GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(REVIEW ARTICLE)

Traumatic brain injury: Future application of nanomedicine

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GSC Advanced Research and Reviews, 2021, 06(02), 020–027

Publication history: Received on 08 January 2021; revised on 04 February 2021; accepted on 06 February 2021

Article DOI: https://doi.org/10.30574/gscarr.2021.6.2.0019

Abstract

Traumatic brain injury (TBI) is currently a rising player in the cause of disability and neurological dysfunction worldwide. TBI is a common occurrence in the military and extreme activities, sports arena and accidents. Severe TBI can be fatal but mild TBI persists and progressively deteriorates brain homeostasis and physiology. Apart from the physical disabilities, psychological complexities arise in people with mild TBI. Despite the seriousness of this hazard, treatments for TBI are not adequate, mostly due to the brain being involved. Nanoparticle (NP) therapy seems to be an effective alternative to combat TBI. This review outlines the state of TBI and describes the probable medical support that nanomedicine can provide.

Keywords: Traumatic brain injury; Blast TBI; Pathophysiology; Blood brain barrier; Nanoparticle therapy

1. Introduction

Traumatic Brain Injury is caused when an external force hits the head, strong enough to modify brain functioning and cause pathological changes. Traumatic brain injury or TBI can result from an accidental impact on the head during a car accident or an impact from a fall or sports activity, also from non-impact events like blast waves, rapid acceleration or deceleration that generates brain movement within the cranium [1, 2]. TBI has been the stealth factor disrupting the ability to speak, see, hear, walk, think, also control emotions. Symptoms of TBI range from mild to severe. Mild TBI often goes undetected initially but 'silently' makes an appearance only to hinder an individual's normal flow of life that can be discussed with special reference to the military forces.

Worldwide incidence of TBI is about 10 million with many deaths. Military cases alone account for 4 lakh cases. The gravity of TBI requires special attention for military personnel since they are in the higher-risk zone for combat and non-combat exposures [3, 4] and often face multiple TBIs. The risk of incessant neurological degradation and pain in case of recurrent injuries pose a serious threat to military personnel. Mild TBI (mTBI) or concussions are a common injury in warfare. mTBI is often listed as one of the prime rationales behind post-traumatic stress disorder PSTD and repetitive mTBIs also pose the threat of depression leading to suicide after deployment [5]. Military TBI is essentially different from civilian TBI. The phases of neural injury from TBI are traditionally divided into primary mechanical injury and delayed secondary injury. The primary process refers to the injury inflicted during the impact while the secondary process points out to the cascade of molecular events after the insult of the primary injury, generally occurring minutes or days later, determined partly by the host response. The military TBI includes two additional modes of mechanical injury - penetrating ballistic injury and blast injury [6]. But TBI due to explosive blast (bTBI) seems to be the prevalent type in the battlefield.

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1.1. TBI due to blast explosion

A bTBI resulting from a bomb or improvised explosive devices (IEDs) explosion is a major concern. bTBI is caused by blast shock pressure waves which last over short periods, milliseconds. The diffuse interaction of the brain with the pressure waves triggers a complex cascade of events that disturb the brain structure and function. bTBI occurs as mentioned by Marklund (2020) (1) the primary blast injury is caused by sudden rise in atmospheric pressure from the explosion itself; (2) the secondary blast injury results from released fragments which may cause a penetrating TBI; (3) the tertiary blast injury occurs when an individual is thrown against or into a solid object by the blast forces, and (4) the quaternary blast injury results from, e.g., blood loss from associated injuries. The more controversial fifth mechanisms may result from markedly delayed injuries due to the initial components released at time of explosion.[7] Most of the head injuries in warfare are bTBI.

1.2. TBI due to penetrative ballistic injury

Another common form of brain injury is penetration by a foreign body. Physical disruption of neurons, glial cells and fibre tracts occur when a foreign object pierces the bony skull and passes into the or through the brain substance. Brain damage may be further complicated by ischemia and haemorrhage [6].

1.3. TBI in military air force

To understand the military air force TBI, firstly it is essential to have a brief idea of the underlying causative factors. When it comes to brain injury, it is convenient to understand forces and the impact of forces on the intra-cerebral pressure and homeostasis of the brain [8]. The repercussions of pushing the body against the natural forces to fly high and battle can be dire in extreme cases. The gravitational force or G force acts on blood and blood vessels. When pushed to the limit, blood collects in the lower extremities of the body blocking the adequate blood supply in the brain. Fighter pilots are trained to manage up to 8 or 9 G for longer periods, where as untrained people may pass out between 3 or 4 G. Fighter pilots are equipped with specialized suits, taught specialized breathing and muscle tensing techniques and trained in centrifuges with artificial Gs. Nevertheless, there is a limit to what people can tolerate. High acceleration of the body in the longitudinal direction (Gz) may lead to loss of vision or even loss of consciousness of the pilot leading to fatal accidents. The unpredictable circumstances of warfare steer accidents where an impact on the head, in addition to the already stressful conditions lead to TBI. mTBI or concussions usually occur between 80-100G.

It is natural for mTBI to go unnoticed, hence the lack of documentation. But the cytoarchitectural and functional damage in the brain due to trauma persists and creates complications. Mostly neurodegenerative diseases follow, along with psychiatric symptoms or disability.

2. Pathophysiology of TBI

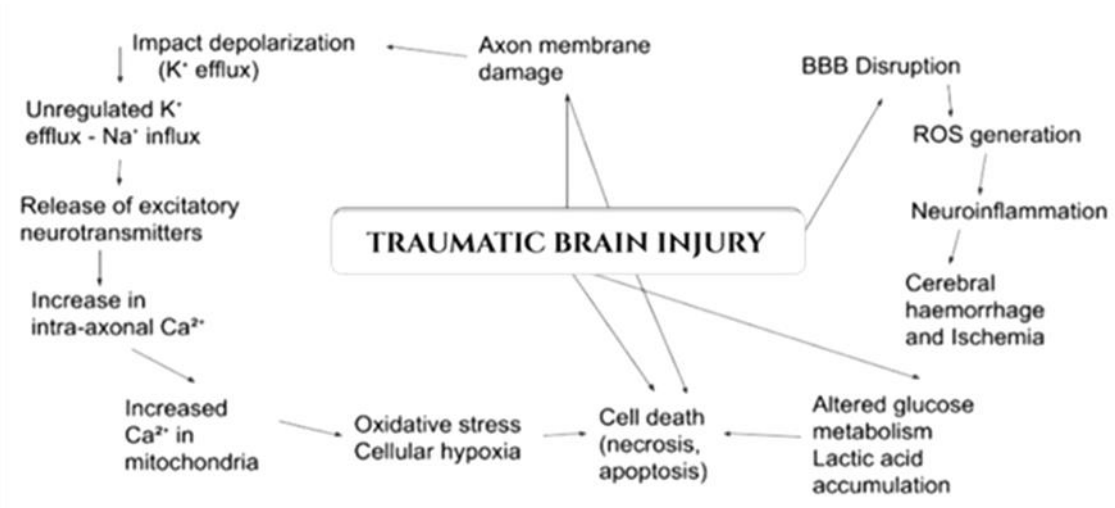

Figure 1 Pathophysiology of TBI

The pathophysiology of TBI represents an intricate system of damage which throws the brain cells in disarray, crippling the natural state.

Severe TBI patients who suffer heavy injury are mainly comatose or with haemorrhage. When hit, the manifestation of TBI triggers mechanical disturbance in cellular integrity. There is a redistribution of ions and neurotransmitters resulting from transient cell membrane disruptions, mainly rapid, unregulated influx of sodium(Na^+), efflux of potassium(K^+) and rise in levels of intra-axonal calcium(Ca^{2+}) [9,10,11] (Figure 1). There may be changes in glutamate stimulated Ca^{2+} signalling. The increasing Ca^{2+} in the axons activates calpain , a protease, initiating proteolysis of cytoskeletal proteins creating irreversible axonal pathology. Ca^{2+} rise also induces N- methyl-D-aspartate (NMDA) receptor activation, further depolarizing the neurons. It has been observed that Ca^{2+} build-up in mitochondria leads to oxidative stress and impairment of mitochondrial function and acidosis and edema due to lactate production. Cognitive deficits in TBI correspond to Ca^{2+} accumulation.

On the other side, axons mainly in the white matter tracts of the brain, also experience rotational and shear forces during rapid acceleration and deceleration which cause diffuse axonal injury. Pressure waves from blast which pass through the brain, stretch the axons and vasculature and compress the glial cells and neurons [12]. A hallmark after TBI is the alteration in cerebral glucose metabolism (CMRglc). After head injury there is a period of hyperglycolysis, followed by a state of glucose metabolic depression, yet the cause of these phenomena is only speculative [13].

Over the time upregulation of aquaporins (AQP1 and AQP4) on endothelial cells disrupts the blood brain barrier (BBB) by allowing passive diffusion of water [14]. Consequently, circulating macrophages, neutrophils and lymphocytes gather promoting inflammation. The cascade of neuroinflammation follows generating reactive oxygen species (ROS), proteolytic enzymes, cytokines and chemokines [15]. Matrix metalloproteinases are also implicated in the destruction of BBB [16]. Continual stimulation of the resident microglial cells, astrocytes accompanied by the infiltration of peripheral immune cells aggravates inflammation. Microglial alteration, with retracted processes, is a distinctive feature of bTBI [17]. TBI also alters the cerebral blood flow (CBF) in the brain. In the case of mTBI, after an initial period of decreased CBF, nitric oxide release leads to unresponsive vasodilation [18]. Activation of Wallerian degeneration along with hypoxia and inflammation is a common scenario of the brain after a traumatic injury [19].

3. Treatment

Primary injury is due to sudden direct impact and cannot be treated. Hence treatment strategies are directed towards alleviating the secondary responses. Currently, the treatment provided is intensive care management and palliative.

No two TBIs are the same. The extent of injury varies in each event and also depends on the host resilience. Thus the symptoms and effects experienced by each person differ and require attention in an almost personalized manner. The severity of TBI is currently determined using the Glasgow Coma Scale (GCS) based on the level of consciousness after the injury (Table 1).

Table 1 Simplified GCS data for classification of TBI

BRAIN INJURY	**GCS**
Severe	<8-9
Moderate	8 or 9-12
Minor	13 or > 13

Over the past two decades, TBI has emerged as one of the leading concerns for the mental health of military personnel. Patients with mTBI suffer concussions that recoup but they are trailed by difficulty in cognitive and motor abilities. Severe TBI patients may be comatose [19]. In spite of the grim situation, the only treatments currently available are pressure dressings and dealing with external wounds. Regardless of the alarming issue, the clinical and pre-clinical trials conducted could not produce successful therapies [20]. Along these lines, the use of nanoparticles in the treatment of TBI is now being actively considered.

As mentioned above, the clinical trials failed at procuring definitive treatments. The primary protagonist of this stalemate is the mighty blood brain barrier (BBB). Although therapeutic drugs have been developed, none are sufficiently effective since they do not reach their destination. The BBB is the anatomical barrier that fortifies the brain

cells against the surrounding vasculature in the brain parenchyma. The BBB is the protective selective filter that coordinates the trading of molecules with the blood vessels due to the presence of brain microvascular endothelial cells (BMECs). BBB also includes astrocytes and pericytes. The BMECs present a single layer of compact, almost non-fenestrated endothelial cells, sealed together by tight junctions. The efflux transporters of BMECs prevent the entry of arbitrary substances, ions and enzymes, in the brain parenchyma while the influx transporters allow the inward movement of essential nutrients and necessary factors to the brain cells [21]. The BBB, thus, competently sustains the brain homeostasis and functional and architectural integrity. Granted, this impediment limits the traditional therapies, it is still a possibility that non-conventional therapies can carry forward the research. The emergence of nanoparticles (NPs) for neurological research is squarely due to this obstacle. The nanoparticles have been shown to traverse the influx transporters into the brain parenchyma. Thus NPs shed a light in this dark corner of brain studies and suggests an optimistic commencement of a new era of neurological studies.

4. Nanomedicine for TBI

The discipline of nanoscale materials, namely particles ranging from 1-100 nm, is rapidly on the rise. The nanostructural elements have found their way in myriad aspects of neuroscience because of their unique properties which have the potential to uncover previously implausible areas. Nanomedicine, in these regards, seems to be the pragmatic alternative for drug delivery to the brain. Biocompatible tunable nanoparticle (NP) carriers have the capacity to cross the BBB. NPs that are biocompatible, biodegradable [22], have higher stability in blood, low immunogenicity and non-toxic for the brain are considered for drug delivery. Therefore mainly organic NPs are used in nanomedicine, viz, liposomes, solid lipid NP, polymeric NP etc. Perhaps the most advantageous characteristics of NPs is their small size and large surface to volume ratio. This feature accounts for the faster rate of drug release and greater bioavailability. For infiltrating the BBB, the NP carriers are coated with biospecific molecules according to requirements in a process called functionalization. This facilitates targeted delivery in the brain [23]. To ensure entry into the brain NPs are tuned to follow mainly three broad pathways. Receptor-mediated transcytosis (RMT) is the process through which NPs are conjugated with ligands whose receptors are present in the apical surface of BBB. Upon ligand binding, the cell membrane invaginates into intracellular coated vesicles and the macromolecule is uptaken, while the receptor is recycled. Another mechanism of transport is the adsorptive-mediated transcytosis (AMT) where NPs conferred with positive charges electrostatically interact with the negatively charged endothelial cells. However, this pathway remains ambiguous due to non-specific drug accumulation tendencies. Lastly, the cell-mediated transcytosis involves immune cell dependent uptake, via neutrophils, monocytes and macrophages. This method is exploited to “hitchhike” NPs into the brain [23].

For greater access to the CNS of NPs, the nasal route of drug delivery has become popular as of late. The roof of the nasal palate is perhaps the sole region of the body where direct uptake of NP into the CNS, bypassing the BBB, is a possibility [21]. It is also advantageous that TBI often results in leaky BBB making NP drug delivery feasible. In the case of TBI, the brain injury is not concentrated in just any single facet, it is varied and a complex network operates. This represents broader prospects of therapeutic targets for NPs. The secondary injury, post-TBI, initiates a cascade of chain reactions that serve as potential targets for NP therapeutics.

To date, there has been quite a good amount of work in targeting NPs within the brain. Perhaps neuroinflammation of the brain post-TBI has been the subject of much research. Microglia and astrocyte damage is one of the major concerns in bTBI. Hubbard *et al* [24] designed hemostatic nanoparticles delivering dexamethasone (hDNPs) functionalized with GRGDS (glycine-arginine-glycine-aspartic acid-serine) peptide targeting platelets, aimed at reducing bleeding and neuroinflammation. hDNPs were shown to reduce microglia and astrocyte degeneration and also reduced apoptosis levels (Figure 2). hDNPs further diminished anxiety, a pressing problem of bTBI among war veterans. Assisting the military personnel and civilians to lead a normal life without the traumatic experience of the injuries is imperative. The administration of hDNPs in blast-exposed rodents increased their survivability after the traumatic event.

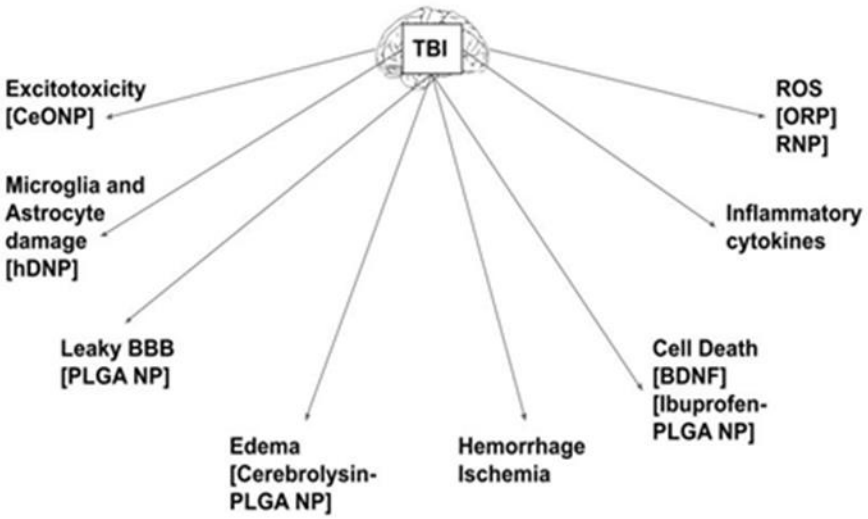

Figure 2 Probable NP therapeutic targets of TBI

Post primary injury, the inflammation of the brain cells is responsible for a large amount of degeneration of neurons and damage in the hippocampus, resulting in behavioural and memory deficits. Thioester core NPs were used to mitigate the ROS generated in the secondary biochemical pathways of TBI. Though further research is warranted, this approach has a potential for future therapies. CeONPs (cerium oxide nanoparticles) have also demonstrated similar ROS scavenging functions. Additionally, CeONPs reduced the glutamate and calcium induced excitotoxicity, consequently reducing neuronal damage and oxidative stress. CeONPs have inherent superoxide dismutase (SOD)- like activity owing to its redox property combined with the increased surface area and nanoscale quantum lattice alterations [25]. Oxygen Reactive Polymer (ORP) NPs lowered the secondary complications due to ROS and abated H^+ O^+ levels by threefold [26].

ROS levels were also cut down by cross-linked NPs, which were synthesized from polysorbate-80. This approach also eases the secondary neuroinflammation and also prevents cognitive and sensorimotor disabilities to some extent [27]. Yet another method was devised where non-steroidal anti-inflammatory drugs, here Ibuprofen, were armed with tocopherol conjugated with tetra ethylene glycol. This nanoprodrug was able to cross the BBB in the injured regions and conferred neuroprotection [28]. Redox-active nitroxide radical-containing nanoparticles, RNPs, administered to scavenge ROS, displayed an effect in enhancing cognitive behaviour, lowering the contusion volume and providing neuroprotection [29].

Breakdown of BBB in TBI fuels the destruction of brain homeostasis. Rouzi *et al* [30] developed PLGA NPs (poly (lactide-co-glycolide) nanoparticles) loaded with cerebrolysin which interfered with BBB breakdown and edema formation in rats with concussive head injury(CHI). The brain-derived neurotrophic factor, BDNF of the neurotrophin family, when transported to the brain via PLGA NPs which were coated with surfactant poloxamer 188, improved neurological state and cognitive abilities of the trauma induced mice [31]. A measure that attempts to minimize secondary neuron degradation is the application of neuroprotective agents. Targeting neurons with siRNA containing NPs, while taking advantage of the leaky BBB after primary impact, may serve to reduce the downstream after effects of TBI [32].

In the case of TBI, timely diagnosis is an important factor for a patient's recovery. But again, mTBI tends to go unnoticed most of the time. NPs have been exploited for diagnostic purposes. Gold NPs coated with silica serve as detection tools for neuron-specific enolase (NSE) and S100-ß proteins which are typical TBI markers [33]. For detection and monitoring of the necrotic brain cells in TBI, PEG-PLGA NPs (polyethylene glycol-PLGA NPs) encapsulating both near-infrared (NIR) fluorophores and perfluorocarbons (PFCs) in conjugation with cyanide dye 800CW is employed [34]. Further, KO et al [35] have used nanofluidics for better identification of TBI markers. Track-Etched magnetic NanoPOre (TENPO) has enabled efficient biomarker profiling, relevant characterization of plasma and serum using biomarkers from healthy and injured patients and prediction of history and intensity of TBI. Nonetheless, there still remains many relatively unexplored areas of TBI for NP therapy like excitotoxicity, ionic imbalance and lipid peroxidation.

5. Discussion

More than 2.6 million victims of TBI are around and the number of people with TBI related physical and mental disabilities is ever increasing. This is especially true when the life of war veterans is looked into. Yet, felicitous facilities are lacking for proper medical support. Preventive measures for TBI are a far cry from a realistic viewpoint. Since the primary injury is unfixable the alternative is to preserve that which remains. The foremost hurdle, in this case, is the missing timely detection of mTBI. The absence of prompt action exacerbates the condition. Soldiers need periodic screening for mTBI. Since each traumatic event is different from the other, the extent of injury varies. This requires special attention to follow the treatment methods with individuality in an almost personalized manner. Even after TBI has been identified the existing surgical and management procedures do not guarantee recovery. The greatest hindrance in treating brain injury as well as other neurological problems is the BBB. Although NPs have successfully overcome this initial barrier, there is still a long way for translational work. Promising *in vitro* studies are all at preclinical levels. Since NP therapy revolves around particles of nanoscale dimensions and their interactions with the brain which itself is an enigma, profound research concerning every aspect of the brain and subsequent effects on the patients has to be carried out meticulously. Moreover, nanomedicine is now at the outset stage. For advancing clinical trials NP production and cost-effectiveness also need improvement. An important factor to be considered is that a neutral zeta potential is critical for successful delivery across the BBB, however, very few reports are currently available [36]. Despite these challenges, the preclinical trials have provided conclusive results which paved the way to clinical trials. Thorough and ample research in this field is the need of the hour where numerous soldiers and civilians suffer from TBI which gradually leads to physical impairments, depression and even suicide.

6. Conclusion

Malaise of TBI has plagued human lives in a rather complicated manner. The paucity of treatment and relief measures have added to the misery. Nanoparticle therapy for TBI is now an active field of research with novel designs cropping up every day. In the future NP therapeutics, in all probability, may emerge as the front in the treatment of traumatic brain injury, raising the quality of life of TBI patients.

Compliance with ethical standards

Acknowledgments

All authors gratefully acknowledge the University of Kalyani, Kalyani Nadia, WB, India for financial support.

Disclosure of conflict of interest

No competing financial or academic interests exist.

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