The Molecular Pathophysiology of Concussive Brain Injury – an Update

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KEYWORDS

• Concussion • Traumatic brain injury • Pathophysiology • Molecular mechanisms

KEY POINTS

- Cerebral metabolism is altered immediately after concussion and may increase vulnerability for an interval after injury.
- Advanced neuroimaging, such as functional MRI, MR spectroscopy and diffusion tensor imaging can demonstrate alterations associated with concussive brain injury.
- Cumulative concussive brain injury has been associated with increased neurocognitive symtpoms.
- Pituitary dysfunction has been reported after chronic repetitive concussions and can affect quality of life.

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INTRODUCTION

Concussion (mild traumatic brain injury [TBI]), particularly with organized sports, has come to the forefront of popular culture. Affecting about 1.6 million to 3.8 million athletes a year, its short-term and chronic effects have been increasingly recognized as notable sports-related injuries.[1–3] Thanks to widely disseminated checklist-based assessment tools and greater symptom awareness in the sports community, it is being diagnosed more frequently in amateur and professional venues alike. Public media have also embraced this condition, chiding collegiate coaches who ignore concussion and producing feature films depicting its chronic effects.

Nearly 20 years ago, the American Association of Neurology (AAN) introduced their grading system for the diagnosis and treatment of concussions.[4] These guidelines were focused on helping clinicians counsel patients to manage their symptoms and return to play. It has since become apparent that it is difficult to predict recovery based on initial concussion severity. The AAN released updated guidelines in 2013, based on a systematic, evidence-based review of the available literature.[5] These guidelines underscored the importance of early recognition of mild TBI to address symptoms and potentially prevent more severe injury. Early assessment tools, such as the Sports Concussion Assessment Tool, are endorsed for sideline nonphysicians with a high positive predictive value for concussion identification.[6] However, much like in consensus statements by the Concussion in Sport Group (introduced in 2001 and thrice updated),[5,7] these guidelines eliminated a severity grading system and, instead focused on factors affecting the timing of an athlete's return to play. This approach is primarily based on the presence and severity of general/neurologic symptoms or demonstrable neuropsychological impairments, as well as an individualized assessment of risk factors for prolonged recovery, such as history of prior concussions; younger age; symptoms of migraine headache, fogginess, and dizziness; learning disability or attention deficit; on-field mental status change; and possibly psychiatric comorbidities such as depression and anxiety.

Experimental animal models have been central to understanding the pathophysiology of concussive brain injury. Typically performed with rodents, techniques include closed-skull weight drop,[8,9] closed-skull controlled impact,[10,11] and lateral fluid percussion injury (FPI).[12,13] Through these models, researchers can glean clinically relevant mechanistic insight and are able to better characterize molecular alterations, ionic and neurotransmitter disturbances, synaptic perturbations, and microstructural changes. More recently, high-resolution MRI, diffusion tensor imaging (DTI)/tractography, functional MRI, and magnetic resonance (MR) spectroscopy have allowed real-time imaging of structural and molecular changes without sacrificing the animal. An added benefit is the cross-availability of these imaging modalities for human data acquisition. Such translational capacity has shown utility for bench-to-bedside research.[9,10,14–16] In particular, DTI and functional MRI have been shown to be reliable research markers of mild TBI-induced injury; identifying neuronal damage or dysfunction in the setting of otherwise normal macrostructural imaging (ie, computed tomography scanning; T1/T2 MRI).[17] Other, more invasive techniques include microdialysis of the injured brain and its histopathologic evaluation.[18,19]

This article updates our previously published article with additional focus on metabolic vulnerability to repeat injury, advanced MRI modalities assessing postconcussive outcomes, chronic changes following repetitive concussive injury, and pituitary dysfunction following prolonged exposure to mild TBI.[20]