

Review

Improving on Laboratory Traumatic Brain Injury Models to Achieve Better Results

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Abstract

Experimental modeling of traumatic brain injury (TBI) in animals has identified several potential means and interventions that might have beneficial applications for treating traumatic brain injury clinically. Several of these interventions have been applied and tried with humans that are at different phases of testing (completed, prematurely terminated and others in progress). The promising results achieved in the laboratory with animal models have not been replicated with human trails as expected. This review will highlight some insights and significance attained via laboratory animal modeling of TBI as well as factors that require incorporation into the experimental studies that could help in translating results from laboratory to the bedside. Major progress has been made due to laboratory studies; in explaining the mechanisms as well as pathophysiological features of brain damage after TBI. Attempts to intervene in the cascade of events occurring after TBI all rely heavily on the knowledge from basic laboratory investigations. In looking to discover treatment, this review will endeavor to sight and state some central discrepancies between laboratory models and clinical scenarios.

Key words: traumatic brain injury, secondary insults, animal models

Introduction

Scientist and medical practitioners conduct research on TBI for two main reasons; Firstly, TBI is the number one cause of disability and death in people at the prime of their lives (under 45 years of age) especially in industrialized countries. TBI is often caused by road traffic accidents. Each fatality comes with different levels of brain damage to the survivors ranging from mild, moderate to severe brain damage¹. Even though TBI is a major socioeconomic and medical problem, its pathogenesis and mechanism is not fully understood because it is extremely challenging to re-enact the proceedings that led to the primary and secondary brain insults^{2,3}. Comparatively, TBI is quantifiable and performed under controlled environments in the laboratory.

Secondly, research conduction is still ongoing and will continue because although a whole lot of

neuro-protective agents have been studied and researched, the very ones that have made or shown promises in laboratory models have failed to provide consistency and strikes in human trials⁴⁻⁷. Evaluating and testing the effectiveness of therapeutic agents in laboratory models will hence continue to be an important precursor to their functions in humans. This review highlights the contributions of different types of animal models especially their strengths in unraveling the neuropathological features of TBI and their weakness that has slowed the translation of experimental results at the bedside. Considerably there has been a lot of investigation into TBI with animal models but no novel therapy has been successfully translated from the bench to the clinic. Despite the fact clinical trials have well described limitations that might be contributing factors to these

failures, several modeling limitations account for the lack of therapeutic progress from bench side to the bedside. TBI models usually omit one or more critical and clinically essential pathophysiological feature. In this review, several important clinical pathophysiologic factors in TBI, namely secondary insults (i.e., hypotension and/or hypoxemia), coma, and aspects of standard neuro-intensive care monitoring and management strategies (i.e., intracranial pressure [ICP] monitoring and ICP-directed therapies, sedation, mechanical ventilation, and cardiovascular support) requiring incorporation into animal models are discussed.

Classification of brain injury

Traumatic brain injuries are classified on different levels. In this article we will categorized them from the clinical point of view as either focal or diffuse injuries⁸. A description concerning brain injuries pertains to all kinds of brain injuries in different environments both civilian and military. Both diffused and focal brain injuries have their distinct features at the clinical level, which are usually visible with the help of radiology. Focal brain injuries for example can be easily identified by using standard imaging modalities such as CT and MRI. From table 1, focal brain injury is usually categorized based on the location of the bleeding with respect to the brain: within the brain (intracerebral hematomas; tissue tears), on the surface of the brain (acute subdural hematoma; subarachnoid hemorrhage; extradural hematoma), or in the cortical gray matter (cerebral contusion). All these kinds of focal brain injuries can be observed in severely or moderately injured population. Nevertheless, in mild head injuries the only focal brain injury that appears is subarachnoid hemorrhage. However, because mild brain injuries with subarachnoid hemorrhage are rare, it is appropriate to state that mild brain injuries are predominantly classified as diffuse injuries. Diffuse brain injuries are defined as injuries not located to just one area of the brain but spread or distributed all over the brain. A common component or a typical feature of diffuse brain injuries is brain swelling that appears over time following injury^{9, 10}.

Consequences of primary traumatic brain injury

Loss of consciousness

Acceleration of human head produces different levels of injury to the brain. An important factor in determining the level of neurological abnormality is the duration of the acceleration; longer periods of acceleration will result in traumatic coma whilst

shorter periods will usually produce subdural hematoma. Loss of consciousness is a feature of all categories of traumatic brain injury (mild moderate or severe injury). In mild injury loss of consciousness persist for few minutes however in severe injury consciousness is lost from days to weeks. The duration of loss of consciousness is also directly related to reactive axons.

Table 1. Brain injury classification

Brain Injuries				
Primary traumatic brain damage (neural or vascular [or both])	Diffuse	Diffuse axonal injury (DAI)		
		Diffuse vascular injury (DVI)		
	Focal	Vascular injury resulting in	Intracerebral hemorrhage	
			Subdural hemorrhage	
			Extradural (epidural) hemorrhage	
		Axonal injury		
	Contusion			
Laceration				
Secondary traumatic brain damage	Diffuse	Diffuse hypoxic-ischemic damage		
		Diffuse brain swelling		
	Focal	Focal hypoxic-ischemic injury		
		Focal brain swelling		

Contusions

Most TBI occur with contusions and a brain with contusions confirms the presence of brain injury as result of trauma. Contusions are also kinds of vascular injury particularly to small blood vessels. Different degrees of contusions exist following brain injury. Amongst them are those at right angles to the cortical surface. Contusions have several effects on the affected brain, typically it affects gyral crest and usually move towards a necrotic area including the sub adjacent white matter. Brain injury contusions have characteristics of continual expansion due to progressive hemorrhage, necrosis and edema. They are also referred to as coup contusions because they often occur beneath the impact site¹¹⁻¹³. Other abnormalities that usually occur with brain contusions are skull fractures and lacerations where there is typical disruption of brain parenchyma. Any contusions that occur opposite to the impact site are termed contrecoup contusions.

Hemorrhage

Hemorrhage occurs in traumatic brain injury because of the tearing of blood vessels at the point of

impact. However, there are also delayed post-traumatic hematomas that occur several hours after initial impact, which cause herniation and intracranial pressure elevation. Following brain injury, different kinds of bleeding may occur in different parts of the brain. The most common of vascular injury is subarachnoid hemorrhage, which is bleeding into the subarachnoid space. Subarachnoid hemorrhage is usually minor and may easily be absorbed into the cerebrospinal fluids. However, they can easily evolve into a space-occupying lesion.

Again, rupturing of bridging veins after an inertial acceleration of the brain leads to subdural hemorrhages that may extend over an entire hemisphere. Another frequent form of bleeding following head impact is intra-ventricular hemorrhage coupled with hematomas in the brain substance (intracerebral hematomas). All over the basal ganglia and central white matter can also be found hemorrhages called the intraparenchymal hematomas.

Lastly are the petechial hemorrhages that occur in diffuse vascular injury that leads to death within minutes after impact. Hematomas together with brain swelling contribute mainly to increase intracranial pressure, distortions, shifts and eventually herniation of brain parenchyma. Generally, edema occurs around brain contusions and intracerebral hematomas.

Axonal injury

Traumatic axonal injury can be categorized as primary axotomy or secondary axotomy. Primary axotomy occurs when there is complete resection of neural tissues along with glial cells and blood vessels whereas secondary axotomy occurs in less severe mechanical insults. In terms of duration, primary axotomy is an instantaneous process unlike secondary axotomy which takes many hours to days to occur¹⁴. Research has shown that between the period of primary axotomy and secondary axotomy lies a window of opportunity for therapeutic intervention^{15, 16}. The help of immunocytochemistry can do detection of axonal injury in TBI where antibodies are deployed to transport proteins such as neurofilament protein, amyloid precursor protein (APP), and synaptophysin. APP staining is the most sensitive technique for axonal injury¹⁷ and it's able to detect axotomy within minutes after impact with an added advantage of minimum background interference since uninjured axons do not stain with APP¹⁸⁻²². Traumatic axonal injury displays several molecular changes to the brain. Early changes after axonal injury include influx of calcium either through receptor-mediated,

voltage-mediated or transient defects in the plasmalemma. Calcium overload causes enzymes such as protease and gene activation manifested as axonal swelling. Complete axotomy occur and become apparent when wallerian degeneration occurs^{16, 23}. Microglia reaction also occurs following axonal injury. Mechanical and ischemic injury contributes or combines to make up the total amount of axonal injury in a brain at any particular time. Staining techniques are however unable to distinguish between these two factors making up total axonal injury²⁴.

Animal models and their types

To understand the basic elements of how the central nervous system responds to injury and mechanical inputs animal models have been the most reliable and significant techniques employed by researchers. The ultimate aims of most or all animal models is to reproduce and replicate as much as possible a clinical TBI in a laboratory setting depicting the morphological, biochemical, molecular and behavioral changes seen after TBI. There is a considerable amount of literature depicting several years of research that has been used to define the scenarios causing TBI in the laboratory using animal models. Research using animal models span on all scales from population-based surveys to the molecular level, all in an attempt to determine the significant signatures of injuries. To be able to maximize the efficacy and achieve useful outcomes and results from animal models for proper translation to the bedside certain clinical and salient points need to be considered and put into consideration. First of all the work must start from the clinical situation and environment to be able to define the incidence and prevalence of injury.

Finally and most importantly, all efforts and desire should be made to translate the laboratory outcomes to find effective countermeasures against insults caused by traumatic brain injury. Enormous amount of animal models of TBI have been developed since the early 1980s using different kinds of species including cats, dogs and nonhuman primates. Recent animal models of TBI have been developed using rodents and remain the most widely adopted species in preclinical studies. Rodents are dominating the TBI field of studies because of several reasons such as ethical issues elimination and easy postsurgical needs. Carry out research with rodents are also cost effective and simple compared to larger animals and human models. At present, several types of animal models of TBI exist, and the strengths and weakness of each model are discussed in table 2.

Table 2. Animal models of TBI

ANIMAL MODEL	STRENGTH	WEAKNESS
Repetitive Brain Injury Model	Effective in characterizing the molecular and cellular bases of repetitive injury.	Do not replicate the head movements, both the rotational and angular acceleration that are common in sports related injury ¹¹⁶
Blast Injury Model	Mimics the real morphological damage seen in the personnel who sustained TBI from the military conflicts results in the unique pathological features seen in blast-induced mild TBI	Do not replicate the posttraumatic seizures, a common consequence of blast - induced mild TBI seen in humans
Penetrating Ballistic-Like Brain Injury Model	helpful in characterizing the immediate and subacute (up to 7 days) changes in intracranial pressure seen after brain trauma ¹¹⁷ . Captures several unique temporal aspects of a ballistic brain injury and may be a highly relevant model of moderate-to severe brain trauma for mechanistic studies. PBBI causes extensive intracerebral hemorrhage on the primary lesion site owing to the penetrating nature of the injury and the temporary cavity that it forms to truly model gunshot wound injuries to the brain.	Primary disadvantage concerns the expertise required of the investigator performing the procedure
Weight-Drop TBI Model	mimics closed head injury with accompanying concussion and contusion, a common type of TBI in humans. Inexpensive, easy to perform, and capable of producing graded diffuse axonal injury.	relatively high variability in injury severity that is produced
Controlled Cortical Impact Injury Model	time, velocity, and depth of impact can be controlled, making it more useful in studying the biomechanical changes that occur following TBI ¹² . lack of rebound injury because the impact delivered by the device is gravity driven ¹¹⁸ .	only unilateral damage is produced, with rare involvement of the contralateral cortex
Fluid Percussion Injury Model	replicate the common pathophysiological features seen in human TBI ¹¹⁹ . Highly reproducible, and the investigator can regulate the severity of TBI.	does not produce skull fracture and results mainly in focal injury, it cannot replicate moderate-to severe TBI in humans where skull fractures and contusions across multiple brain regions are present ¹²⁰ .

Physiological changes observed with animal model TBI

Animal models of TBI causes several physiological changes that are typical of clinical changes observed in human TBI. Categorically changes observed with animal models of TBI can be considered as either acute systemic, cerebrovascular, neurological or anatomical after injury. Acute systemic changes observed in some animals immediately after low levels of injury include an increased mean arterial blood pressure that remains at higher levels for the first 10-15minutes²⁵ compared to the mean arterial blood pressure before injury. However, for a higher level of injury in some TBI models the laboratory species usually become hypotensive within an hour post injury. Nevertheless, in certain species tachycardia or bradycardia may be observed in the first minutes after injury.

Another prognostic factor that changes and is affected acutely in animal models is intracranial pressure. Intracranial pressure rises transiently within the first 20minutes to about 50mmHg²⁵. Traumatic brain injury leads to an increase in central nervous system activity that will eventually compel plasma glucose levels to be elevated exponentially. Increased

glucose levels tend to proportionally increase its utilization in the ventral tegmental nucleus of Gudden and the areas of the anterior thalamic nucleus²⁶. These areas with increased metabolism are considered to be exhibiting functional changes of neural activity after injury.

A vital parameter that also increases transiently after traumatic brain injury is cerebral blood flow (CBF). The brain's inability to auto regulate CBF is related to endothelial lesions that appear after injury. Activation of processes that leads to Synthesis of prostaglandins and release of free radicals after mechanical injury to the brain plays a major role in these microvascular abnormalities. Studies have revealed also a transient break down in the blood brain barrier in vital anatomical parts of the brain especially in the brain stem regions after brain injury^{27, 28}. Break in blood brain barrier allows for hemorrhages to occur as deep as pontomesencephalic junction²⁵. At the clinical level measurements such as electroencephalography (EEG) are observed to vary after traumatic brain injury compared to the uninjured brain. EEG amplitude depresses acutely coupled with pupillary dilatations and apnea after brain injuries. The above physiological changes give insights into the respiratory, pulmonary, cardiovascular and cerebrovascular consequences of

traumatic brain injury. Cerebrospinal fluid analysis following brain injury shows increased levels of acetylcholine which is a cholinergic neurotransmitter²⁹. The clinical state of a patient depends on the levels of acetylcholine.

Significance of TBI animal models

By all standards our knowledge of the pathophysiology of TBI has been widened and broadened because of the development of clinically relevant experimental models of TBI³⁰. Below we will elicit some of the pathophysiological findings that experimental TBI models have been able to reveal to scientist and researchers.

- Following TBI there be will be long term impairments of cognitive and neuromotor function³¹.
- There is a relationship between the extent of cognitive dysfunction and severity of TBI as well as neuronal loss^{32, 33}.
- Neurological motor deficits shows signs of recovery within 1 year while cognitive deficits persists up to 1 year after severe TBI³⁴.
- Axonal degeneration continues in the corpus callosum, striatum and injured cortex for as long as half a year and a year in the thalamus³⁴.
- Ventriculomegaly, thalamic degeneration, shrinkage of the hippocampal pyramidal cell layer, progressive bilateral neuronal death in the dentate hilus, reactive astrocytosis, and progressive atrophy of the cortex, thalamus, hippocampus, and septum endures up to 1 year following brain injury^{35, 36}.
- Substantial tissue loss occurs in the impact region after TBI.
- Neuronal cell loss happens in the hippocampus following TBI.
- A relationship tends to exist between neuronal cell loss and behavioral deficits^{12, 37-39}.
- Cell death following TBI is primarily caused by necrosis⁴⁰.
- Cell death occurs both in the acute and chronic phases after brain injury in neocortex, thalamus and hippocampus regions of the brain⁴¹.
- Primary and secondary axotomy both occur after traumatic brain injury however it is secondary axotomy that is widely regarded as the main pathological finding^{15, 42}.

Limiting factors in TBI animal models

In the following sections, we will discuss some of the shortcomings or variables that investigators fail to incorporate into TBI animal models. These factors are

extremely important in finding positive results from TBI animal models.

Secondary Insults

Secondary insults such as hypotension and hypoxemia occur following traumatic brain injury. Close to about 30% of severe TBI patients will exhibit hypotension and/or hypoxemia⁴³. Even though the frequencies of secondary insults with TBI patients are comparatively high, animal models of TBI barely incorporate them. From the period of 1996 -2000 of the 168 cases of animal models of TBI reviewed in the journal of neurotrauma, only about 7 percent had incorporated a secondary insult⁷. Between secondary hypotension and secondary hypoxemia the later has been incorporated quiet often in animal models of TBI, technical ease being the most likely reason for this. A few rodent models of TBI have had posttraumatic hypotension been incorporated even so they do happen in conjunction with hypoxemia. Despite the fact that intracranial hypertension is a common factor associated with TBI in the clinic impact-acceleration models without secondary insults demonstrated no intracranial hypertension or neuronal death. Models that have tried to explain the effects of posttraumatic hypotension have done so more commonly in larger animals such as pigs and cats relatively to rodents. It is worth nothing that many and several studies have been conducted on the effects of fluid resuscitation strategies after traumatic brain injury⁴⁴⁻⁵⁰ while posttraumatic hypotensive effects have been poorly dealt with in the laboratory environment. Majority of these animal models of TBI have been able to include parameters such as intracranial pressure monitoring, cerebral blood flow, oxygen delivery and so on but very few have been able to be compared with secondary insults, hence it is easy to speculate that these models have been limited in their capacity to specifically explain the mechanisms of neuronal damage intensified by secondary insults leading to some of the failures pertaining to translating laboratory results to the bedside. This is not to say that fluid resuscitation models are not needed because optimal approach to fluid resuscitation for hypotensive patient following traumatic brain injury needs to be investigated. Studies have compared restoration of mean arterial pressure by either fluid restoration or treatment with the vasopressor; phenylephrine using a pig cerebral injury model and revealed that fluid resuscitation causes earlier cerebral blood flow⁵¹. In the other words restoration of mean arterial pressure alone will not counteract the many biochemical events of injury produced by hypotension.

Post traumatic Coma

Virtually all patients suffering from severe traumatic brain injury will go into coma. Posttraumatic coma is an important prognostic factor in quantifying mortality and morbidity⁵² after brain trauma. At the clinical level coma after the Glasgow Coma Scale (GCS) that ranges from a score of GCS3 - GCS15. This measures trauma important prognosticator is caused by several insults after brain injury. Compression of brain stem, diffuse axonal injury, and mass effect from hemorrhage are some of the etiologies of coma⁵². Incorporating coma into animal models is very crucial because GCS is able to predict the functional outcome of a traumatic brain injured patient. With an established fact that coma is such an important parameter for translating experimental results to the bedside modeling coma in laboratory animal models of TBI has proven to be tedious. The first successful model of post-traumatic coma in primates happened in 1982⁵³. The very few models that have shown some signs of hope have had their own form of limitations for example all the animals that were used to model posttraumatic coma by acceleration in the sagittal plane could not demonstrate DAI or coma but only concussive injury which is comma lasting for just a period of 15mins or less⁵³. In an attempt to achieve better results with the modeling of posttraumatic coma in a laboratory setting acceleration in the coronal plane have been deployed; the end result to that approach was a coma lasting for more than 6 hours in half the population of animals used. Literature review shows that several attempts have been made to model this insult via modifications of the planes of acceleration that produces traumatic brain injury in a laboratory environment⁵⁴. Although some knowledge and findings into posttraumatic coma have been actualized the duration and relationship between DAI and coma has been unsatisfactory⁵⁵. DAI modeling has seen much success compared to coma. Several types of animal models (impact acceleration model, CCI, angular acceleration models) in larger animals have failed to produce coma⁵⁶⁻⁵⁸. The task involved in producing DAI with coma in TBI animal models may be connected to the difference in brain structure. Asphyxia insults have been used to make some advances in modeling coma using FPI however this does not accurately epitomize DAI -induced coma^{59, 60}. In addition to the many means adopted to model traumatic coma in animal models mass effect has also been deployed⁶¹ and its proven futile in rodent models. Mechanical inputs alone is unable to produce coma in animal models of TBI, in the same vein unconsciousness has been produced without mechanical inputs⁶². The above varying result

obtained from the experimental table has affected the advancement of therapeutic interventions in the clinic.

Neurointensive Care Monitoring and Management Strategies

Herniation of brain parenchyma as well as ischemia after TBI prompts clinicians to administer neurointensive care in an attempt to treat and improve patients' neurological deficits. Neurointensive care and monitoring is a function of both intracranial pressure (ICP) and cerebral perfusion pressure (CPP). The use of neurointensive strategies to counter the devastating consequences of ischemia has shown promising results⁶³. Deeper understanding of ICP and CPP and the concept of neurointensive management are paramount for severe brain injury patients. Neurological deterioration after traumatic brain injury has been shown and demonstrated to be strongly linked to intracranial hypertension and ICP. The clinical significance of ICP is overwhelming but it is barely investigated in TBI models. Majority of models apply unclosed craniotomies that limit the monitoring of ICP. Also, those models with intact cranium often have skull fractures that also limit ICP monitoring. Although skull fractures and open craniotomies limit the monitoring of ICP and CPP they have been investigated and assessed at the acute phase in some laboratory TBI models^{64, 65, 66}. A couple of other means to monitor ICP/CPP indirectly has been conducted by investigating posttraumatic brain swelling/edema instead of ICP^{67, 68, 69, 70} directly. Continual studies into the dynamics of ICP and CPP therapeutic interventions are required for the sub-acute period of traumatic brain injury. Compared to functional outcome investigations after traumatic brain injury very little has been done to discover the mechanisms underlying neurointensive care strategies after brain injury. Unfortunately, there are just few studies that target posttraumatic edema and intracranial hypertension. The overall severity of some animal models of TBI especially rodents is not entirely high so doesn't require mechanical ventilation and strict neurointensive care thus limiting the usefulness of these models in the clinical environment. The behavior of experimental models are therefore different in relation to the clinical settings as paradigms such as herniation and de-compressive craniotomies have not been effectively modeled⁶¹. Several other important aspects of neurointensive care that have poorly been addressed in TBI models include oxygen therapy, surgical decompression, catecholamine therapy and so on. Provision of oxygen after traumatic brain injury attenuates secondary

ischemia and other secondary insults⁷¹ in the resuscitation phase. The absence of oxygen therapy in many experimental models of TBI has limited progress of novel therapeutic modalities in the clinical setting. Exogenous catecholamines that are administered to severe TBI patients to control mean arterial pressure (MAP) and CPP are also poorly investigated and understood. Models that have done some work in this regard have shown promising signs^{72, 73}. Surgical de-compressive approaches that are common in the clinical setting have not been applied vigorously in TBI models. The size of infarct reduces significantly following de-compressive surgery⁷⁴. Clinical trials have not been beneficial with several models lacking incorporation of surgical approach. It is possible that the lack of all these paradigms in experimental models has delineated clinically relevant strategies.

Table 3. Classification of secondary brain insults.

Systemic Insults	Ischaemia	hypotension
		anaemia or changes in haemodynamics
	Hypoxemia/ Hypercarbia	respiratory obstruction
		Pulmonary complications
		suppression of respiratory
	Hyperthermia	post-traumatic cerebral inflammation
		thrombophlebitis
		drug reaction
		direct hypothalamic damage
	Electrolyte abnormalities	hypernatremia
		hypomagnesaemia
		hypocalcaemia
		hypomagnesaemia
	Hyperglycaemia	anaerobic metabolism
increase inflammation response		
aggravate brain ischaemia		
Polytrauma	bone fracture	
	liver laceration	
	other organs injury	
Infection/Sepsis	increase brain inflammation	
	brain metabolic alterations	
Thrombocytopenia/ Coagulopathy	new or progressive haemorrhagic changes	
Ethanol consumption	abnormal haemodynamic response	
	Excessive release of BNP	
	suppression of ADH	
Intracranial Insults	Increased ICP/ Cerebral hypoperfusion	
	Brain shift/ Herniation	
	Brain oedema/ swelling	
	Cerebral angiospasm	
	Hydrocephalus	
	Epilepsy	

Recommended Clinical Secondary Insults Requiring Incorporation into TBI Animal Models

To achieve better results from laboratory TBI animal models we will recommend insertion of some of the variables depicted in table 3 in future research.

Hyperglycemia

Hyperglycemia is one of the most reliable prognosticator after traumatic brain injury^{75, 76}. Hyperglycemia causes lactic acidosis and neuronal injury in the brain by influencing anaerobic metabolism and production of excitatory amino acids. Even though there isn't a specific standard glucose level; clinicians adopt strict glucose control measures after traumatic brain injury to reduce devastating effects of hyperglycemia⁷⁷. For such an important clinical factor without a specific or standardized guideline it is paramount that clinicians and researchers delve deeper to acquire more knowledge. In creating TBI models that will cater for hyperglycemia and its mechanistic effect one should consider TBI severity as well as the amount of glucose infusion. Currently TBI models complicated by hyperglycemia have had inconsistent results with some studies stating that hyperglycemia has a negative outcome on TBI patients whilst others have stated otherwise⁷⁸⁻⁸¹. We suggest that the timing of glucose infusion after or before TBI should be further investigated. Secondly different combinations of time of glucose infusion and TBI severity needs to be assessed to gain much understanding about hyperglycemia and TBI correlations. Hyperglycemia does not cause adverse effects after traumatic brain injury without other secondary insults such as ischemia⁸² hence TBI models complicated by hyperglycemia will be appropriate to be further complicated with ischemia for effectiveness and clinical importance.

Hyponatremia

TBI is often associated with electrolyte abnormalities including hypernatremia and hyponatremia. Hyponatremia tends to have a much higher prognostic effect on TBI outcomes compared to hypernatremia⁸³. Hyponatremia can be classified as either mild or severe with different clinical outcomes. It's been proposed that hypopituitarism, volume overload, syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) and cerebral salt wasting syndrome (CSWS) cause posttraumatic hyponatremia⁸⁴. TBI models complicated with hyponatremia require further research so as to be able to answer such critical questions:

1) What is the real mechanism underlying the causes of hyponatremia after TBI?

2) Is hyponatremia just a symptom or it's an insult leading to poor outcomes after TBI?

Even though hyponatremia is a common insult observed in TBI patients they have not been really imposed on laboratory TBI models. Previous work on hyponatremia and TBI could not clarify the pathogenesis of how hyponatremia aggravates brain injury⁸⁵. Another study has linked the adverse effects of hyponatremia to hypoxic or ischemic factors instead of distorted blood brain barrier⁸⁶. Another avenue that could be deployed to model hyponatremia in TBI model is relying on the idea that hyponatremia results from hypopituitarism⁸⁷.

Last but not the least infusion of ethanol to TBI models can also be sorted to reproduce hyponatremia⁸⁸. Should some of these avenues be investigated further and deeper there is greater chance that some of the laboratory results could be translated to the bed side for effective therapies against TBI.

Hyperthermia

Post-traumatic hyperthermia is a state of body temperatures without background infections that is higher than normothermic patients. Basically, temperature elevations after trauma are caused by inflammations, or direct hypothalamic provocations. Posttraumatic hyperthermia is a neurogenic fever that is comparatively resistant to antipyretic drugs^{89, 90}. Irrespective of the causes of hyperthermia, it periodically causes high metabolism as well as high levels of leukocyte activation. The cumulative effects of posttraumatic hyperthermia worsen the outcome of patients^{90, 91}. Traumatic brain injury patients require to be maintained at a normal core temperature⁹². This review aims to discuss post-traumatic hyperthermia since its pathophysiology is poorly understood both at the experimental and clinical levels. Moreover current strategies for controlling post-traumatic hyperthermia remain ineffective and unreliable⁹². Some research conducted in the past about TBI linked the damaging of hypothalamus to hyperthermia^{90, 93}. Efforts to incorporate hyperthermia into TBI models so as to help understand the mechanisms underlying why hyperthermia aggravates neuronal damage and loss has also been conducted⁹⁴ and found promising results. Post-traumatic hyperthermia was however incorporated at different periods after CCI or FPI (delayed⁹⁴ and immediately^{95, 96}). Special attention should be paid to investigating both core and brain temperature after traumatic brain injury since both play critical role in neutrophils elevation. Whole body hyperthermia leads to the elevation of

neurotoxic zinc affecting the hippocampal neurons⁹⁷,⁹⁸ while cortical hyperthermia increases extracellular glutamate levels⁹⁹. These and many other results buttress the suggestion that posttraumatic hyperthermia increases and induces inflammation after TBI.

To further the advancement of clinical therapies involving TBI patients, researchers will have to focus their attention on incorporating posttraumatic hyperthermia in their animal models for all kinds of TBI grading / severities (mild, moderate and severe).

Hypoxemia/hypotension/ischemia

The brain by default is an organ with high rate of metabolism which increases further after traumatic brain injury¹⁰⁰. An increase metabolism requires high oxygen supply to meet the demands however the brain lacks oxygen reservoir hence it is extremely sensitive to hypoxemia. In addition to high rates of metabolism other insults that causes hypoxemia following traumatic brain injury includes pulmonary disorders such as pneumothorax or atelectasis¹⁰¹.

Finally, respiratory failure as a result of disrupted brain pathways also contributes to brain hypoxemia after TBI. Mortality and morbidity rates are significantly affected by hypoxemia or hypotension after traumatic brain injury^{91, 102}. The significance of hypoxemia as far as finding therapeutic interventions of clinical TBI cannot be overemphasized for the very reason that severe hypoxemia increases the neurological deficits observed after traumatic brain injury as well as the aggravation of the injured brain¹⁰³. Correlations of hypoxemia with high energy phosphate¹⁰⁴, cerebral blood flow¹⁰⁵ and blood brain barrier dysfunction¹⁰⁵ proves that TBI models require the incorporation of hypoxemia to increase their efficacy and clinical significance. Other factors that require attention when incorporating hypoxemia into TBI models include the connection between hypoxia and the severity of TBI. In building and developing TBI models it is recommended that arterial oxygen pressure be maintained at a steady rate and efforts made to set the FiO₂ at 21%. Should these factors and issues be dealt with appropriately when developing animal TBI models several adverse effects as a result of hypoxemia can be displayed and understood^{101, 106-111}. Experimental studies show that hypoxemia has more adverse effects than hypotension after TBI^{106, 112-114} whilst clinical studies have suggested hypotension to be the sole prognosticator after TBI⁹¹. These conflicting results warrant further research and investigation into the synergistic effect of hypoxemia and hypotension^{43, 114, 115}.

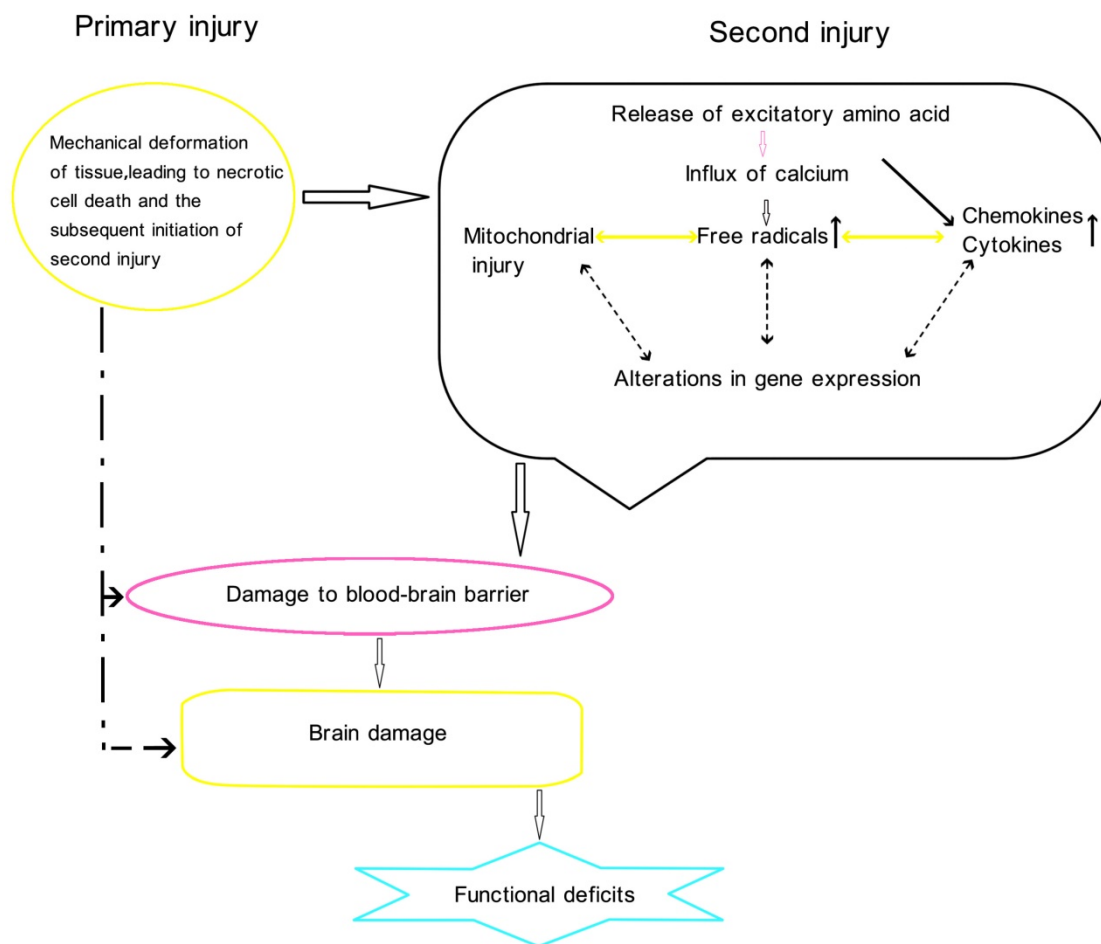


Figure 1. Physiology of traumatic brain injury

Conclusion

Several TBI models has assisted in explaining the molecular and biochemical basis of traumatic brain injuries to a greater extend this has helped in finding treatments to intervene the cascades of events that occur after primary injury to the brain. Despite all the carefully conducted TBI researches; damaging insults to the brain as a result of trauma still continues to be a greater burden to clinician-scientist. This review has sighted that the discrepancies in translating bench results to the bedside could be due to the lack of secondary insults in laboratory TBI models. Future models of TBI should make necessary effort to incorporate secondary insults to achieve as close as possible clinical scenarios in the laboratory.

Abbreviations

TBI: traumatic brain injury; ICP: intracranial pressure; CT: computer topography; MRI: magnetic resonance imaging; DAI: Diffuse axonal injury; DVI: Diffuse vascular injury; APP: amyloid precursor protein; PBB: Penetrating Ballistic-Like Brain Injury; CBF: cerebral blood flow; EEG:

electroencephalography; GCS: Glasgow Coma Scale; CCI: cortical compact injury; CPP: cerebral perfusion pressure; SIADH: syndrome of inappropriate secretion of anti-diuretic hormone.

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Competing Interests

The authors have declared that no competing interest exists.

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