later symptoms (days to weeks) include persistent headaches, sleep disturbance, diminished concentration and attention, memory dysfunction, and irritability. The ability to recognize mTBI and prevent a second, possibly more severe injury, is key in the algorithm; however, the algorithm was based more on expert consensus than on evidence-based medicine and is currently being revised and updated to reflect ever-accumulating data. Many other groups have provided guidelines or recommendations as to the identification and/or management of sports-related concussions, with the Concussion in Sport Group (CiSG) consensus statements being, perhaps, the most widely used. The CiSG statements have been updated twice since 2001 (in 2005 and in 2009) and reflect both the current published literature as well as the consensus of many recognized experts in the field. The CiSG statements focus less on attempting to grade concussion severity and more on controlling the timing of an athlete’s return to play based on the presence or absence of symptoms or demonstrable neuropsychological impairments.

Although clinical studies have focused predominantly on descriptive or observational investigations into qualitative symptoms or semiquantitative analysis of cognitive impairments, important elements of the underlying pathophysiology of mTBI or concussion have been delineated through experimental models. There are several different experimental models of mTBI or concussion, mostly using rodents, such as mice and rats. Some of the most frequently used techniques are closed-skull weight drop, closed-skull controlled impact, and lateral fluid percussion injury (FPI). These experimental paradigms can provide clinically relevant mechanistic insights and are helpful to characterize molecular alterations, ionic and neurotransmitter disturbances, synaptic perturbations, and structural changes. More recent technology such as high-resolution magnetic resonance imaging (MRI) has allowed for real-time imaging of structural and molecular changes without killing the animal. Imaging findings in these animals can be used to delineate pathophysiologic mechanisms that may then be correlated with imaging studies in humans. The translational capability of this technology is evident and has begun to show utility in allowing for a faster bench-to-bedside research approach. Recent human studies of traumatic brain injury (TBI) include using structural and functional MRI to further understand axonal disruption, molecular disturbances, and the time course of these changes. More invasive techniques include microdialysis analysis of the injured brain as well as histopathologic evaluation while operating for TBI. The application of advanced imaging is endless, with exciting research opportunities presenting regularly.

**NEUROMETABOLIC CASCADE OF CONCUSSION**

Immediately after a mechanical trauma to the brain, acceleration and deceleration forces initiate a complex cascade of neurochemical and neurometabolic events.
These events begin with a disruption of the neuronal cell membranes and axonal stretching, causing indiscriminate flux of ions through previously regulated ion channels and probably transient physical membrane defects. This process then causes widespread release of a multitude of neurotransmitters, particularly excitatory amino acids (EAAs), resulting in further ionic flux. The Na\(^+/\)K\(^+\) ATP-dependent pump then works at maximal capacities to reestablish ionic balance, depleting energy stores (Fig. 1). These molecular cascades may result in subsequent cerebral hypofunction or permanent damage. In the setting of a single mTBI or concussion, it is considered that these changes are generally self-limited and transient, although there is evidence that repeat injuries may result in a more lasting pathobiologic condition.

![Neurometabolic cascade after traumatic injury](image)

**Fig. 1.** Neurometabolic cascade after traumatic injury. Cellular events: (1) nonspecific depolarization and initiation of action potentials, (2) release of excitatory neurotransmitters (EAAs), (3) massive efflux of potassium, (4) increased activity of membrane ionic pumps to restore homeostasis, (5) hyperglycolysis to generate more ATP, (6) lactate accumulation, (7) calcium influx and sequestration in mitochondria, leading to impaired oxidative metabolism, (8) decreased energy (ATP) production, (9) calpain activation and initiation of apoptosis. Axonal events: (A) axolemmal disruption and calcium influx, (B) neurofilament compaction via phosphorylation or sidearm cleavage, (C) microtubule disassembly and accumulation of axonally transported organelles, (D) axonal swelling and eventual axotomy. AMPA, D-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Glut, glutamate; NMDA, N-methyl-D-aspartate. (From Giza CC, Hovda DA. The neurometabolic cascade of concussion. J Athl Train 2001;36(3):230.)
GLUTAMATE RELEASE AND IONIC FLUX

After a biomechanical injury to the brain, the neuronal membrane deforms, resulting in an excessive potassium efflux into the extracellular space. The same membrane deformity results in indiscriminate release of EAAs, particularly glutamate, that binds to the kainate, N-methyl-D-aspartate (NMDA), and D-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) ionic channels. NMDA receptor activation in particular causes further depolarization and influx of calcium ions. These ionic perturbations are mediated predominantly through NMDA receptors (NMDARs) because these effects are resistant to tetrodotoxin application but are attenuated by kynurenic acid (an NMDAR antagonist).20 The resulting depolarization results in a widespread relative suppression of neurons, creating a condition resembling spreading depression.23–25 The pathophysiology of spreading depression was originally described by Leao and has been proposed as an underlying mechanism for migraine; however, it may also be implicated in seizures and was more recently implicated with secondary neural injury after more severe TBI.26–29

To restore the ionic balance, ATP-dependent Na⁺/K⁺ pumps are activated, requiring high levels of glucose metabolism, most of which is conducted aerobically under normal conditions. After injury, however, ionic pump activation quickly reduces intracellular energy stores and causes the neurons to work overtime via rapid, but inefficient, glycolysis. This increase in glucose metabolism occurs immediately and may last from 30 minutes to 4 hours after an experimental TBI in rats.22 Concurrently, oxidative metabolism is disrupted, likely from mitochondrial dysfunction.30,31 Lactate production is rampant and this results in its extracellular accumulation.32 Lactate accumulation can contribute to local acidosis, increased membrane permeability, and cerebral edema.33 Lactate may also be used as an energy source by neurons, once mitochondrial function resumes.34–36

GLUCOSE METABOLISM AND MITOCHONDRIAL EFFECTS

After a concussive injury, 2 major alterations of glucose metabolism have been described, hyperglycolysis and oxidative dysfunction. Local cerebral metabolic rates for glucose are increased within the first 30 minutes after a lateral FPI, up to 30% to 46% above control levels.21,22,37–39 After 6 hours, there is a relative glucose hypometabolism (approximately 50%, depending on the brain region) that can last up to 5 days. A similar profile of hyperglycolysis followed by glucose hypometabolism has been reported based on fluorodeoxyglucose F 18–positron emission tomography measurements after a TBI in humans. The duration of late hypometabolism may last months after a moderate to severe TBI.40 Post-TBI hypometabolism is believed to recover more rapidly after milder injuries, although short-duration, longitudinal, within-subject positron emission tomographic studies have not yet been conducted in patients with concussions.

Activation of NMDA channels after concussive brain injury results in a significant influx of Ca²⁺ which then accumulates in mitochondria, causing concomitant glucose oxidative dysfunction.30,31,41,42 Molecular metabolic biomarkers such as ATP/ADP ratio, NADH/NAD⁺ ratio, and N-acetylaspartate (NAA) levels were all decreased after repeat mTBI in rats.7 This decrease was maximal for injuries with an interval of 3 days. Cytochrome oxidase expression, a marker of mitochondrial oxidative function, is downregulated after FPI. This enzyme activity, as determined by histochemistry, is decreased out to 10 days.43

This combination of cellular ionic disturbances, decreased cerebral blood flow (CBF), and glucose metabolic dysfunction has been hypothesized to set the stage
for more severe brain injury after a repeated concussion, described clinically as the second impact syndrome. However, definitive description of this clinical entity has been controversial, and the role of glucose hypometabolism on brain injury has not yet been determined to be protective or exacerbating after a second insult.

Alternative energy sources may be used by neuronal cells in the uninjured brain, as well as after injury. However, recent studies in rats noted a decrease in creatine (Cr), creatine phosphate (CrP), NAA, and phosphatidylcholine levels and in ATP/ADP ratio after a mTBI. The decreased NAA/Cr ratios were confirmed on magnetic resonance spectroscopy (MRS) in concussed athletes. A more recent study further suggests that the Cr/CrP system is not a useful source of ATP for the injured brain.

Ketone bodies have been known to be an alternative fuel source for the body during times of stress or starvation. Emerging data suggest that although glucose metabolism is perturbed after a concussive TBI, glucose may not be the best fuel for the injured brain. Rats that were in ketosis or had a ketogenic diet demonstrated decreased glucose metabolism in an age-dependent fashion. Subsequent studies suggest that cerebral contusion volume and behavioral outcomes improve with a ketogenic diet. Ketosis induced by fasting may be most applicable in the first 24 hours after a moderate, but not severe, TBI. The neuroprotective implications of ketosis after mTBI have yet to be investigated systematically.

**CBF**

The effects of severe TBI on CBF are well characterized, although there is ongoing debate about the degree of post-TBI ischemia. Based on inpatient studies of cerebral arteriovenous delivery of oxygen, cerebral metabolic oxygen consumption, and vasospasm (measured by transcranial Doppler ultrasonography), there seems to be a triphasic response to severe TBI. On postinjury day 0, there is cerebral hypoperfusion with an average CBF of 32.3 mL/100 g/min. During postinjury days 1 to 3, there is cerebral hyperemia with an average CBF of 46.8 mL/100 g/min and elevated middle cerebral artery velocities (86 cm/s). Subsequently, during postinjury days 4 to 15, there is a period of cerebral vasospasm with decreased CBF of 35.7 mL/100 g/min and elevated middle cerebral artery velocities (96.7 cm/s). This triphasic response may occur in mTBI to a lesser extent; however, this has not yet been well studied.

Animal studies confirm the presence of cerebral edema in some models or severities of TBI. Perilesional edema in the ipsilateral hippocampus is viewed via MRI for 4 days after severe experimental TBI (cortical impact). The edema gradually recovered over the next 2 weeks and its recovery correlated with the neuroscore (a behavioral scale of neurologic function). Restricted diffusion and reduced CBF were reported in the first few hours after a milder experimental injury (FPI), but no major imaging abnormalities were observed after a weight-drop injury that induced cognitive symptoms without overt histopathologic findings.

**AXONAL INJURY**

Diffuse axonal injury, also termed traumatic axonal injury, is a well-described phenomenon that occurs after severe blunt head injury. The mechanical stretching of the axonal cell membranes has a multitude of effects including ionic flux and diffuse depolarization, calcium influx and mitochondrial swelling, and neurofilament compaction. Neurofilament compaction can occur in the acute phase (5 minutes–6 hours) by either phosphorylation or calpain-mediated proteolysis of sidearms. From 6 to 24 hours postinjury, the calcium influx can also destabilize the microtubules. These
pathophysiologic processes have been shown to interfere with axonal transport, resulting in axonal blebbing and eventual disconnection.\textsuperscript{65–67}

Although traumatic axonal injury has been best described after severe TBI, there is some evidence that it also occurs, perhaps reversibly, after mTBI. Molecular studies in mice evaluating cell body, myelin integrity, and axonal damage (via amyloid precursor protein) after mTBI suggest predominant damage at the axonal level, with minimal effect to the neuronal cell bodies or myelin sheaths.\textsuperscript{68} This axonal damage was found to progress through various cortical and subcortical structures over 4 to 6 weeks, and this effect correlated with impaired navigation in the Morris water maze (MWM) test, a sign of spatial learning and memory deficits.

Advances in neuroimaging studies, using high-resolution (3-tesla) MRI and diffusion tensor imaging (DTI) sequences, have confirmed axonal damage in mTBI in humans. Axonal damage has been demonstrated in pediatric, adolescent, and adult patients after mTBI/concussion and, in some cases, was correlated with subtle findings of cognitive deficits.\textsuperscript{69–71} Fractional anisotropy (FA), a measure of linear water diffusion, decreases when directionality of white matter tracts is disturbed, as might occur after axonal disconnection or damage to myelin sheaths.\textsuperscript{72,73} Increase in FA values occurs with ongoing developmental myelination, but after injury, the increase has been hypothesized to be related to transient axonal swelling.\textsuperscript{70}

FA value is decreased in white matter subcortical regions (inferior frontal, superior frontal, and supracallosal) but unchanged in the corpus callosum in pediatric TBI patients.\textsuperscript{74} Motor speed, executive function, and behavioral ratings showed a correlation with these findings.

Decreases in FA values are also seen chronically after mTBI in adults, affecting regions such as the genu of the corpus callosum, the cingulum, the anterior corona radiata, and the uncinate fasciculus (\textbf{Fig. 2}). In this study, there was a direct correlation between decreased FA values in specific white matter structures and specific cognitive deficits.\textsuperscript{75}

Corpus callosal findings of increased FA values were seen in the adolescent brain early (6 days) after mTBI. These findings correlated with postconcussive symptoms confirmed by cognitive, affective, and somatic scores on the Rivermead Post-Concussion Symptoms Questionnaire and the Brief Symptom Inventory.\textsuperscript{70} The increased FA was hypothesized to be indicative of axonal swelling in the early post-concussive phase, and is in distinction to other more chronic studies showing reduced FA.

These studies suggest that DTI of axonal injury is a sensitive and effective measure of the effects from mTBI. Future research in this field is necessary to further understand the relationship between altered FA, cognition, and axonal pathophysiology.

\textbf{ALTERED BRAIN ACTIVATION}

Calcium regulation after TBI depends on various factors including membrane permeability, excitatory neurotransmitter release, and glutamate receptor modulation. The NMDAR is especially interesting because it requires 2 signals to be activated: membrane voltage change and glutamate binding. The voltage change releases a $\text{Mg}^{++}$ ion within its working channel and glutamate binding then allows calcium flux into the neuron. The channel is a tetramer consisting of 2 NR1 subunits and 2 NR2 subunits. During development, there is a shift from NR2B (slower channels) predominant expression to NR2A (faster channels) predominant expression in the rat brain.\textsuperscript{76}

After lateral FPI in pediatric (postnatal day 19) rats, the relative expression of the NR2A subunit is downregulated by postinjury days 2 to 4.\textsuperscript{10} This downregulation
returns to normal by postinjury day 7. There is no apparent change in NR2B or NR1 subunit expression, suggesting a possible intrinsic neuroprotective mechanism of calcium ion regulation after TBI.

The NMDA channels have a strong association with learning, specifically long-term potentiation (LTP) and long-term depression.77,78 Not surprisingly, after an experimental TBI, LTP induction is impaired at postinjury day 2 but seems to recover by postinjury days 7 through 15.79,80 However, maintenance of LTP deficient up to 8 weeks postinjury.81 Clinically, after concussion patients can demonstrate cognitive deficits associated with abnormal activation of neural circuits. Blood oxygen level–dependent sequences obtained in functional MRI before and after cognitive tasks demonstrate a hyperactivation in the postconcussive brain at week 1 (Fig. 3).82 When abnormal activation is seen after a concussive brain injury, the affected athletes seem to have a more prolonged clinical recovery.83,84

**ACUTE RESPONSES TO REPEAT CONCUSSION**

Aside from the acute effects of concussion and the subjective and objective symptoms that limit the patient, a major concern for return to activity is the second impact syndrome.44,85,86 This syndrome is a catastrophic cerebral edema after an apparent mTBI/concussion. It results in coma and severe neurologic deficits and is often fatal.

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**Fig. 2.** Region of interest (ROI) placement for DTI. Shown are the corresponding ROIs for the right hemisphere. The solid ellipse within yellow outline indicates the location and size of the ROI. (A) uncinate fasciculus, (B) inferior longitudinal fasciculus, (C) genu of corpus callosum, (D) anterior corona radiata, (E) cingulum bundle, and (F) superior longitudinal fasciculus. (From Niogi, Mukherjee P, Ghajar J, et al. Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury. Brain 2008;131:3212.)
Although the clinical consequences of individual concussions have been described in some detail, the predictive factors and the interval for return to activity are still heavily debated. Although avoiding possible second impact syndrome is the more dramatic rationale put forth for delaying return to play, the stronger argument may simply be that cerebral physiologic conditions are disturbed after concussion and this physiologic disturbance renders the brain less functional and more vulnerable. In other words, concussion-induced pathophysiologic conditions, as manifested by metabolic perturbations, altered blood flow, axonal injury, and abnormal neural activation, reduce cerebral performance and make the brain more susceptible to cellular injury. Several animal studies focusing on mTBI-induced dysfunction have been described, and current data support the concept of transient metabolic and physiologic vulnerabilities that may be exacerbated by repeated mild injuries within specific time windows of impairment.7,8,87

Fig. 3. Representative individual z score differences between baseline and either a postconcussion session (concussed, left) or postseason baseline sessions (control, right). Colored areas show regions of activity that significantly increased from the baseline value of the bimanual sequencing task. Although both concussed and control subjects demonstrate some increases in region of activity, those of the concussed players are considerably larger. Activity is significantly increased in the medial frontal gyrus (medFG), middle frontal gyrus (MFG), inferior parietal lobe (IPL), and bilateral cerebellum. (From Jantzen Anderson B, Steinberg FL, et al. A prospective functional MR imaging study of mild traumatic brain injury in college football players. AJNR Am J Neuroradiol 2004;25(5):741.)
As described in the previous sections, the concussed brain acutely experiences significant alterations in ionic balance, neurotransmitter activation, axonal integrity, and energy metabolism. Logically, a patient with such a metabolically stressed state is ready neither for optimal performance nor to sustain a second injury. Vagnozzi and colleagues demonstrated in a rat weight drop experiment that levels of NAA and ATP and the ATP/ADP ratio decreased significantly when measured 2 days after repeat concussion. Maximal metabolic abnormalities were seen when the occurrence of 2 mild injuries were separated by a 3-day interval; in fact, the metabolic abnormalities in these animals were similar to those occurring after a single severe experimental TBI. In a follow-up study, similar perturbations were found to persist as late as 7 days after double impact, indicating prolonged metabolic effects from repeat mTBI in this model.

The metabolites analyzed are a reflection of the energy status of the brain, particularly the reductive capacity of the mitochondria. Other markers of impaired reductive capacity include the lactate/pyruvate ratio. This ratio is commonly measured and is found to be increased in patients with severe TBI. Therefore, a significant contributor to acute TBI and its susceptibility for repeat injury is likely mitochondrial dysfunction.

Clinically, markers for this altered metabolism are observed using MRS in athletes with concussions. Thirteen athletes who sustained concussions were studied with 3-tesla MRS at specific postinjury time points. The NAA/Cr ratio of injured patients versus age-matched control patients was diminished by 18.5% (1.8 vs 2.2, P < .05) at 3 days postinjury. This ratio improved but was still low at 15 days (1.88) and was back to control values by 30 days postinjury. Interestingly, 3 patients sustained a repeat concussion 3 to 15 days after their initial injury. These patients had a similar initial decrease in their NAA/CA ratio (1.78) but had further decrease at 15 days (1.72) rather than a partial resolution. These ratios took 45 days to resume to control levels. The patients who sustained a single concussion reported no symptoms during the 3-day study, whereas the patients who sustained double concussions stated the same at the 30-day time point. However, no standardized symptom assessments or questionnaires were administered and no symptom assessment was conducted at intermediate time points. These findings have recently been reported in a larger cohort of concussed athletes in a multicenter study.

Axonal damage occurs concurrently after experimental mTBI. Interestingly, this effect is amplified with repeat mTBI. A repeat-concussion animal model with a 3-day interval between injuries demonstrated a significant increase in cytoskeletal damage and axonal injury. As mentioned earlier, white matter abnormalities have been described using DTI after mTBI in humans; although these findings are not universal, there are no specific human studies of DTI conducted early after repeated concussive injuries.

Behavioral deficits are a chronic difficulty in a subset of patients postconcussion. Acutely, animal studies have shown that repeat mTBI induces spatial memory deficits in tests such as the MWM and these impairments are related to the impact severity and the number and timing of repeated injuries. In the National Collegiate Athletic Association concussion study, athletes who sustained repeat concussions (3 or more) were at a higher risk of an additional concussion. More importantly, a larger proportion of multiple-concussed athletes these had a significantly longer duration of postconcussive symptoms than those with only 1 concussion (30% vs 14.6%).

**POTENTIAL FOR CUMULATIVE INJURY AND CHRONIC SEQUELAE**

Chronically, multiple concussions have been associated with cumulative effects on cerebral function and cognition, including early onset of memory disturbances and
even dementia. Molecular markers associated with this decline in function include amyloid and tau protein deposition, presence of apolipoprotein E-4 allele (ApoE-4), and overall structural damage, particularly axonal injury.

In transgenic mice overexpressing human amyloid precursor protein, repetitive mTBI resulted in significant deposition of amyloid-β peptide (Aβ) and isoprostanes. There was an associated increased latency in the MWM test for these transgenic injured animals. Others have shown increased hippocampal cell death after injury, with concomitant Aβ deposition.

More recently, tau protein deposition has been described in chronic traumatic encephalopathy, demonstrated on brain histopathology in autopsies from boxers, football players, and other contact sport athletes. Immunohistochemistry demonstrates neurofibrillary tangles and neuritic threads consistent with a generalized tauopathy. Multiple animal studies also show TBI-induced abnormalities in tau and other cytoskeletal proteins.

Apolipoprotein E subtypes have been associated with different risks of posttraumatic cognitive disturbances and dementia. Specifically, the ApoE-4 allele is linked with the development of clinical signs and symptoms of chronic traumatic encephalopathy. In boxers who sustain chronic TBI, there is a correlation with increased cognitive deficits, the number of boxing matches, and the ApoE-4 allele. Particularly, all patients with severe impairment as measured by the chronic brain injury scale have at least one ApoE-4 allele. Animal models of Alzheimer disease used in TBI experiments reflect this link, with ApoE-4 transgenic mice developing more diffuse plaques than controls. This finding has yet to be proven in repeat TBI animal models.

Similarly, chronic TBI has a lasting effect on axonal integrity. Professional boxers demonstrate evidence of increased axonal injury via DTI. FA and whole brain diffusion coefficients are significantly altered in boxers compared with nonboxers. This finding has not yet been confirmed in chronic TBI animal models.

In long-term studies of professional football players, there is an increased incidence of cognitive deficits and early Alzheimer disease development. In addition, there are behavioral findings including early depression. This finding was significantly associated in players who had sustained 3 or more cumulative concussions.

**SUMMARY**

Concussion, or mTBI, has both acute and chronic consequences on the brain. After concussion, there is a cascade of molecular changes in the brain that affect performance acutely and increase vulnerability for repeat injury. Repeat brain injury causes a multitude of cerebral deficits that are studied clinically, histopathologically, and by neuroimaging. These effects can be long-lasting and potentially debilitating. Prevention of single and repeat concussions should be the goal of athletes and their physicians, whether amateur or professional. Following a concussion, adequate time for physiological recovery should be allowed to minimize the risk of recurrent injury or development of cumulative impairments.

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