Role of microvascular disruption in brain damage from traumatic brain injury

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Abstract

Traumatic brain injury (TBI) is acquired from an external force, which can inflict devastating effects to the brain vasculature and neighboring neuronal cells. Disruption of vasculature is a primary effect that can lead to a host of secondary injury cascades. The primary effects of TBI are rapidly occurring while secondary effects can be activated at later time points and may be more amenable to targeting. Primary effects of TBI include diffuse axonal shearing, changes in blood brain barrier (BBB) permeability, and brain contusions. These mechanical events, especially changes to the BBB, can induce calcium perturbations within brain cells producing secondary effects, which include cellular stress, inflammation, and apoptosis. These secondary effects can be potentially targeted to preserve the tissue surviving the initial impact of TBI. In the past, TBI research had focused on neurons without any regard for glial cells and the cerebrovasculature. Now a greater emphasis is being placed on the vasculature and the neurovascular unit following TBI. A paradigm shift in the importance of the vascular response to injury has opened new avenues of drug treatment strategies for TBI. However, a connection between the vascular response to TBI and the development of chronic disease has yet to be elucidated. Long-term cognitive deficits are common amongst those sustaining severe or multiple mild TBIs. Understanding the mechanisms of cellular responses following TBI is important to prevent the development of neuropsychiatric symptoms. With appropriate intervention following TBI, the vascular network can perhaps be maintained and the cellular repair process possibly improved to aid in the recovery of cellular homeostasis.

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Introduction

Traumatic brain injury (TBI) represents an enormous societal burden both with regard to prevalence/incidence and economic cost (initial treatment and long-term care due to high morbidity), largely irrespective of initial injury mechanism. In fact, TBI is the leading cause of trauma-related morbidity and mortality in developed countries, with over 55 million people affected internationally (24). Interestingly, the mechanism of TBI sustained is often related to the patient's age with younger patients more likely suffering TBI as the result of motor vehicle accidents, sports, or battlefield exposure to blast waves whereas the elderly population is generally afflicted by falls (neurogenic or cardiogenic in origin). TBI is also distributed bimodally with peak incidences between 15–24 years, and after 75 years of age. Notably, after age 65, patients have increased mortality and worse functional outcome following TBI (169). The most prominent cause of TBIs is motor vehicle collisions (38). Concussive injuries are also high amongst professional athletes and the active military due to the high-risk for a neurotraumatic event to occur on the job (59, 143). These sub-populations should therefore be the focus for future translational studies.

TBI is unique in that it is always acquired from an external force. One difficulty when treating TBI patients is that we never know when, or how, a TBI will occur. Therefore, the contribution of genetic predisposition and comorbidities to overall post-injury outcomes are hard to ascertain. A valuable scale, called the Glasgow Coma Scale (GCS), is used to assess verbal, motor, and eye-opening responses in order to classify TBI severity (80). The score is based on a 15-point scale. Mild injury correlates with a score of 13+, moderate with a score 9–12, and severe with a score of <8. Its clinical utility is mostly to help determine patient status in relation to intracerebral pressure (16). As such, the clinician can use the score to determine the need for appropriate treatment or management. The values obtained from the GCS help define the severity of TBI and allows clinicians to address the injury more appropriately (52). In addition, patients can display cognitive, emotional, and sensory impairments following mild TBIs and even exhibit physical impairments following more severe forms of TBI. Research now suggests that visible signs, or symptoms, of neurological dysfunction from sports-related TBI may not develop for an extended period of time (15).

Imaging modalities have recently been used to detect some of the subtle injury changes associated with TBI. Microdialysis in combination with nuclear magnetic resonance imaging was used to determine that TBI patients have increased anaerobic metabolism dependent on the pentose phosphate pathway (73). Diffusion tensor imaging has been used with mixed success in detecting white track lesions following concussion (163). Functional magnetic resonance imaging (fMRI) has been used to tease out differences in Salience Network functioning following TBI indicative of failed cognitive control (76). In the clinic, Czosynka's pressure reactivity index can be used to establish a dynamic target for cerebral perfusion pressure (42). Another important consideration is monitoring of cerebral blood flow to prevent the occurrence of ischemia following TBI. Positron emission tomography, perfusion-weighted MRI, and the perfusion computed tomography scan may be used for this endeavor (148).

Two general forms of TBI exist: closed head injury and penetrating head injury (134). TBI is grouped into three levels of severity: mild, moderate and severe (135). Further subclassification of injury is based on symptoms. Subconcussive injury can have no initial symptoms, concussive injury (acute) presents with cognitive, emotional, and sleep symptoms, while juvenile head trauma syndrome presents with a lucid interval and unconsciousness. Post-concussive syndrome involves concussive symptoms lasting greater than 3 months, and chronic traumatic encephalopathy involves a several year symptom free stage followed by onset of neuropsychiatric symptoms (110). Mild TBIs are common and can go undetected with conventional screening tools, although balance tests and cognitive measurements have been used with varied success rates (61, 152). Typically, mild TBI leaves the subject conscious with mild symptoms; however, rodent students have shown that secondary effects often lead to chronic deficits in cognition, memory, and behavior (60, 112). Molecular mechanisms of the secondary effects of mild and moderate TBI are being investigated due to the increased awareness of how these effects contribute to chronic neuropsychiatric symptoms (84). Severe TBI is often life-threatening and requires immediate care. Fewer basic scientists study severe TBI because its effects are more likely irreversible in both the short-term and the long-term.

We have limited knowledge of what brain regions are most affected after a TBI, due to the fact the injury can either be focal or diffuse depending on the type and severity. As such, clinicians struggle with identifying which brain regions have been affected after injury. The brain's response to TBI is more often globally distributed with a vast number of dilated perivascular spaces (71). Pathologic changes are scattered throughout the brain as well and are highly dependent on neuroinflammation as evident from gliosis (168). With the many different forms of TBI, the diagnosis and treatment plans must be adaptable and situational specific.

To date, the primary focus of TBI research has been on neurons with little emphasis on glial cells or the cerebrovasculature. Indeed, for this review, we identified 1030 published reports that assess neurons, and only 326 reports that assessed other brain cell types, including 46 reports on brain microvessels. The current skewing of research in TBI literature toward neurons is understandable, given the underlying goal of protecting neurons and preserving brain function. A neurocentric approach however has not resulted in successful translation of therapeutics in TBI (78, 102), or other models of neural injury (85). It is clear other approaches are needed to be successful. Microvessel disruption plays a substantial role in primary, secondary and chronic effects of TBI, and understanding the response of the vascular system on brain trauma is critical to our ability to effectively treat brain trauma. As such, it is clear other approaches are needed and this review deals with the response of all brain cell types to trauma and focuses on the potential role of microvessel damage to neuronal loss and dysfunction.

Forms of Traumatic Brain Injury

In human subjects, there are a number of causes of TBI and include motor vehicle collisions, falls, sport-associated injuries, blast exposure, and shaken baby syndrome in infants (Table 2)(189). Besides characterizing the injury based on a specific inciting event, the injury can

be described as open or closed head injury, focal or global injury, and impact or blast in origin. Blast injury can be subdivided further into primary, secondary, tertiary, or quaternary injury, a level of detail beyond the scope of this review but discussed in detail elsewhere in the literature (33, 185). The different forms of neurotrauma can further be classified based on clinical features through the GCS assessment, pathological features through advanced imaging assessment, or a combination of the two.

While numerous causes of neurotrauma exist, TBI is uniformly associated with both primary and secondary injury mechanisms. The primary injury is induced instantaneously by the application of external forces to the skull and associated brain tissue, depending on the form of TBI. Impact TBI induces focal brain contusions (170), while blast TBI globally shears axons (140) and damages brain microvessels (2) (see Fig 1, Adapted from (175)). The secondary injury follows the primary injury temporally and rodent studies have shown it is associated with induction of signaling cascades that alter metabolic, cellular and molecular events, ultimately leading to alteration in cellular function and/or death (145). This period of secondary injury can last from minutes to years and is mediated by biochemical processes that may be targeted by and amenable to therapeutic development (141); whereas primary injury can only be prevented (through safety devices, preventative measures, reduced exposure, etc).

To improve understanding of TBI pathophysiology, as well as develop potential therapeutic agents, an array of TBI models have been created and utilized. Some of the most commonly utilized models include the fluid percussion models; variations of the impact acceleration or weight drop models, the controlled cortical impact models, and variations of the shock tube blast models. These models and others such as penetrating injury models are reviewed in depth elsewhere (5, 9, 182, 189). Importantly, TBI represents a highly heterogeneous condition due to the various mechanisms involved and range in forces that are applied/ sustained. As such, it is unlikely that one model is adequate for all TBI research and consequently a multi-faceted approach is likely required. This is reflected in the approach taken by oversight and advisory groups in which consortiums have been formed to evaluate proposed therapeutics across a range of models in search of identifying not only promising therapeutic candidates but also the most appropriate scenarios in which to clinically test agents (83).

Importantly, the diversity of pathophysiological processes involved in neurotrauma has been increasingly recognized with recent studies investigating the role of non-neuronal cell types, such as astrocytes and microglia in neurotrauma, as well as the role of the neurovascular unit and associated blood-brain barrier (BBB). Emerging evidence with *in vivo* models has implicated these cell types and the BBB in outcomes following neurotrauma, with a particular emphasis on both microvascular and macroscopic components of vascular disruption (75, 96, 111, 114, 137, 186). This is particularly relevant clinically as macroscopic bleeds, such as epidural and subdural hematomas, may be managed neurosurgically, and microvascular/microscopic bleeds have been implicated in neurodegeneration associated with neurotrauma (111, 180).

Traumatic Brain Injury Effects on Neurons

Following TBI there are *immediate* primary effects and *sub-acute* secondary effects. Primary effects to the brain from TBI cause damage to neurons, glia, and the vasculature (Table 3). Secondary effects to the brain from TBI include: inflammatory responses (18), cellular stress (50), and apoptotic cascades (31). The physical forces of TBI can shear axons (140), break down plasmalemma (36), and rupture brain microvessels (10). When an axon is torn, or a cell membrane is broken from the external forces of TBI, the neurons can rapidly depolarize and activate voltage gated Ca^{2+} channels; thereby, increasing intracellular Ca^{2+} (58). Appropriate modeling of the primary effects of TBI will enable researchers to effectively study therapeutic options for the secondary effects.

Axonal injury has emerged as one of the most important pathological features of TBI. The rotational and acceleration/deceleration components of blast-induced TBI, commonly tears axons apart leading to a robust gliosis response and axonal degeneration (34, 56, 95). Axonal swelling and bulb formation are common morphological hallmarks observed following TBI and contribute to decreased action potential firing (44, 45). Axonal injury is a result of TBI and is evident in the white matter areas of the brain (94), and is the initial pathology in neurodegenerative diseases (3). Injury to axons is present in all severities of TBI and may represent a key hallmark of TBI for modeling purposes (77). Therefore, defining the neurodegenerative mechanisms induced by axonal injury would allow us to better model the injury and identify specific targets for neuroprotection.

The mechanical forces of brain trauma can also rupture microvessels (2). Specifically, the traumatic force causes an intracranial pressure spike which causes cerebral microvessels to burst (10). When an external force damages brain microvessels they can release cytotoxic levels of iron into the brain parenchyma (98, 125). Iron promotes Ca^{2+}-dependent mechanisms, which can stimulate cell survival, or trigger cell death depending on severity and duration of iron exposure (119, 120). Ca^{2+}-dependent mechanisms observed following TBI include the unfolded protein response (50, 146), proteasomal degradation (157), autophagy (20), apoptosis (32, 121), and neurodegeneration (155). TBI-induced intracellular Ca^{2+} increase also prompts reactive oxygen species (ROS) accumulation (30), triggers neuroinflammatory cascades (172), and can influence excitatory amino acids release (164). These secondary effects could potentially be targeted for therapy and warrant further investigation.

Vascular Effects of Traumatic Brain Injury

The external forces of a TBI induce vascular damage with both the initial insult and the ensuing secondary effects (149). It has been proposed that secondary effects can be therapeutically treated because they are driven by pathogenic alterations to signal transduction mechanisms. The vascular effects of TBI include vasospasms, hemorrhage, hypoxia inflammation and BBB disruption. Determining how TBI leads to cell death will provide a better understanding of the secondary effects and provide better therapeutic options. Targets could include BBB restoration after injury, or even using the injury to advantageously deliver drugs during a time window where the BBB is more permeable. This

approach will allow pharmacological investigation of mechanisms using drugs that do not easily cross the BBB.

Vasospasms, Subarachnoid Hemorrhage, Edema and Ischemic Hypoxia

Cerebral vasospasm can be a serious outcome of TBI due to the resulting cerebral hypoperfusion (72). TBI can trigger molecular mechanisms that rapidly mediate vascular tone (See Fig. 2) (29). One such mechanism is the release of a potent vasoconstrictor, endothelin-1, from damaged pericytes (46, 131). Parenchymal contusions and fever increase the risk for vasospasm (162). Up to 68% of individuals with TBI experience short duration vasospasms (87), which are especially common in soldiers exposed to blast TBI (6). Vasospasms resulting from TBI can lead to ischemic episodes, energy depletion and cell necrosis; in other words, an inability for brain cells to compensate for increased metabolic functional overload (97). Vasospasms are frequently associated with recurrent intracranial hypertension and subarachnoid hemorrhage (142, 181). Blast TBI, in particular, can cause cerebral vasospasms that last for more than 30 days and are associated with altered mental status (103). Severe vasospasm must be adequately treated to avoid permanent neurologic deficits or ischemic stroke (17). CT angiography is the diagnostic gold standard for vasospasm (156). Endovascular treatment and vasodilator therapy have both proven to be successful treatment approaches (11, 81).

Mild TBIs typically exhibit subdural hemorrhaging, while more severe TBIs can display traumatic subarachnoid hemorrhage—increasing the likelihood of diffuse axonal injury, edema, and skull fracture (109). CT imaging is the gold standard for diagnosis of subarachnoid hemorrhage severity (108). The recent establishment of the clinical course score has allowed for the improved monitoring of subarachnoid hemorrhage over time (23), and follow-up CT scans are only needed if new bleeding is a concern (150). TBI has the highest average years of potential life lost for all neurological disorders partly due to traumatic subarachnoid hemorrhage (147). Subarachnoid hemorrhage can lead to increased mortality, extended hospital stays, and central diabetes insipidus (67). Most importantly a likely complication of subarachnoid hemorrhage is cerebral vasospasm (51). A common treatment option for hemorrhagic change that infiltrates the ventricles is a ventriculostomy followed by ventriculoperitoneal shunt placement (28). In severe cases of TBI with subarachnoid hemorrhage where herniation is anticipated, decompressive craniectomy can be performed (90). Fortunately, most intracerebral hemorrhages are minor and will resolve on their own with time (93).

Brain edema following TBI can cause serious complications by limiting brain oxygen delivery and increasing intracranial pressure (124). The pressure increase is more common in children experiencing TBI than adults (48) Hounsfield unit values from brain CT mapped across an intracranial area can be used to accurately predict brain edema following TBI in children (82). A new imaging modality, shear wave elastography, has also been tested in rodents and gives an accurate representation of edema (184). Ulinastatin, a serine protease inhibitor, is currently being investigated for reduction of edema in rodents following TBI (35). Decompressive craniectomies are common in clinical practice (124). Decompressive craniectomies can prevent the intracranial pressure rise and potential herniation associated

with edema (22). Decompressive cranectomies are not without risk and a recent report showed 83% of patients developed hygromas and 50% of patients developed aseptic bone resorption (133). Continued work is necessary to find viable alternatives for the treatment of edema.

A primary complication of ischemic hypoxia following TBI is hemispheric hypodensity (53). Ischemic hypoxia can cause the toxic release of hypoxia-inducible factor 1-alpha (159), leading to inflammatory cascades (139). Outcomes from the inflammatory cascade include axonal injury and central myelin damage (178). Point in time monitoring revealed that ~10% of TBI patients experience some ischemic hypoxia (128). Ischemic hypoxia following TBI is associated with poorer functional independence measures (37). Applying techniques for brain oxygen optimization in clinical care has produced the most successful treatment results (105). Continuous neurophysiologic recordings are imperative for appropriate patient management (8). In extreme circumstances, red blood cell transfusion may be required (86). Experimental treatment with mild hypothermia has produced profound preclinical neuroprotection in a variety of TBI models (54, 113) and initial human clinical trials (92) have proved promising.

Blood-Brain-Barrier Disruption: Neuroinflammation and Reactive Oxygen Species Formation

The neurovascular unit can become damaged with TBI. The neurovascular unit controls blood flow to the brain, nutrient delivery, and maintenance of BBB integrity (62). The BBB is an anatomical structure that plays a key role in normal brain physiological regulation. The BBB is composed in part of astrocyte podocytes, a basement membrane, pericytes, and the endothelium connected with tight junction proteins. (14). With regard to TBI, little is known about the role of BBB disruption in disease pathology (7).

Neurovascular inflammation can lead to the formation of ROS (1). Neuronal injury can occur when ROS exceeds the brain's defense and clearance mechanisms (4). ROS are generated from mitochondrial damage as well as the nicotinamide adenine dinucleotide phosphate-oxidase system at the plasma membrane (188). ROS can eventually contribute to disruption of the BBB, edema, and neuroinflammation (138). ROS contribute to downregulation of tight junction proteins at the microvessel interface (2). In addition, formation of ROS ultimately triggers glial cell activation producing additive injury to the brain parenchyma (149). Oxidative stress stimulates the release of inflammatory factors: interleukin-1beta, tumor necrosis factor-alpha, and transforming growth factor-beta (1). ROS also disrupt the vasculatures ability to self-regulate and constrict (43). Ultimately, ROS depression of cerebral metabolism can have long-term consequences manifesting in chronic neurodegeneration and behavioral abnormalities (173). Proton therapy through use of hydrogen infused saline can limit the damage to endothelial cells by preventing BBB disruption and the formation of ROS (74). Another means of limiting oxidative stress is maintenance of mitochondrial homeostasis (130). Uncoupling the mitochondrial oxygen cascade early following TBI has proved beneficial in limiting ROS formation and calcium overload (129). Cerebral microdialysis has been proposed as a diagnostic test for detecting the concentration of free radicals within the brain (65).

BBB disruption is common amongst TBI patients. Approximately 44% of patients who experience severe TBI have BBB breakdown (66). In addition to being effected by ROS, BBB breakdown itself can lead to enhanced neuroinflammation and the formation of ROS (See Fig. 3) (1). Damage to the BBB also leads to the release of neurotoxic proteins into the brain parenchyma (63, 64). Prolonged inflammation can eventually contribute to myelin loss (55). Omega-3 supplementation in rodents can limit BBB breakdown by inhibiting matrix metalloproteinase 9 activity (153). Targeting estrogen receptors may also be a viable therapeutic target due to decreased BBB permeability following TBI in female rats (12).

Tight junctions between endothelial cells maintain vascular integrity, but are often sheared following TBI (183). Blast TBI, in particular, causes a rapid blood pressure spike leading to disruption of the tight junction proteins at the BBB (186). Alternatively, astrogliosis can also lead to BBB modulation over time (100). Astrocytes support endothelial cell function at the neurovascular unit and direct control of permeability (115). Astrocytes and neurons help support the basement membrane surrounding the endothelial cells (161). Podocytes from astrocytes contain vascular endothelial growth factor, which can be released when the BBB is damaged (154). The biomarker, pituitary adenylate cyclase activating polypeptide, offers promising diagnostic potential for determining BBB disruption (25). Currently, digital imaging quantification is the primary method of diagnosis (21).

Secondary Effects of Traumatic Brain Injury

Shortly after TBI, biochemical mechanisms assist in repairing cells that survive the primary insults of TBI. On the other hand, those same mechanisms can cause injured cells to die in order to preserve energy for other cells undergoing the energy-dependent repair process. The brain plays a game of *checks and balances* (using energy as currency) to determine which neuronal cells are *worth* saving after TBI. Programmed cell death, or apoptosis, is a necessary mechanism following neuronal injury and may be beneficial to the CNS. However, the resulting effects from an apoptotic event can cause further damage within the brain through the process of neuroinflammation (1).

Even after mild TBI neuronal apoptosis is evident around perivascular regions, indicative of cerebral vascular injury (2). Brain damage from TBI was reported to be associated with decreased mitochondrial membrane potential and increased release of cytochrome C in rodents—both indicative of cellular apoptosis (179). Cleaved-caspase-3 and caspase-3 enzyme activity was reportedly increased in TBI animals versus control (32). Models of TBI have also shown upregulation of caspase gene expression (88). These results indicate that caspase activity contributes to brain tissue loss, and that caspase inhibition may prove to be an effective treatment strategy for TBI.

The secondary effects of TBI can be attenuated with therapeutic interventions given at the right time following neurotrauma. The series of molecular, neurochemical, cellular, and pathophysiological mechanisms resulting from TBI can be targeted with drug therapy designed to manipulate the signaling mechanisms of various cellular and subcellular processes. The secondary mechanisms of TBI include: neuroinflammation, oxidative stress, endoplasmic reticulum (ER) stress, glutamate excitotoxicity, calpain processing, apoptosis

and tau hyperphosphorylation (see Fig. 4). The timing and duration of each event is dependent on the type and severity of the TBI in question; therefore, each treatment strategy could be individualized to the specific type of TBI. The aforementioned secondary mechanisms are described in more detail below.

Endoplasmic Reticulum Stress, Excitotoxicity and Calpain Processing

TBI occurs over a very short duration, and is often mild in nature, compared to other neural injuries. TBI often goes undetected and chronic deficits often take years to develop (126, 127). TBI harms neurons by perturbing Ca^{2+} homeostasis in an energy-independent process. The damage done by TBI makes membranes more permeable to Ca^{2+} and even to extracellular proteins (10). What is known is that neural injury, in particular TBI, causes massive neuronal depolarization and a resulting large influx of Ca^{2+}. Cells which withstand the immediate physical injury from TBI, will have disrupted intracellular Ca^{2+} levels and oxidative stress (104). As described previously, oxidative stress can induce neuroinflammation, which is known to cause neuronal death and is associated with chronic disease pathology (27).

ER stress has been implicated in a variety of TBI models (19, 50, 151). ER stress then triggers the unfolded protein response (UPR) as an endogenous means of cellular repair. TBI-induced Ca^{2+} perturbations cause proteins to unfold, and when the ER becomes overwhelmed and struggles to re-fold the unfolded proteins, the UPR ensues (89). In the short-term, the UPR can promote cell survival through three separate mechanisms: (1) attenuation of global protein translation, (2) upregulation of stress response genes, and (3) degradation of unfolded proteins (118). Apoptosis and neurodegeneration are the end-game consequence if ER stress and the UPR are prolonged (40, 117). The UPR has only recently been addressed by TBI investigators because of its new found link to neurodegeneration (116). The timing and duration of the UPR and how exactly it develops into a neurodegenerative phenotype warrants further investigation.

Another secondary mechanism of TBI also involving calcium disruption is glutamate signaling and the phenomenon known as excitotoxicity. TBI triggers a massive depolarization which promotes excessive glutamate release (79). This disrupted regulation in glutamate signaling plays a role in the pathophysiology of TBI through the initiation of secondary injury cascades (26). High extracellular glutamate promotes high levels of intracellular Ca^{2+} following TBI (174). Secondary injury cascades initiated by glutamate receptors and the disruption of Ca^{2+} homeostasis will activate calcium-dependent proteases, disrupt energy-dependent processes, and produce oxidative stress (49, 187). Using drug therapy to regulate glutamate release may help to attenuate the secondary effects of TBI exposure.

Loss of microvascular integrity and BBB compromise are often related to brain injuries involving Ca^{2+} perturbations. In brain trauma models acute and sustained activation of the calpain family of proteases has been implicated in neuronal death and TBI (99). Calpains are acutely activated following TBI within the injured hippocampus and frontal cortex (144). Calpain activation has been observed in degenerating dendrites and atrophic neurons after TBI, providing evidence that calpain activation may participate in neuronal loss after

neurotrauma (69). Activation of Ca^{2+}-dependent proteases, such as calpain, is a predicted outcome of membrane depolarization and loss of Ca^{2+} homeostasis. Its regulation of cytoskeletal dynamics contributes to plasticity (57) and is consistent with injury deficits in axonal architecture and disruption of synaptic plasticity (39). Animals exposed to TBI can exhibit damaged axonal hillocks, suggesting detrimental changes to their synaptic function (13). Moreover, calpain-dependent processes in TBI models have been suggested to attenuate overall electrophysiological responses (132) and invoke more neuronal death (158).

Chronic Effects of Traumatic Brain Injury

Alteration of cerebral blood flow has been linked to delayed neuronal death in the contusion penumbra (47). Hemorrhagic shock causes immediate reduction in mean arterial pressure with continued apoptosis over time due to perpetual lack of perfusion (41). At extended time points TBI continues to cause disruption in the autoregulation of cerebral vasculature (137). A primary mechanism is temporal changes in V1a vasopressin receptors (171). Vasopressin receptor stimulation contributes to cerebral edema that leads to increased intracellular uptake of H_2O from the blood (107). The disruption in vascular supply can contribute to perivascular nerve damage (177). In addition, systemic hypotension can contribute to chronic neurodegeneration (101). Persistent activation of calpain proteases is another mechanism by which persistent hypotension leads to neuronal pathology (123). Calpains cleave the contractile components of vascular smooth muscles inhibiting their ability to contract (122).

Not surprisingly, cerebral hypotension has been associated with neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (91). A genetic mutation in Neurogenic locus notch homolog protein 3 increases the risk for small vessel disease following TBI and has been linked as well to Alzheimer's disease (106). Interestingly, microvasular defects may be linked to Alzheimer's disease due to the increased incidence of neurological disease in TBI patients (41). Preventative treatment approaches are limited, but a few experimental techniques appear promising. Closely regulated hypothermia therapy can prevent chronic microvessel changes and contustion expansion (190), while compressing the internal jugular vein has also been shown to mitigate axonal injury and vascular disruption (167, 176). Because TBI cannot be predicted a post-injury therapy that mitigates the detrimental chronic effects is therefore needed.

Tau protein hyperphosphorylation and amyloid beta oligomers are well-known markers of neurodegenerative disease. TBI has been shown to hyperphosphorylate tau protein (56), and produce amyloid beta oligomers (166), through mechanisms that are not completely understood. These neurodegenerative factors are activated immediately following TBI and can advance profoundly over time (see Fig. 5). The cellular repair mechanisms associated with these factors are more drawn out, and may contribute to neurodegenerative disease progression and brain matter loss (68, 160). Cortical tissue loss and white matter atrophy resulting from TBI are associated with cognitive deficits (70). Cognitive deficits in rodents have been observed at chronic time points following TBI (136), indicating neurodegenerative disease progression in rodent models of TBI. How the primary effects of

TBI manifest into chronic disease states is an area of ongoing investigation. The brains of professional athletes and military veterans are currently being examined with new imaging modalities to discover underlying causes behind neuropsychiatric symptoms such as post-traumatic stress disorder, chronic traumatic encephalopathy, and Alzheimer's disease (165). Moving forward, TBI research needs to emphasize vascular effects, glial responses and resulting neurodegeneration.

Future Directions

Primary and secondary mechanisms of TBI are undergoing continued investigation. What remain to be determined are the tertiary mechanisms that mark the transition from acute injury to chronic neurodegeneration. Studying the broader role of cerebrovascular changes and how these changes interact with neurons and glia must be carefully considered in future investigations. Chronic mechanisms might very well deal with the vasoregulation of cerebral vessels and how microvessels respond to inflammatory markers. In addition, the theory of 'inflamm-aging' is likely to take precedence, because aged neurons and glia respond differently to injury-induced stimuli. How these aged cells interact with concurrently aged and previously injured vascular system has not been fully elucidated. Chronic disease states are subject to the effects of both age-related comorbidities and aging itself.

Future studies must incorporate a broader approach utilizing more representative models. Animal models of TBI have been developed, but therapeutics have not yet translated successfully to the clinic. Therefore, an increasing need exists for the development of more *clinically relevant* TBI models, and the use of advanced MRI and PET imaging to map the dynamics of brain injury responses. This will enable us to devise more effective therapeutic interventions for the amenable secondary effects. Further studies utilizing BBB compromise following TBI could be advantageous for pharmaceutical researchers attempting to alter brain mechanisms. In addition, the balance between protein phosphatases vs. kinases will need to be heavily investigated. Marking the transition to amyloidopathy and/or tauopathy will provide important insight into effective treatment windows. More importantly, understanding chronic mechanisms of injury will allow a more tailored and individualized approach to patient care.

Conclusion

TBI has profound and measurable effects on cerebral vasculature. Due to the variable expression of TBI in the hospital setting, as characterized by the GCS and advanced imaging, individual treatment approaches are a necessity. Understanding complication of TBI such as subarachnoid hemorrhage, vasospasm, and ischemia are necessary in appropriate patient management. Mechanism of injury such as acceleration/deceleration, axonal damage, and BBB disruption are also important to keep in mind. The most promising targets include secondary injury cascades such as oxidative stress, neuroinflammation, and ER stress. Future approaches may target chronic mechanisms involved in the development of neurodegenerative disease. Better pre-clinical models are necessary to map more complex systems such as glutamate toxicity and calpain mediated cell death. Moving forward, treatment of secondary mechanisms affecting vascular dynamics is critical both acutely and

chronically. Consideration of age and comorbidities remains a constant factor in any form of neuronal injury. Neurodegeneration and cellular apoptosis are common following TBI, but improved management acutely can prevent the common sequelae of symptoms. In order for successful therapeutic options to translate to the clinic, TBI research needs to move away from the common neurocentric approach and change focus towards vascular effects, glial responses and neurodegeneration.

Acknowledgments

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Cross-References & Further Reading

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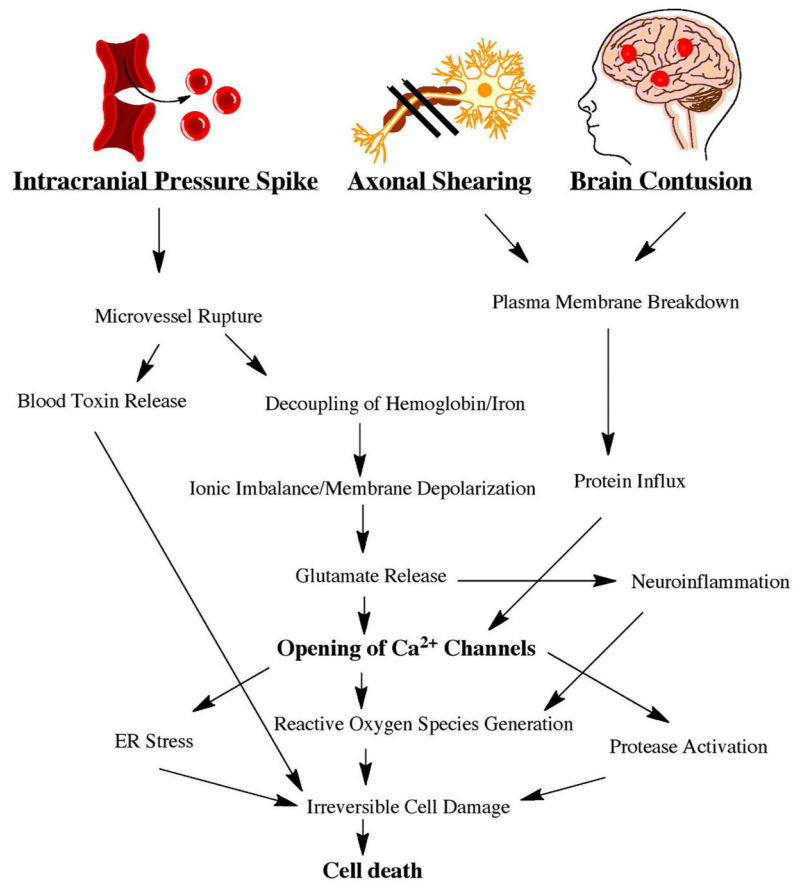
Figure 1.
Pathophysiology of Neuronal Cell Death Following Traumatic Brain Injury. An intracranial pressure spike, axonal shearing, and brain contusion contribute to secondary mechanisms that lead to an increase in Ca^{2+} channel opening. The generation of reactive oxygen species can ultimately contribute to cell death.
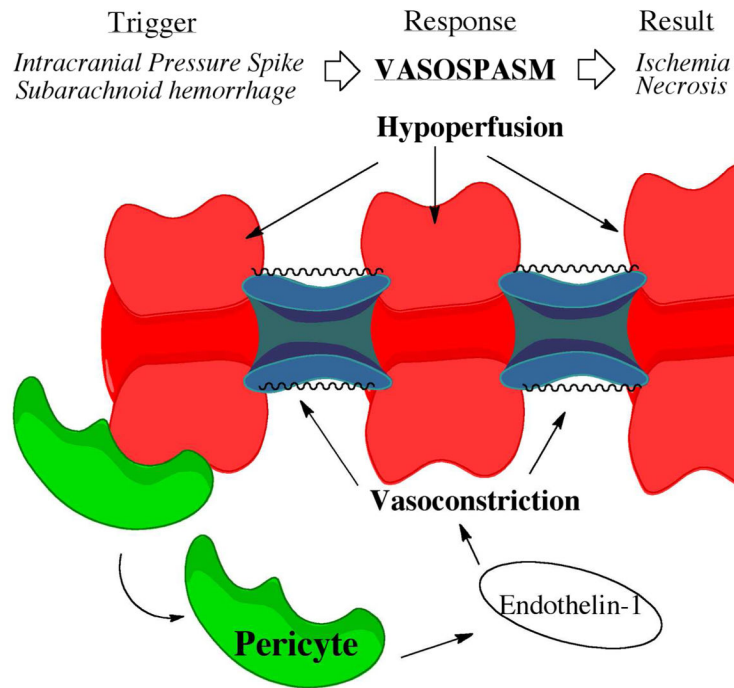
Figure 2.
Depiction of a Vasospasm Resulting from Traumatic Brain Injury. Vasospasm can be triggered by subarachnoid hemorrhage or blood pressure spikes. Pericytes near vessels release endothelin-1, which triggers vasoconstriction.
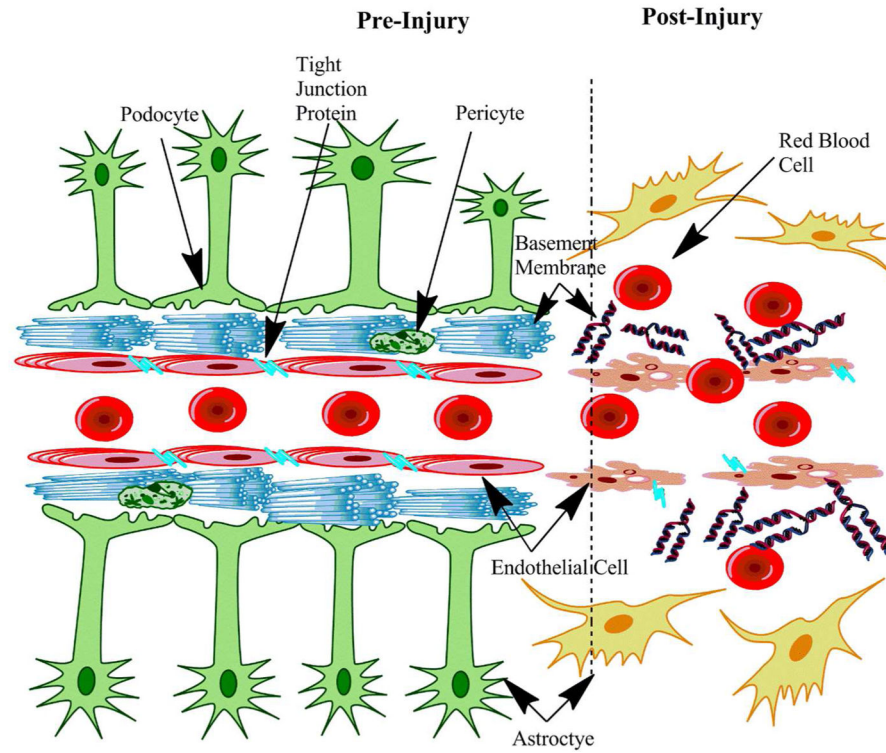
Blood Brain Barrier

Figure 3.
The Effects of Traumatic Brain Injury on the Blood-Brain-Barrier. TBI can cause disruptions of tight junction proteins connecting endothelial cells. Astrocytes can undergo astrogliosis and the basement membrane can become disrupted. Ultimately these changes increase the likelihood of red blood cell extravasations.
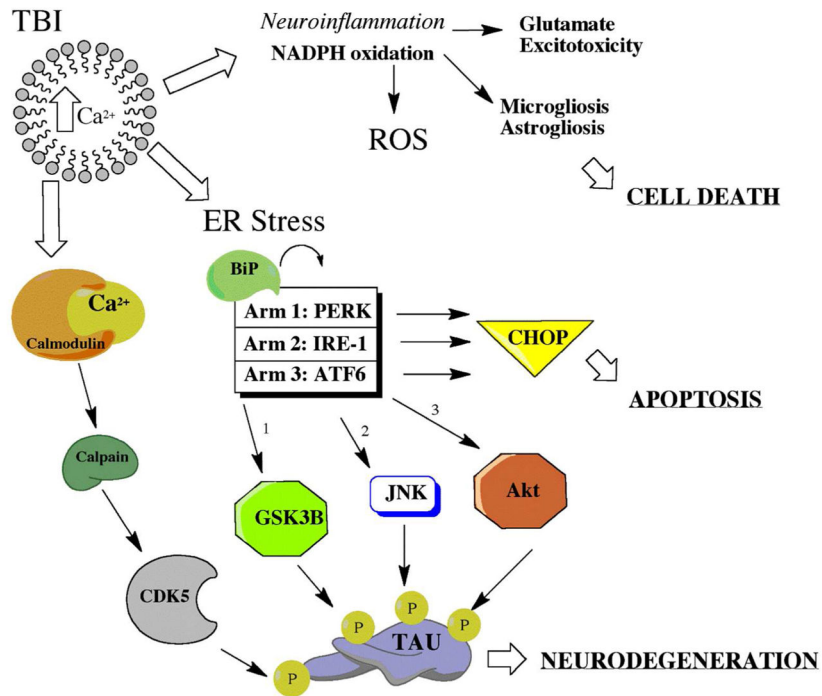
Figure 4.
Complex Interplay of Secondary Mechanisms Following Traumatic Brain Injury. Secondary mechanisms of injury have multiple known effects. A few included are cellular necrosis, apoptosis, neurodegeneration, and tauopathy. Timing of activation and pathway connections are still being teased out with preclinical models of TBI.
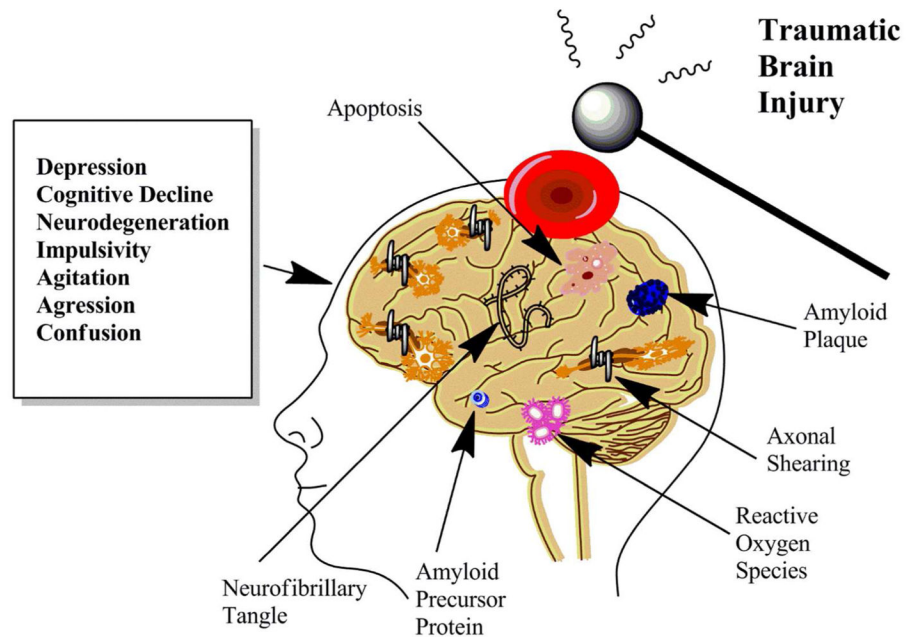
Figure 5.
The Chronic Effects of Traumatic Brain Injury. Some individuals experiencing TBI are more susceptible to chronic effects than others. Environmental and genetic factors play a role. Pathologic changes that may develop include neurofibrillary tangles, axonal shearing, and amyloid plaques to name a few. Neuropsychiatric symptoms may also develop such as depression, impulsivity, cognitive decline, and confusion. This area of chronic deficits following TBI is a topic of growing importance receiving renewed research focus and funding.

Table 1

Abbreviations

TBI	Traumatic Brain Injury
GCS	Glasgow Coma Scale
BBB	Blood Brain Barrier
ROS	Reactive Oxygen Species
NMDA	N-methyl-D-aspartate
ER	Endoplasmic Reticulum
UPR	Unfolded Protein Response
CT	Computerized Tomography
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
CNS	Central Nervous System

Table 2

Forms of Traumatic Brain Injury

TYPE	DESCRIPTION	ANIMAL MODEL	REFERENCES
Blast Traumatic Brain Injury	Blast energy generated from an explosive device contacts the skull and causes acceleration/ deceleration injury	Blast model with short driving section for clinical accuracy	Alford et al., 2011, Arun et al., 2013, Cho et al., 2013, DeWitt et al., 2009, Turner et al., 2013
Closed Head Impact	Blunt object strikes the skull without fracturing the bone	Impact-acceleration model	Li et al., 2013, Skandsen et al., 2010, Turner et al., 2012
Concussion and subconcussion	A temporary state of shock due to a violent blow to the head	Controlled closed-head impact with helmet	Angoa-Perez et al., 2014, Bailes et al., 2013, Bailes et al., 2014, Petraglia et al., 2014
Contusion	An area of injured brain where blood capillaries have been ruptured	Fluid Percussion model	Brodhun et al., 2001, Greer et al., 2013, Truettner et al., 2007
Falls	Rapid impact between ground or object with skull due to effects of gravity	Weight drop TBI model	Albert-Weissenberger and Siren, 2010, Asl et al., 2013
Penetrating injury	Fragment from shrapnel or blunt object that fractures skull and causes protrusion into brain parenchyma	Controlled cortical impact with craniectomy	Begum et al., 2014, Clark et al., 1997
Shaken baby syndrome	Abusive head trauma due to rapid acceleration and deceleration of skull when shaken	Controlled cortical impact with intact skull	Dileonardi et al., 2009, Foster et al., 2014, Larner et al., 2004
Spinal Cord Injury	Injury to any part of the spinal cord that leads to inflammation and secondary effects on the CNS	Spinal impact model	Faden et al., 1989, Roth et al., 2014, Xiong et al., 2013

Table 3

Neurotoxic Events in Traumatic Brain Injury

Primary	Acute Phase Physiology	References
Intracranial Pressure Spike Hemorrhage	Vascular pressure spike bursts brain microvessels; Brain hemorrhage releases blood-borne toxins and iron into parenchyma	Arun et al., 2012, Abdul-Muneer et al., 2014
Axonal Shearing	External forces physically tear axons; impairs axonal transport and synaptic function	Raghupathi et al., 2004 DiLeonardi et al., 2009
Vasospasm Ischemia	Blood flow disrupted via uneven constriction and dilation in brain vasculature	Izzy et al., 2014 Foster et al., 2014
Secondary	**Sub-Acute Phase Physiology**	
Reactive Oxygen Species Oxidative Stress	Mitochondria Ca^{2+} imbalance, mixed with energy failure and NADPH oxidation, triggers oxidative stress and neuronal cell death	Deniaud et al., 2008 Cho et al., 2013
Neuroinflammation	Cytokine release from glial cells promotes cytotoxic effects through macrophage differentiation	Chodobski et al., 2011 Roth et al., 2014
Blood-Brain-Barrier Disruption	Release of Blood toxins into brain parenchyma promoting inflammation and neuronal death	Abdul-Muneer et al., 2013 Alves 2014
Endoplasmic Reticulum Stress	Overabundance of unfolded proteins and intracellular $Ca2+$ triggers the unfolded protein response	Truttner et al., 2007, Rubovitch et al., 2011, Larner et al., 2004
Glutamate Excitotoxicity	Reduced glutamate uptake activates NMDA receptors	Bullock et al., 1998 Katayama et al., 1990
Protease Activation	Intracellular Ca^{2+} binds to calmodulin forming calpain kinase; calpain activation cleaves p35 into toxic p25	Ringger et al., 2004 Huh et al., 2006
Apoptosis	Intrinsic pathway activation both in mitochondria and Endoplasmic reticulum; Ca^{2+} dependent processes	Clark et al., 2000 Nakagawa et al., 2000
Chronic	**Chronic Phase Physiology**	
Tau Phosphorylation	Tau kinase/phosphatase imbalance leads to hyperphosphorylation of tau	Goldstein et al., 2012 Begum et al., 2014
Amyloid Beta	Increased amyloid precursor protein promotes the toxic oligomerization of amyloid beta	Smith et al., 2003 O'Connor et al., 2008
Neurodegeneration Cognitive deficits	Tau hyperphosphorylation forms neurofibrillary tangles near perivascular regions; promoting neurodegenerative disease and cognitive decline	Mckee et al., 2009 Bailes et al., 2014