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## **The Potential Role of Antioxidant-based Therapeutic Intervention in the Management of Traumatic Brain Injury**

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Brain injuries were quite common in our earliest civilizations:

- The Edwin Smith Surgical Papyrus, a copy of a manuscript dating back 5,000 years, is the oldest recorded medical document. It shows us that the ancient Egyptians were well aware of the myriad of disturbances brought about by injury to the brain.
- The ancient Greeks also understood that intellect and reasoning had their seat within the brain. Physicians of the Hippocratic school some 2,400 years ago discovered that incising a wound on one side of the brain caused "a spasm in the opposite side of the body."
- Galen wrote that "a loss of memory for words" might follow head injury.<sup>1</sup>

The statistics of head injury are sobering. The mortality from head injury in the last 12 years has exceeded the cumulative number of Americans killed in all wars since the founding of this country. The number of nonfatal injuries is conservatively estimated to be more than two million each year, with an overall economic cost to society of about \$25 billion per year.<sup>2</sup> More recently Gennarelli<sup>3</sup> reported this figure to be \$45 billion, with 1.54 million patients treated outside of the hospital setting. The incidence is about 200 cases per 100,000 Americans.<sup>4</sup> Eighty percent of the 400,000 admissions to hospitals each year for brain trauma are diagnosed as "mild." Males are injured more than twice as often as females.<sup>5</sup>

Motor vehicle trauma is the single most important agent in both fatal and mild brain injuries, accounting for 67% of cases.<sup>3</sup> Earlier reports ranged from 40%<sup>6</sup> to 60%<sup>5</sup> caused by MVA, with the most common diagnosis given being concussion.<sup>6</sup> Many of these MVA-related injuries are the result of blunt head injury (aka soft head injury) which describes contact with some object, but without penetration of the skull. An example would be striking the steering wheel or door post. The term of choice today is traumatic brain injury (TBI), since it is the brain, rather than the head, that we are usually most concerned with.

## Mechanism of Injury

The mechanism of the trauma was previously thought to be a shearing of axons which result from abrupt acceleration and deceleration of brain tissue.<sup>7</sup> During a low speed whiplash injury (7 mph) the head may be accelerated to 9-18 g.<sup>8</sup> Since the brain is a soft structure, shear strains are created as the outer part of the brain moves at a different pace than the inner part of the brain. This is intensified as the momentum of the head changes rapidly in a sagittal direction during a whiplash trauma. Ommaya and Hirsch<sup>9</sup> studied the tolerances of primates to whiplash and calculated, by interpolation, that angular accelerations of 1,800 rad/sec<sup>2</sup> would result in a cerebral concussion in man about 50% of the time. They noted, however, that this threshold may very well be as low as 1600 rad/sec<sup>2</sup>. The most important factors in whiplash-induced concussion are angular acceleration, flexion/extension tensions in the neck, and intracranial pressure gradients.<sup>10</sup>

Liu et al.<sup>11</sup> measured the subcortical EEG in rhesus monkeys subjected to whiplash trauma. They discovered evidence of concussion in many animals, even though the animals did not lose consciousness. Portnoy et al.<sup>12</sup> measured significant rises in intracranial pressure in baboons exposed to whiplash. Contacts with rounded head restraints resulted in greater intracranial pressure changes than with vertical restraints. All EEG data was normal. The rise in pressure was attributed to brain movements.

Bilston et al.<sup>13</sup> have developed a model that predicts a caudal movement of the brain stem through the foramen magnum during the flexion phase of whiplash. They also found that at higher strain rates the spinal cord becomes stiffer and, therefore, more susceptible to injury.

Gennarelli et al.<sup>14</sup> subjected primates to three different types of loading to determine the potential contribution of each to head trauma. They found noncentroidal motion in the coronal plane to be most injurious and noncentroidal acceleration in the sagittal plane to be least injurious. The former would simulate a side impact and the latter a rear or front impact.

This same group<sup>15,16</sup> simulated these motions in models of baboon and human skulls, complete with surrogate falces. These models were filled with silicone gel to simulate brain tissue. Within this material was painted a grid and the flat surface was covered with Plexiglas. This model was then subjected to noncentroidal accelerations in sagittal and coronal planes. The deformations of the grids were recorded with high speed film. Consistent with their animal study, they found strain forces to be greatest in coronal plane accelerations and least in sagittal plane accelerations. This was due to the restraining effect of the falx. The

tentorium exerts similar intracranial mechanical stresses.

This clearly suggests that lateral whiplash motions of the head are much more likely to produce the diffuse axonal injury (DAI) than rear impacts. Unfortunately, the threshold for DAI has yet to be measured directly, although an envelope for injury based on angular velocity and angular acceleration has been described.<sup>17</sup> Most studies have produced DAI in animals at forces that are probably well in excess of this threshold. However, an interesting study by Jane et al.<sup>18</sup> proved conclusively that noncentroidal accelerations of the head (without contact) could produce damage to axons in the inferior colliculus, pons, and dorsolateral medulla. Animals were subjected to noncentroidal accelerations of 60 degrees within a span of 5-25 msec. This is equivalent to 4,190-21,000 rad/sec<sup>2</sup>. These animals experienced a brief loss of consciousness. The authors discussed the work of Povlishock et al.,<sup>19,20</sup> who have described the pathogenesis of the DAI and suggested that the mechanism of trauma is not necessarily an immediate shearing of axons, but rather a reactive degeneration secondary to trauma. As pointed out by Gennarelli,<sup>3</sup> mild TBI should be considered a process, rather than an event.

This work is also consistent with the work of Windle et al.<sup>21</sup>, who demonstrated chromatolysis in the vestibular nuclei following minor injuries. Whatever the pathogenesis, it is clear that these lesions do result from relatively minor trauma and the implications to the public health and the economy are obvious and substantial.

## **Pathobiologic Injury**

The precise nature of the diffuse axonal injury (DAI) is thought to be a reactive swelling and retraction of damaged axons found throughout the brain, but concentrated at the corticomedullary and nuclear-medullary junctions, corpus callosum, and cerebellum.<sup>19,20,22</sup> Refinements in the mechanism of DAI have been recently reported by Povlishock.<sup>23</sup> Direct brain trauma results in intra-axonal changes in the 68-kd neurofilament subunit, which then loses its alignment and interferes with axoplasmic transport. This causes axonal swelling and eventual disconnection. The neurofilament change may be due either to direct damage to the cytoskeleton, or a biochemical event that results in neurofilament disassembly. The temporal progression of these events are related to the severity of the injury. Other brain injuries are also reported.<sup>24</sup>

Recent studies have provided further insight into the phenomenon of acceleration induced brain injury. At the time of injury, the brain is subjected to massive depolarization and tissues are damaged through transient shear forces that mechanically deform axons and microvessels. Movement of the brain within the skull

results in high intracranial pressure gradients. There is little evidence for initial energy depletion, and subsequent tissue edema and microvascular perfusion shunting probably produce areas of focal ischemia. It is postulated that such events culminate in a final common pathway of neuronal death that involves cellular calcium homeostasis, the production of free radicals, and tissue acidosis.<sup>25</sup> Tissue microhemorrhages develop between 12 and 96 hours after injury. CSF lactic acidosis appears to be independent of tissue ischemia and might be explained by this massive depolarization, and by activation of phospholipases and the release of free arachidonic acid, free radical generation, and lipid peroxidation, with consequent membrane degradation and mitochondrial uncoupling. Free radicals are deleterious to biological systems because they initiate chain reactions, where one free radical forms another, and another, and so on, leaving behind damaged molecules.

Even in relatively mild brain injuries, an excessive release of excitatory neurotransmitters, such as acetylcholine and excitatory amino acids, can contribute to the pathobiologic reaction in the brain resulting in permanent deficits.<sup>26</sup> This process may be mediated by a loss of calcium homeostasis. Endogenous opiates may mediate some of the neurologic damage. Minor TBI can produce diffuse reductions in cerebral metabolic activity and disrupt the blood-brain-barrier.<sup>26</sup>

Most brain injuries are minor, defined as producing a Glasgow Coma Scale of 13 or more, and the term mild traumatic brain injury (MTBI) is most useful. These injuries constitute a very extensive subgroup of patients. From within this subgroup, the spectrum of injury ranges from mild concussion (i.e., without a loss of consciousness, but with some amnesia or confusion) to the classical concussion with brief loss of consciousness, amnesia, and cognitive changes that can be permanent. The postconcussion syndrome (PCS) can develop from either. Posttraumatic headaches (PTHA) are very common residuals and may last anywhere from six months to several years. They are usually an integral part of PCS.

MTBI presents a risk of PTHA of about 40-60%,<sup>4</sup> and many of these head injuries are too subtle to be caught in the snares of most of the diagnostic tests available today. Barnat<sup>27</sup> has shown that whiplash injuries are the second most common cause of PTHA in this country (see Table 1).

**Table 1:** Etiological factors in PTHA

Blunt head contact	57.3%
Whiplash	43.6%
Object hit head	13.7%
Other	13.7%
Body shaken	9.4%

## **Antioxidants as Therapy**

Over the past decade, and particularly as the metabolic pathways of the pathophysiologic consequences of TBI have been elucidated, researchers have increasingly turned their attention toward the potential role of antioxidants in the treatment of TBI patients. While most work has focused on animal models and the more severe range of human brain injury, some extrapolation to mild TBI in humans is allowable.

Antioxidants, such as vitamins C, E, A, bioflavonoids, and the ultra trace element selenium, can limit the amount of cellular neuronal damage induced by free radicals that result as part of the pathobiological cascade occurring in the aftermath of TBI.

Vitamin C is the generic term for L-ascorbic acid and its close molecular relatives. L-ascorbate can be oxidized to the monodehydroascorbate free radical, which quickly dismutates or is converted to dehydroascorbate. Ascorbate is a direct antioxidant and can reduce or "recharge" other antioxidants, especially tocopherol (vitamin E), thus providing a protective role during the formation of free radicals after trauma.

Vitamin E's role is to scavenge free radicals in all tissues,<sup>28</sup> facilitated primarily by its ability to inhibit lipid peroxidation. Transition metals, such as iron and copper, when present in certain unbound states, can catalyze the formation of even more potent reactive species called hydroxyl radicals. From the attachment of molecular oxygen, peroxy radicals, and eventually, peroxides are formed. Antioxidants work by acting as chain breakers; they are modified by free radicals into stable radicals that do not damage other molecules. They are then disposed of or regenerated by various mechanisms. Thus low levels of antioxidants can prevent large amounts of biological damage.

In the case of vitamin E, the stable radical formed is called chromanoxyl. Ascorbate, glutathione, dihydrolipoate, coenzyme Q10, and superoxide anion can all recharge (i.e., reduce) oxidized vitamin E back to its original form.<sup>28</sup> This free radical scavenging ability of vitamin E stabilizes membranes against

damage by phospholipase activity. Thus, by several mechanisms, vitamin E is important for membrane integrity and function.

Selenium is an essential ultra trace nutrient, exerting most of its biological effect through the formation of selenocysteine residues at the active site of glutathione peroxidase (GPx) enzymes.<sup>29</sup> GPx is a major cellular antioxidant and is active against hydrogen peroxide, hydroperoxides, and phospholipid peroxides, using glutathione as a rechargeable intermediate. Reduction of vitamins C, E, and thioredoxin (another antioxidant) is facilitated directly or indirectly via GPx activity and glutathione.

Bioflavonoids are a common class of compounds found in plants. From their early postulated role in the prevention of capillary permeability, they were also known as vitamin P. Because of their common structures, bioflavonoids share properties of enzyme inhibitions, especially for cyclooxygenase, lipoxygenases, phospholipases, and hyaluronidases.<sup>30</sup>

Most bioflavonoids possess antioxidant activity, scavenging hydroxyl radicals, lipid peroxides, and reactive oxygen species. One of the mechanisms of action is through the binding of free iron and other heavy metals that catalyze free radical formation. Commercially available supplement sources are mixtures of citrus bioflavonoids, rutin, quercetin, hesperidin, catechins, Ginkgo biloba extracts, milk thistle seed extracts, and wine proanthocyanidins.

Free radical scavengers and iron chelators have been proposed as therapeutic devices in the treatment of TBI.<sup>31</sup> When hemorrhage occurs in the brain as a result of injury, excessive activations of glutamate receptors has been postulated to contribute to neuronal loss. Regan and Panter<sup>32</sup> recently demonstrated that this effect could be attenuated in mice by the administration of an iron chelator deferoxamine and the alpha-tocopherol analogue Trolox.

Low molecular weight antioxidants are normally present in the brain to regulate normally occurring low levels of reactive oxygen species. Researchers have demonstrated a rapid drop in these endogenous antioxidants subsequent to brain injury in rats. This effect was attributed to the large scale scavenging of free radicals occurring during the aftermath of injury.<sup>33</sup>

In another study using the rat model, it was shown that both polyethylene glycol-conjugated superoxide dismutase (pegorgotein, Dismutec) and lidocaine could effectively reduce the posttraumatic motor deficits related to damage mediated by free radical formation in the brain following TBI.<sup>34</sup>

Showing great promise in a number of recent trials is a 21-aminosteroid compound called tirilazad mesylate (Lazaroid). It has been shown to be a potent inhibitor of lipid peroxidation in a number of experimental models and is currently in phase III clinical trials in brain injury, spinal cord injury, ischemic stroke, and subarachnoid hemorrhage.<sup>35-37</sup> The mechanism of action is largely brought about by its ability to protect the microvascular epithelium and consequently to maintain a normal blood-brain barrier permeability and cerebral blood flow autoregulatory mechanisms. However, due to its limited penetration of brain parenchyma, the drug failed to prevent delayed damage to the selectively vulnerable hippocampal and striatal regions of the brain in experimental animals.

More recently, Hall et al.<sup>38</sup> have reported the discovery of a novel group of antioxidant compounds known as pyrrolopyrimidines. They have been shown to possess even greater bioavailability, increased efficiency, and potency in protecting against iron-induced lipid peroxidative injury. Moreover, they have been able to better protect the vulnerable hippocampal area of the brain than tirilazad mesylate, even after a four hour delay in treatment. The authors of this study also suggested that the drug might be useful in certain chronic neurodegenerative disorders in which lipid peroxidation plays a role.

Other authors have demonstrated that lipid peroxidation and antioxidant activity could be regulated by the administration of amphetamine (Phenamin) or piracetam, following experimental brain injury in rabbits,<sup>39</sup> suggesting that lipid peroxidation could be controlled by the modification of the functional state of the central nervous system without special antioxidant therapy.

## **Conclusions**

The studies reviewed in this paper suggest that early treatment of TBI with antioxidant compounds, often in conjunction with other antiinflammatory drugs such as methylprednisone, can reduce the degree of damage that occurs as a result of free radical formation in the brain due to a pathobiological cascade of secondary chemical and neurohormonal reactions. It is also clear from reading the literature that a window of opportunity for effective management exists, and that this may be as short as several hours or as long as several days.

The endogenous level of antioxidants present in the brain at the time of injury is also an important factor in limiting cellular neuronal damage, and this suggests an important role of dietary supplementation of naturally occurring antioxidants such as vitamins A, C, and E, selenium, and bioflavonoids. And, while clinical cases of mild concussion, which represent the lower range of TBI (and the most commonly

occurring TBI) would not be treated medically with aminosteroid drugs and steroids, clinicians should recommend temporary regimens of supplemental antioxidants, such as vitamins A, C, and E, along with selenium and bioflavonoids. In addition, the role of vitamin B complex in regulation of the nervous system and other functions is well known. Thus, a multivitamin and mineral supplement is also an important component of mild TBI management. Meanwhile it is not clear what effect, if any, antioxidant therapy will have on the outcome of TBI when administered beyond a few days postinjury.

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