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New Treatments for Concussion: The Next Millennium Beckons

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Abstract: As increased understanding of the pathophysiology of mild traumatic brain injury and concussion develops, so the scientific rationale for interventional pharmacological therapy becomes paramount. A number of agents have been postulated or have been the subject of anecdotal noncontrolled trials. This paper reviews the published evidence in this regard. To date no effective pharmacological therapy exists that satisfies Class 1 evidence-based medicine criteria.

Key Words: Concussion—Traumatic brain injury—Drug therapy—Pharmacology.

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INTRODUCTION

Until recently, the medical treatment of concussion in sport has been one of close observation and "masterly inactivity." We currently have the ability to individualize patient management through the use of neuropsychologic testing, and potentially determine when it is safe for the athlete to return to play. We have not, however, had the ability to therapeutically intervene to shorten the recovery period. Such a development would be a boon to professional sport, where pressure is exerted on medical staff to ensure both optimal management and rapid return-to-play strategies.

At the present time, the clinician has no evidence-based pharmacological treatment to offer the concussed athlete. The ability to treat concussion with specific drug therapy requires an understanding of the pathophysiological changes that accompany concussive injuries. In the past, anecdotal treatment strategies have arisen through the misguided assumption that concussion was similar to severe brain injury in that there was a structural injury that was "treatable" in the same fashion.

PATHOPHYSIOLOGY OF SPORT-RELATED CONCUSSION

Traumatic brain injury has long been thought to evoke immediate and irreversible damage to the brain. While this may be true in moderate-to-severe traumatic brain injury, the evidence that this occurs in milder injuries such as concussion is not compelling. Recent experimental evidence suggests that the pathogenesis of axonal dysfunction resulting from head trauma is complex.[1] Alteration in axolemmal membrane permeability induced by impact ("traumatic depolarization") may cause alterations in ionic flux and exert either direct or indirect effects upon the axonal cytoskeleton.[1]

In addition, studies have revealed that a cascade of neurochemical, ionic, and metabolic changes occur following experimental brain injury.[2] Most notably, an injury-induced ionic flux across the cell membrane due to the release of the excitatory amino acids has been shown to increase glycolysis leading to an excessive build-up of lactic acid.[2,3] Also, the same brain regions experiencing this glycolytic increase have been shown to go into a state of metabolic depression due to a decrease in both glucose and oxidative metabolism accompanied by a decrease in cerebral blood flow. Each element of the cascade has a different time window that may have important implications in treating concussed individuals.[2]

Important changes that occur at the molecular level include:

- Induction of immediate early genes c-fos and c-jun
- Increased levels of mRNA for inducible heat shock protein (hsp 72)
- Expression of basic fibroblast growth factor gene[4]
- Elevations of cytokines: interleukin-1 beta, interleukin-3, interleukin-6, interferon-gamma, transforming growth factor-beta, nerve growth factor, and tumor necrosis factor[5]

The brain has evolved several strategies to protect itself against environmental insults. These include signals released from injured cells that are capable of initiating a cascade of events in neurons and glia designed to prevent further damage. Alterations in the expression of neurotrophic factors and their receptors may be involved in modulating the neuronal response after brain injury.[6] Various neurotrophins are released, and these can attenu-

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ate neuronal injury initiated by traumatic brain injury including excitotoxins, ischemia, and free radicals.

In human brain injury cases, alterations in cerebral blood flow have also been demonstrated. Where ongoing postconcussive symptoms have been present, reduced cerebral circulation time[7] and cerebral vasoconstriction with altered CO reactivity have been demonstrated.[8]

The relationship of alteration in intracranial pressure following head injury has also been studied. In severe brain injury or where "malignant" brain edema[9] complicates an acute injury, a prolonged and marked increase in intracranial pressure frequently occurs and may be sufficient to cause death due to respiratory arrest.[10] In concussive injury, no change in intracranial pressure has been demonstrated in animal models.[11] Similarly, it has been shown that diffuse axonal injury is not due to raised intracranial pressure.[12]

TREATMENT OPTIONS

There are many options that have been proposed in the literature for all grades of severe brain injury. The list below is not meant to be exhaustive or encyclopedic in extent. Readers are referred to some of the larger texts and recent reviews on these topics for more complete discussion.[13,14] The list below outlines some of the recent developments and areas where treatment may have a role. In many cases, the evidence is based on studies of severe brain injury, and readers need to interpret this in light of the discussion above. These are summarized in Table 1.

1. Corticosteroids

Corticosteroids, particularly methylprednisolone, have been used for many years, particularly in experimental neurotrauma, initially based on their ability to stabilize lysosomal membranes and reduce tissue edema. There are a number of studies that suggest both positive and negative benefits of using corticosteroids in severe brain injury.[15] Interestingly in acute spinal cord injury, a randomized controlled trial of high-dose methylprednisolone has been shown to be of benefit when administered within 8 hours of injury.[16] Why steroids should benefit one area of the central nervous system (CNS) and not another may reflect methodological differences between trials or that lower doses of steroids were used in the head injury trials. This issue is currently the subject of an international multicenter randomized placebo-controlled study. Other compounds, particularly the lazaroids or 21-amino steroids, which inhibit lipid peroxidation also have protective benefit in neurotrauma models. One such compound, tirilazad mesylate, has been shown to improve behavioral recovery in mice.[17]

2. Free Radical Scavengers and Antioxidants

Traumatic injuries, particularly if severe, may release free radicals by a number of mechanisms. Treatment with vitamin C or E, if administered preinjury, has been shown to provide protection in various models of CNS trauma.[18,19] Some concern, however, has been raised by the large scale epidemiological studies of antioxidant use for cardiovascular disease where antioxidant therapy was associated with an increase in cancers. The mechanism for this in not known.

3. Drugs Inhibiting Arachidonic Acid Metabolism

Potential toxic breakdown products of arachidonic acid metabolism may exacerbate CNS injury. These include thromboxanes, peptidyl leukotrienes, and free radicals. Studies of cyclooxygenase inhibitors (e.g., ibuprofen) and mixed cyclooxygenase–lipoxygenase inhibitors have shown therapeutic benefit in animal models of spinal cord injury.[20] No specific trials of this therapy have been performed with mild traumatic brain injury. It is interesting to note that many, if not all, athletes in collision sports such as football routinely use antiinflammatory agents during the season for the management of soft tissues trauma. Whether these agents exert a protective effect with regard to concussion remains speculative.

4. Drugs That Modify Monoamine Function

The role of catecholamines in the pathophysiology of CNS injury remains unclear. There is a well-documented sympathoadrenal response following traumatic brain injury, however, whether blocking this response has a therapeutic benefit is unknown. It has been known anecdotally since the Second World War that cholinergic antagonists such as scopolamine can reduce the behavioral deficits following brain injury. A recent randomized trial, however, was terminated prematurely because of unacceptable psychomimetic side effects suggesting that this agent may not be a practical treatment option.[14]

5. Glutamate Receptor Antagonists

Severe traumatic injuries to the brain release large amounts of glutamate and aspartate into the extracellular space within the first few minutes following injury. Increased extracellular levels of these chemicals correlate with injury severity.[21] Treatment with NMDA antago-

TABLE 1. *Summary of treatment options*

Treatments that are possibly effective	Treatments unlikely to be effective	Treatments that may place the athlete at risk of adverse events
Drugs inhibiting arachidonic acid metabolism	Neurotrophic factors	Free radical scavengers
Calcium channel antagonists	TRH/TRH analogs	Antioxidants
Corticosteroids		Drugs that modify monoamine function
Opiate receptor antagonists		Hyperbaric oxygen therapy
		Hyperthermia
		Glutamate receptor antagonists

TRH, thyrotropin releasing hormone.

nists, AMPA antagonists, and magnesium have suggested a protective benefit in animal and limited human studies.[21] These agents may be of increasing importance once safety and other issues are dealt with.

6. Calcium Channel Antagonists

It has been proposed that the entry of calcium through voltage-dependent channels may contribute to secondary tissue injury. Despite the intuitive logic of treatment with calcium channel blockers, a number of randomized trials of various agents have failed to demonstrate protective benefit.[22,23] Recently a novel calcium channel agent, S-emopamil, has been shown to be beneficial in experimental injury.[24]

7. Opiate Receptor Antagonists

Endogenous opioids contribute to secondary damage following CNS trauma. Studies have suggested that the kappa opioid receptor or its isoforms may be significant in the modification of these injuries. Reanalysis of data from randomized trials of spinal cord injury have suggested a benefit from naloxone, although the dose studied may have been too high.[16,25]

8. TRH and TRH Analogs

Thyrotropin releasing hormone (TRH) was initially used in the treatment of acute spinal cord injury because of its ability to antagonize many of the actions of endogenous opioids. This agent also may have effects on platelet function, leukotriene activation, and excitatory amino acid release. Protective effects in CNS injury are dose related and are found even when treatment is delayed up to 24 hours.[26,27] In direct testing, TRH analogs appear to be superior to other classes of treatment studied to date.[28]

9. Neurotrophic Factors

The ability of injured neurons in the adult brain to recover from injury depends on the expression of growth-related genes and the responsiveness to survival and growth signals in the environment. These signals include neurotrophic factors and substrate molecules that promote neurite growth.[29]

Nerve growth factor: The neuroprotective efficacy of intracerebral nerve growth factor infusion has been demonstrated during the acute phase of experimental head injury. This beneficial effect of nerve growth factor may be related to its ability to attenuate traumatically induced apoptotic cell death.[30]

Insulin-like growth factor-1: Intravenous insulin-like growth factor-1 has been evaluated for the treatment of moderate-to-severe head injury in a phase II safety and efficacy trial.[31]

Bcl-2: This proto-oncogene has actions similar to those of brain-derived neurotrophic factor in promoting the regeneration of severed CNS axons in the mammalian CNS.[32] The mode of this action likely is via extracellular signaling pathways that are involved in both neuronal survival and axon elongation.

10. Hypothermia

Significant morbidity and mortality of patients with traumatic brain injury is associated with posttraumatic inflammatory complications. Hypothermia has been suggested as a treatment to lessen these inflammatory reactions. Hypothermia, applied immediately after the traumatic brain injury, reduces the posttraumatic increase in interleukin-1 beta-mediated nerve growth factor production.[33] Thus hypothermia, while reducing the inflammatory response, may also hinder the brain's intrinsic repair mechanism. In phase 1 and phase 2 trials, short (<48 hours) periods of moderate (32–33°C) hypothermia are well tolerated and provide limited evidence of a beneficial effect on the outcome following moderate-to-severe traumatic brain injury. Phase 3 randomized controlled trials are currently under way.[13]

11. Hyperbaric Oxygen Therapy

The delivery of high concentrations of oxygen under pressure has been proposed as a means of enhancing cerebral oxygenation and injury recovery postinjury. Possible mechanisms of action include cerebral vasoconstriction, improvement in glucose metabolism, and reduction of cerebral edema. Hyperbaric oxygen also may have a potentially harmful effect on the injured brain by supplying oxygen for free radical reactions that result in iron-catalyzed lipid peroxidation. In severe brain injuries, randomized trials have demonstrated an improved mortality rate with hyperbaric therapy; however, there was no improvement in functional outcome at 12 months.[34] Many questions remain unanswered by this type of therapy. The concern over potential adverse effects of therapy remain paramount, especially in the treatment of mild brain injury. Future trials of hyperbaric therapy in conjunction with a neuroprotective antioxidant agent may be useful to answer some of these questions.

12. Other Treatment Strategies

There are a number of other agents that have been used either in small clinical trials, experimental studies, or reported anecdotally to be of benefit. Agents such as anion transport inhibitors[35] and cytokines[14] have been proposed, as well as combination therapy directed at a number of elements of the injury cascade.[28] Even nutritional supplements such as creatine have been proposed to be of benefit in severe traumatic brain injury.[36] Further randomized controlled trials are necessary with all these agents prior to consideration of widespread clinical use.

CONCLUSION

In summary, at the present time the clinician has no evidence-based pharmacological treatment to offer the concussed athlete. It is likely that as we understand the pathophysiological changes that develop postinjury, then treatments specific to each therapeutic window will be developed. Until that occurs, the use of "shotgun" therapy to treat concussion or postconcussive symptoms is not advised. Not only do many of the proposed treatments have significant side effects, but also the other therapeutic modalities (e.g., hyperbaric oxygen) may cause problems. Any proposed intervention would have

to be shown to be both safe and effective in controlled trials.

Although as physicians we often feel the need to treat "something" rather than sit idly by and observe the clinical state, it is critical that we bear in mind the Hippocratic aphorism: *Primum non nocere.*

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