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Traumatic Brain Injury and their Possible Therapeutics

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Commentary

Traumatic brain injury (TBI) is the leading cause of morbidity, disability, and mortality in all age groups. Over 50 million people worldwide suffer from TBI each year. As of 2005, approximately 3.17 million TBI survivors suffer from post-traumatic complications ranging from neurological and psychosocial problems to long-term disability. Huge spending on clinical management of TBI patients and the associated socio-economic problems place a heavy burden on the healthcare system and society. A better understanding of the clinical features of TBI and the underlying complex pathophysiological mechanisms has led to the development of new promising therapeutic approaches that have shown promising effects in preclinical and Phase I / II trials. However, most of them have proven to be phased unsuccessful III clinical trials. In fact, over the last 30 years, more than 30 clinical trials of TBI drugs aimed at diagnosis or treatment have failed. This review provides an overview of molecular and cellular events in the etiology of TBI [1]. It provides up-to-date information on potential drug discovery targets and new treatment directions, followed by discussions on different approaches to controlled delivery of these therapies.

Damage to nervous tissue associated with TBI falls into two categories: (i) Primary damage directly caused by mechanical force at the time of initial damage. The direct effects of various mechanical attacks on the brain can cause two major types of injury: localized and diffuse brain injury. Studies have shown that in patients with moderate to severe TBI, both types of injury are common. Diffuse axonal injury (DAI) accounts for about 70% of TBI cases. As a result of the forces of lacerations, compressions, and concussion, closed head and penetrating TBI show localized brain injury with evidence of skull fracture and local contusion in the center of the injured site. The necrotic areas of nerve and glial cells are concentrated in a coup with impaired blood supply, causing the appearance of hematomas, epidural, subdural, and intracerebral hemorrhage in a limited layer of the brain. Secondary bruise can occur in tissues facing or surrounding a coup d'etat due to the secondary impact of the brain rebounding and hitting the skull. Cognitive impairment, behavioral changes, and hemiplegia can occur, depending on the severity of the injury. In contrast to localized injury, the main mechanism of diffuse brain injury is the non-contact force of rapid deceleration and acceleration, which causes shear and extension damage to the brain tissue of the brain. Strong tensile forces damage nerve axons, oligodendrocytes, and blood vessels, resulting in cerebral edema and ischemic brain damage [2]. Diffuse TBI is characterized by extensive damage to axons, primarily in subcortical and deep white matter tissues such as the brainstem and corpus callosum, with impaired axonal transport and degradation of the axonal cytoskeleton. Notably, this axonal injury can persist up to several months after TBI, suggesting an association between hemorrhage and delayed secondary pathology of cerebral edema. The degree of axonal injury and neurodegeneration determines the severity of TBI [3]. Interestingly, the explosive blast TBI is the result of shock waves rather than inertial forces, but is characteristic of typical diffuse brain injury. (ii) Secondary damage. Refers to further tissue and cell damage after primary damage. Biochemical, cellular, and physiological events that occur during primary injury often progress to delayed and long-term secondary injury that can last from hours to years [4]. Mechanically, many factors contribute to secondary damage, including excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, neuroinflammation, axonal degeneration, and apoptotic cell death.

Since number one accidents in TBI typically contain acute bodily damages and necrotic mobileular loss of life which might be not going to be reversible, remedy regimens particularly purpose to stabilize the webweb page of damage and save you it from secondary damage. Secondary accidents are due to an array of threat elements and expand in an innovative manner [5]. This offers a window for healing intervention of occasions that would set off in addition lack of neurons and glial cells past the damage epicenter, which consist of continual inflammatory response, excitotoxicity, oxidative pressure and apoptotic mobileular loss of life.

Combating chemical stress to neurons and glia through anti-oxidants and anti-inflammatory and anti-apoptotic agents

The immunosuppressive drug cyclosporine A, a potent regulator of mPTP, has been shown to have neuroprotective effects in experimental models of TBI. Although the exact mechanistic effects of cyclosporin A are not yet well understood, post-TBI administration is associated with a reduction in Ca^{2+} accumulation due to the binding of the cytosol phosphatase calcineurin to the mPTP Cyp-D. Cyclosporine treatment also inhibits mitochondrial cytochrome c release and Ca^{2+} influx into mitochondria. In addition, cyclosporine A exhibits antioxidant properties by down regulating lipid peroxidation [6]. These effects lead to improved axonal damage and mitochondrial dysfunction, reduced cortical damage and improved neurological outcomes. Nonetheless, a small randomized clinical trial with cyclosporine A at TBI surprisingly showed improvements in patient neurological outcomes and biochemical parameters compared to healthy subjects. It should be noted that it was not done. Nonetheless, a European multicenter phase II / III clinical trial using NeuroSTAT, a drug containing cyclosporine A as an active ingredient developed by NeuroViVe, has recently begun and its results have not yet been evaluated. Methylprednisolone is a synthetic glucocorticoid that is widely used in the clinical management of acute CNS injuries, primarily due to its anti-inflammatory properties and control of injured CNS edema. Interestingly, due to its antioxidant properties, high doses of methylprednisolone have a neuroprotective effect that specifically weakens post-traumatic lipid peroxidation. Little is known about the mechanism of the antioxidant

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action of methylprednisolone, but it is thought to be incorporated into the structure of the lipid bilayer, hardening the cell membrane and thereby limiting the mobility of lipid peroxy radicals. In particular, methylprednisolone should be given at optimal concentrations in the early stages of CNS injury to ensure maximum anti-inflammatory and neuroprotective effects. Methylprednisolone was previously included in a randomized, placebo-controlled trial called CRASH in 2004. A large sample size of more than 10,000 TBI patients was enrolled in the study with a 2-week follow-up period. Nevertheless, with increasing mortality, the results were undesirable. In fact, rats treated with methylprednisolone also showed a significant increase in neuronal apoptosis in the hypothalamus, pituitary gland, and hippocampus [7]. These are associated with memory and learning disabilities. Primary damage to the TBI is primarily irreversible. The resulting damage occurs, progresses, and has access to therapeutic intervention over months to years. Because the delayed phase of this injury involves numerous events such as excitotoxicity, apoptotic cell death, inhibition of axonal regeneration, neuro inflammation, and oxidative stress, the development of effective treatment strategies has been multiple over time. You need to target the mechanism. The availability of a depot system for regulated and sustained delivery of therapeutic agents that can enter cells by penetrating the plasma membrane is clearly an additional bioavailability of existing drugs will allow improvement. More importantly, it offers the opportunity to explore the therapeutic potential of new compounds for drug-worthy targets. In fact, this therapeutic approach has been applied to the treatment of many neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, and Parkinson's disease.

The feasibility of this strategy in the treatment of TBI has not yet been demonstrated, but events during secondary injury of TBI that require continued availability of bioactive therapeutic agents at non-cytotoxic concentrations. Looks promising because of the slow progress of. TBI has become a major health and socio-economic problem worldwide, imposing a significant health burden on modern societies in need of more effective treatments. This is also an important issue in defense science, as modern technology provides better protection from the dead, which dramatically increases subtle CNS damage in the military.

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