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Pathophysiology of Sports-Related Concussion: An Update on Basic Science and Translational Research

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Context: Concussions that occur during participation in athletic events affect millions of individuals each year. Although our understanding of the pathophysiology of concussion has grown considerably in recent years, much remains to be elucidated. This article reviews basic science and relevant translational clinical research regarding several aspects of concussion.

Evidence Acquisition: A literature search was conducted using PubMed from 1966 to 2010, with an emphasis on work published within the past 10 years. Additional articles were identified from the bibliography of recent reviews.

Results: Basic science and clinical data both indicate that there is a period of increased vulnerability to repeated injury following a concussion and that its duration is variable. Growing evidence indicates that postinjury activity is likely to affect recovery from brain injury. Data suggest that long-term sequelae may result from prior concussion—particularly, repeated injuries. The unique aspects of cerebral development may account for differences in the effects of concussion in children and adolescents when compared with adults.

Conclusions: The available pathophysiologic data from basic science and clinical studies have increased the evidence base for concussion management strategies—the approaches to which may differ between young athletes and adults.

Keywords: concussion; sports; pathology

Traumatic brain injury (TBI) related to sports affects an estimated 1.6 to 3.8 million people annually in the United States.[47] The majority of these injuries are mild TBI, more commonly referred to as *concussion*. It has been proposed that concussions be classified as a subset of mild TBI because most of these injuries appear to resolve without permanent consequences.[60] Given the difficulty in classifying these injuries and because much of the literature does not make this differentiation, the terms are used interchangeably in this article. Additionally, there is no universal definition of a concussion; however, for the purposes of this article, a concussion is defined as a biomechanically induced transient disturbance of neurologic function that may or may not be associated with loss of consciousness.[1,60]

Sports-related concussions occur with the greatest frequency in the pediatric and young adult age ranges, although they can occur at any age. This includes the common acute signs and symptoms of headache, disorientation, confusion, amnesia, dizziness, and incoordination. These clinical signs and cognitive impairments typically resolve over a short period. However, there is growing evidence that concussions can have more lasting sequelae,[12,15,31] which may manifest owing to timing or number of repeated concussions,[12,31,54] genetic risk factors,[41,55] or other clinical variables. The cumulative effects of multiple concussions over an extended period have been associated with early onset of cognitive decline and dementia.[31,62] The pressing issues facing clinicians depend on identifying and managing the symptoms, determining the appropriate timing of return to play, evaluating the potential for permanent sequelae, and identifying risk factors for worse outcomes. This article reviews current evidence regarding the acute metabolic cascade, postinjury neuronal activation, chronic cumulative effects, and specific considerations in young athletes.

ACUTE METABOLIC CASCADE

Animal Studies

The physiologic basis for concussion and postconcussive symptoms has its origins in experimental animal work following diffuse brain injury.[26,85] After an experimental

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concussive brain injury, there is indiscriminate release of the excitatory neurotransmitter glutamate, in conjunction with massive depolarization of neurons.[42,43] This depolarization can be measured in vivo using cerebral microdialysis, which detects dramatic increases in extracellular glutamate and potassium concentrations after concussive injury. To restore ionic homeostasis, membrane ionic pumps work overtime, requiring ATP (adenosine triphosphate) as an energy source and causing a tremendous increase in cerebral glucose metabolism.[92] During this hyperacute phase, cerebral blood flow may not meet metabolic demand; this uncoupling can predispose brain cells to long-term damage.[44,76] Following the period of hyperacute increase in glucose metabolism, there is a much longer period of glucose metabolic depression, which can last 7 to 10 days in adult rats and which has been correlated with cognitive deficits.[36]

In addition to sodium and potassium ionic shifts, glutamate activation of NMDA (N-methyl-D-aspartate) receptors results in excessive intracellular calcium accumulation.[20,67,68] This calcium flux can have additional effects on cell viability by compromising mitochondrial respiration, reducing energy production, and activating intracellular proteases, thereby initiating the process of programmed cell death (apoptosis).[74,82]

A recent study of metabolic responses after a concussive weight drop injury in rats showed significant changes in markers of mitochondrial metabolism, including ATP, NAA (N-acetylaspartate), NAD (nicotinamide adenine dinucleotide), and others.[89] When concussive injuries were separated by 5 days, the responses of these metabolic markers were equivalent. However, when the injuries were separated by only 3 days, there was an amplification of mitochondrial dysfunction. Biochemical markers of oxidative and nitrosative stresses also showed this pattern of maximal compounded dysfunction when concussive injuries were separated by 3 days.[83]

Human Studies

The basic pathophysiologic responses described above have been reported following human TBI. Elevations of glutamate and potassium have been measured with cerebral microdialysis in head-injured patients in the intensive care unit.[9,90] Positron emission tomography (PET) scanning is used to measure cerebral glucose metabolism in vivo after human TBI, and it has shown a similar pattern of early hyperglycolysis followed by glucose metabolic depression.[5,6] Although the initial studies of post-TBI glucose metabolism were in patients with severe TBI, patients with milder TBI have been imaged.[5] Profound glucose metabolic depression was seen after mild TBI, to the same degree as severe TBI.[4] Metabolic recovery generally takes weeks to months after moderate to severe TBI.[5] Similar longitudinal clinical studies using PET after mild TBI have yet to be done.

Studies of repeat human mild TBI using magnetic resonance spectroscopy provide interesting parallels to the animal studies of metabolic markers. Diminished spectroscopic signals for NAA were detected in concussed athletes, which took 30 days to return to baseline.[87] These abnormalities showed a longer time to recover (45 days) in the subset of athletes who sustained a second concussion before full metabolic recovery.[88] These results have been expanded to include 40 athletes examined longitudinally at 3 centers using different scanners.[87]

POSTINJURY ACTIVATION

Following injury, neurons and neural networks may be unable to undergo normal function.[25,28,59,56] In such cases, external activation may serve as a stimulus for recovery, however premature activation of a damaged cell or system may actually serve as a metabolic stressor and cause further damage.[29,39]

Animal Studies: Effects of Exercise on Recovery and Risk of Reinjury

Two paradigms related to postinjury neural activation following concussive injury in the rat are reviewed here, and they provide insight to mechanisms of recovery after TBI. The first paradigm is that of forced overuse.[37,38,46] Following an experimental lesion to motor cortex, rats show impaired use of the contralateral forelimb. When the ipsilateral (good) forelimbs were casted postinjury, the rats preferentially overused the contralateral forelimbs. Forced overuse within the first week of experimental injury actually worsened the animal's recovery, causing greater cell death in the brain and hampering neurologic recovery.[37,38,46] When the period of forced overuse was delayed by 1 week, neurologic recovery was more complete, although, interestingly, the amount of cell death was not affected. It is worth noting that this window of abnormal neural activation roughly corresponds to the duration of cerebral metabolic depression.[92]

An alternative paradigm is that of voluntary exercise.[28,29] Within 24 hours of a concussive brain injury, rats will run on a wheel voluntarily. Uninjured animals show increases in brain growth factors after voluntary exercise.[28] BDNF (brain-derived neurotrophic factor) expression correlates with the amount of running and with improvements in cognitive function.[28] If the animal runs within 1 week of a mild injury, however, BDNF levels do not increase and cognitive performance actually suffers.[29] As injury severity increases, the window of abnormal response to exercise lengthens (up to 3 weeks after severe lateral fluid percussion injury).[28]

Animal studies like these suggest that properly timed exercise-induced activation can beneficially affect recovery after concussive brain injuries. However, premature activation, either through forced or voluntary exercise, is deleterious to the injured brain, leading to molecular, anatomical, and behavioral deficits.[28] The period of vulnerability to premature activation appears to follow the known abnormal metabolic state after experimental TBI in the rat, which is approximately 7 to 10 days.[92]

Animal studies suggest that the effects of repeated injury are greatest within the first week following injury. Longhi et al[49] found that mice subjected to repetitive concussive brain injury developed impairment of cognitive function when a

second TBI was imposed within 3 to 5 days after the first but not when the second injury was applied at 7 days. This is consistent with work described above showing maximal metabolic impairment (reduced NAA, ATP) when repeated mild TBI was separated by 3 days.

Human Data: Effects of Exercise on Recovery/Risk of Reinjury

Studies of collegiate football have shown that approximately 90% of concussed players experience symptom resolution within 7 days, with a mean duration of 3 to 5 days.[33,58] Prolonged symptom recovery (> 7 days) occurs in 10% to 14% of sports-related concussion[33,58] and is associated with prior concussion.[33] Thirty percent of NCAA (National Collegiate Athletic Association) football players with a history of 3 or more concussions were symptomatic for more than a week, compared with 15% of those with no more than 1 prior concussion.[33]

As suggested by the animal data above, excessive postinjury activity may adversely affect recovery from concussion. A recent clinical study of postconcussion activities found that both the highest and the lowest activity levels were associated with the worst scores on neurocognitive testing; those with "moderate" activity fared the best.[52] In addition, the NCAA concussion study showed an apparent association between returning to play the same day and having a delayed onset of symptoms.[33] These human data indicate that premature activity may exacerbate postconcussive symptoms.

The risk of a concussion appears to increase when the brain has suffered a prior concussive injury.[33] Collegiate football players with a history of concussion were 3.4 times more likely to suffer a concussion that season. Furthermore, 6.5% of football players had a repeat injury in the same season.[33] The risk for repeat injury appears to be greatest within 10 days following the initial concussion. Seventy-five percent (9 of 12) had a recurrent injury within 7 days of the first injury, and 11 of 12 recurred within 10 days. High school athletes with 3 or more concussions are 5 to 8 times more likely to lose consciousness and suffer anterograde amnesia and confusion.[12] Interestingly, this was not observed among the collegiate cohort.[33]

Second impact syndrome (SIS) has been defined as a second brain injury that occurs before the symptoms of a prior injury have resolved, resulting in catastrophic cerebral edema and neurologic collapse.[10] A series of case reports of suspected SIS described fatal outcomes in athletes who suffered head trauma while reportedly still symptomatic from a recent head injury.[61] However, of 17 published cases of suspected SIS, none fulfilled the 4 proposed diagnostic criteria.[61] Alternatively, delayed onset cerebral edema (frequently not associated with structural brain injury) resulting in death has been described in children with minor head trauma without prior head injury.[7,81] Thus, it is plausible that the cases reported to be a result of SIS may have actually been due to a single injury that caused diffuse cerebral swelling. In either case, malignant cerebral edema following seemingly mild TBI appears to occur predominantly in children and adolescents.[7,61,81]

CHRONIC CUMULATIVE EFFECTS

Long-term neurocognitive problems have occurred in professional boxers.[41] Seemingly benign concussions in football, soccer, ice hockey, and other sports may also cause long-term impairments.[11,15,54] Caution should be used when interpreting these findings, given that these studies included relatively small numbers and lacked baseline data on the brain function of the participants.

Animal Studies: Repeat Concussion Models and Molecular Markers of Dementia

A number of animal studies has described experimental models of repeat concussion,[§] but none has focused on long-term anatomical and cognitive sequelae. However, cognitive deficits and microstructural damage may become detectable with recurrent injury in these models.[16,49,71]

Molecular markers associated with dementing processes have been studied after experimental TBI.[21,34,70] Alzheimer disease is characterized by accumulation of tau and amyloid β (Aβ) protein. Whereas rodents do not readily develop Aβ plaques, transgenic models (PDAPP mice) can accumulate Aβ plaques. When these animals were engineered to express variants of APOE alleles and subjected to controlled cortical impact, Aβ accumulation was greatest in those with the APOE4 allele.[34] In wild-type rats, controlled cortical impact induced expression of cleaved tau protein, which was detectable as a biomarker in serum.[21] As determined via the fluid percussion technique of experimental TBI, injured rats showed widespread increases in amyloid precursor protein.[70]

Human Data: Chronic Neuropsychological and Motor Deficits

Chronic impaired cognitive performance has been reported in football and soccer players with a history of concussion. Matser[54] found that performance in memory and planning functions was inversely related to the number of prior concussions in soccer players. Among NCAA football players, a history of 2 or more concussions was associated with lower cognitive performance on neuropsychological tests.[11]

De Beaumont et al[14] found a prolongation of the cortical silent period (CSP) in asymptomatic players with a history of concussion. The CSP is an electrophysiologic measurement that reflects the integrity of the inhibitory (GABA receptor) system in the motor cortex.[91] These findings were not affected by the time since the last concussion, thus suggesting that these abnormalities may persist. Further lengthening of the CSP was observed among those who suffered another concussion during the study period. Severity of concussion is associated with prolongation of the CSP.

[§]References 16, 17, 35, 48, 49, 71, 89.

Former ice hockey and football players with a history of concussion more than 30 years prior have evidence of cognitive and motor differences, although the changes detected did not result in overt functional impairment.[15] A more recent study, which combined traditional and computerized neuropsychological testing, did not find an association between concussion and cognitive performance among collegiate athletes.[8]

Human Data: Risk of Dementia/ Traumatic Encephalopathy

Classic studies in retired boxers have described motor, cognitive, and behavioral impairments[13,53,63,77] Clinically, such cases have been termed *chronic TBI*, *dementia pugilistica*, and *chronic traumatic encephalopathy*.[62,66,73] Computed tomography and magnetic resonance imaging may demonstrate a cavum septum pellucidum, a cerebrospinal fluid–filled space between the 2 lateral ventricles, which may be a nonspecific finding.[69] Single-photon emission computed tomography (SPECT) scanning may reveal perfusion defects in the frontal and temporal lobes, regions associated with higher cognitive functions, such as attention, impulse control, and memory.[27] APOE4, a risk factor for Alzheimer disease, is associated with severe chronic TBI in boxers, suggesting genetic links to long-term impairment.[41]

Retired professional football players with a history of 3 or more concussions are 5 times more likely to demonstrate mild cognitive impairment, earlier onset of Alzheimer disease, and clinical depression.[31,32] Autopsies of former professional football players have demonstrated evidence of chronic TBI with tau deposition in neurofibrillary tangles and neuropil threads.[62,66]

PEDIATRIC ISSUES

Animal Studies: Altered Neuroplasticity and Incomplete Myelination

Experimental concussive injury in young rats does not result in appreciable neuronal death, thus providing a good model for pediatric concussion.[30,72] The immature rat recovers more rapidly than the mature rat in many physiologic parameters, such as glucose metabolism and calcium flux.[68,84] However, other elements, such as neural plasticity and axonal function, may be vulnerable to injury during brain development.

The developing brain is suited to alter its structure and function based on the environment that it encounters, a phenomenon referred to as *experience-dependent plasticity*.[78] This can be studied by rearing animals in an enriched environment (EE), a large cage filled with many toys that are changed daily, multiple cagemates, and access to exercise wheels, ladders, and tunnels. Rats reared in EE develop more elaborate neuronal connections, increased cerebral cortex thickness, higher levels of plasticity-related molecules (BDNF and NMDA receptors), and superior cognition.[78]

After concussive brain injury, immature rats do not respond to rearing in an EE.[19,25,40] Rats do not show increases in cortical thickness; they show less complex dendritic arborization; and they lose the cognitive advantage of the EE rearing.[19,25,40] There may be a period after concussive injury where the immature brain is less responsive to environmental stimuli.[25]

It is well known that white matter fiber tracts continue to myelinate throughout adolescence and into young adulthood, particularly in the frontal lobes.[22,23] Unmyelinated white matter fibers appear more vulnerable to experimental concussion than those that are fully myelinated.[75] The frontal lobes are also the neuropsychological substrate for complex cognitive tasks, such as those of working memory, attention, and executive functions—cognitive tasks that show impairment after concussive brain injury.[11,54] There may be age-dependent vulnerabilities to mild TBI, particularly with regard to higher cognitive functions.

Human Data: Age-at-Injury Responses

Clinical studies of age at injury following concussion are generally limited to those including athletes from high school to college.[18,24,51,80] High school athletes have shown memory dysfunction 7 days postconcussion, whereas college athletes generally recovered by 3 days.[18] Self-reported symptoms did not correlate well with objective demonstration of cognitive deficits. In the high school athletes, subjective symptoms often resolved while neuropsychological deficits persisted.[18] These results and others suggest that a longer period of altered cerebral function following concussion may persist in the maturing brain.[18,51,57,80] Differences in neuropsychological test parameters and more rapid change in baseline cognitive skills raise another clinically important developmental distinction in younger children.[24,59]

Finally, with regard to postconcussive subjective symptoms and outcome, substantial literature suggests that a single mild TBI has no lasting cognitive sequelae in most children.[2,3,65,79] Children and adolescents may be susceptible to family and parental influences independent of the injury.[45,86] In a case-control cohort study of 301 children between the ages of 4 and 15 years with various injuries, parents of children with concussion were 2.7 times more likely to express concern that symptoms such as headache, learning difficulties, and sleep disturbances were attributable to the injury.[64] Children may be influenced by parental concerns.

CONCLUSIONS

Concussion is a complex injury that results in a series of metabolic events within the brain, and it includes distinct phases of injury and recovery. These phases of concussive injury have been observed in the clinical setting using advanced neuroimaging. Studies of animals and humans show that following concussive brain injury, a vulnerable period to repeat injury exists. Furthermore, recent clinical data have raised concern about the long-term effects of prior concussion on cognitive and motor function. The role of genetic markers is not clear in the acute response to concussion and the development of chronic cognitive impairment. Finally, the unique aspects of cerebral development in children and

adolescents suggest that the pathophysiologic effects of concussion may be different than in adults.

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