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Review Article

Experimental animal models in traumatic brain injury research: a comprehensive review of methods and outlook

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ABSTRACT

Traumatic brain injury (TBI) remains a significant public health concern worldwide, necessitating effective research models to elucidate its pathophysiology and develop therapeutic interventions. Animal models play a crucial role in TBI research, offering valuable insights into injury mechanisms and potential treatments. However, selecting the appropriate model can be challenging due to diverse array of available options and their respective advantages and limitations. In this comprehensive review, we examine four commonly used animal models of TBI: the weight drop, fluid percussion, cortical impact, and blast injury models. Each model is characterized by distinct injury mechanisms, allowing researchers simulate various aspects of TBI pathology. We discuss the unique advantages and disadvantages of each model, providing insights into their applications and considerations for model selection based on research objectives and outcome measures. Furthermore, we highlight emerging directions in TBI modelling, emphasizing the importance of refining and innovating models to replicate the complexity of human TBI. By critically evaluating and understanding the subtlety of different TBI models, researchers can make informed decisions to enhance the translational potential of preclinical TBI research and ultimately improve clinical outcomes for TBI patients.

Keywords: TBI, TBI animal models, TBI pathophysiology, Weight drop TBI model, Cortical impact TBI model, Fluid percussion TBI model

INTRODUCTION

Traumatic brain injury (TBI) is a major public health concern, affecting millions of people worldwide. TBI can result from a variety of causes, including falls, motor vehicle accidents, and sports-related injuries. Over 50 million people worldwide experience TBI each year. An estimated 1.74 million TBIs occur annually in the United States, and they account for 33% of all injury-related mortality. After being admitted to the hospital for an acute injury, 43% of patients are released with a long-term disability associated with their TBI. Even with the substantial financial burden, there are limited therapies available to treat TBI, which only serves to increase the problem's complexity and calls for the creation of more efficient diagnosis and treatment approaches.[1-3]

TBI stands as a leading cause of mortality and disability worldwide, necessitating effective research models to advance understanding and treatment strategies. Several models have been created due to the heterogeneous nature of human TBI. Among these, including the weight

drop, fluid percussion, cortical impact, and blast injury models which fall into either focal, diffuse, or mixed injury category.[2,4] Each model offers distinct advantages and limitations, contributing to the complexity of model selection for researchers. The weight drops models induce injury by dropping a weight onto the exposed skull, simulating blunt-force trauma commonly seen in TBI cases. The fluid percussion model involves the delivery of a fluid pulse to the exposed dura, replicating the biomechanical forces associated with TBI. Cortical impact models mimic focal brain injury through controlled cortical impactors, while blast injury models simulate the effect of explosive blasts observed in military and civilian settings.[5,6]

Choosing the appropriate model requires careful consideration of research goals and outcome measures. While each model offers unique insights into TBI pathophysiology, differences in injury mechanisms and outcome must be weighed. This review aims to elucidate the distinctions between these models, providing researchers with a comprehensive understanding to guide model selection aligned with their specific research objectives and desired outcomes.

PATHOPHYSIOLOGY OF TBI

TBI is a complex, multifaceted disorder that results from external forces that cause damage to the brain. From mild concussions to severe and potentially fatal damage, it encompasses a broad range of injuries.[7,8] Understanding the biology of TBI is essential for developing treatment strategies that work and enhance patient outcomes. TBI's pathophysiology is divided into two stages: mechanical injury/primary damage and delayed injury/secondary damage. The TBI's primary and secondary injuries are intertwined and impact one another rather than being mutually exclusive. Genetic and environmental factors, as well as the scope and duration of both injuries, all influence the severity and prognosis of TBI.[8,9] Reducing both primary and secondary brain injuries should therefore be the goal of TBI prevention and treatment.

Mechanical injury/primary damage

The TBI pathology commences with the primary mechanical insult that can arise from a range of mechanisms, including sports-related impacts, falls, or motor vehicle accidents.[9-11] The primary injury results from applying stress on the brain tissue, which ultimately causes complex structures to be sheared and deformed. Local injuries resulting in contusions, hematomas, or lacerations in the impact area might immediately impair neuronal function (Figure 1).[12,13] Moreover, the main effect of primary injury often includes both focal and diffuse axonal damage (DAI), the latter being the result of rotating forces acting on the brain. Particularly in white matter tracts, these pressures cause extensive axonal damage (Figure 1).[14] DAI is associated with neurological abnormalities and cognitive impairments and plays a substantial role in the pathophysiology of moderate to severe TBI.[7] Primary injuries are generally irreversible. However, they can be prevented with the use of seat belt or helmet.

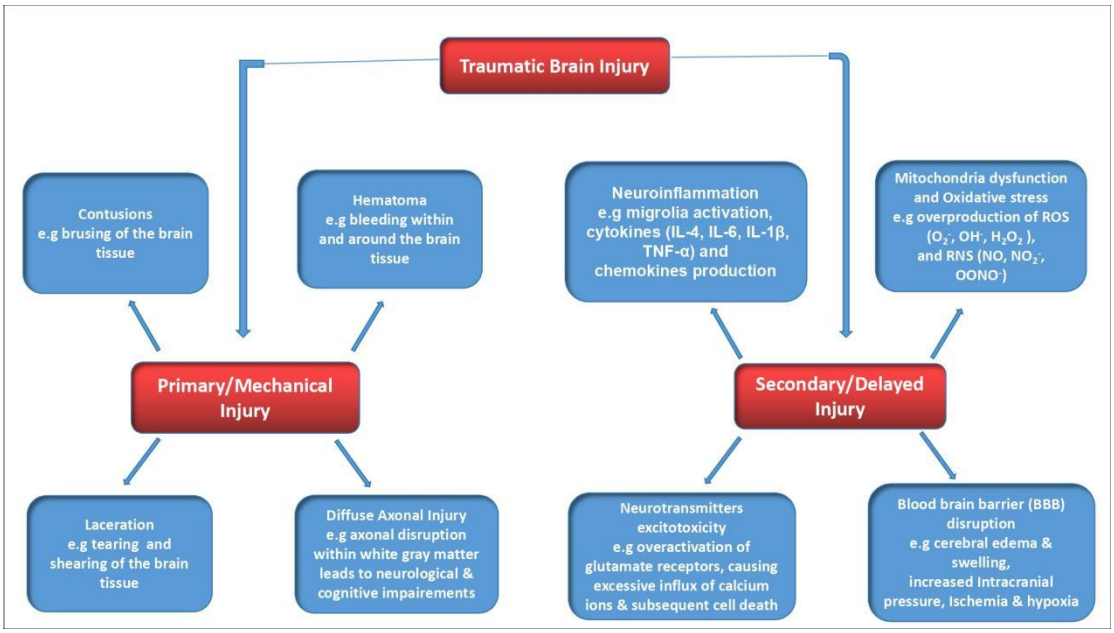

Figure 1: Pathophysiology of TBI.

Delayed injury/secondary damage

It is recognized that secondary injuries can develop minutes to months after the initial damage. The brain's response to the initial injury sets off a cascade of events that include neuroinflammatory processes, excitotoxicity of neurotransmitters, mitochondrial cellular dysfunction, disruption of the blood-brain barrier (BBB), and

oxidative stress (Figure 1). A series of chronic injuries could arise from these secondary damage processes such as white matter degeneration and subsequently, neuronal and glial cell death.[10,14,15] Major causes of death for TBI patients from BBB's disruption and increased permeability include swelling and brain edema brought on by elevated intracranial pressure (ICP). Severe cerebral edema and increased ICP might aggravate ischemia damage and neuronal cell death by obstructing blood and oxygen delivery to the brain (Figure 1).[16] Moreover, a harmful cycle of inflammation triggered by reduced blood flow, which would accelerate the development of secondary damage processes and cognitive impairment after TBI.[6,8] Currently, no pharmaceutical treatments that offer TBI patients effective neuroprotection.[8,10] However, secondary injury offers a therapeutic intervention opportunity that may help avoid or lessen brain damage and speed up the healing process for the patient.

TBI pathology is a complex process involving two stages: primary injury and secondary injury. Primary injury includes both focal and diffuse axonal injury, which present as laceration, contusion, hematoma, and diffuse axonal injury. Secondary injuries, which manifest within minutes to months, involve neuroinflammation, excitotoxicity, mitochondrial cellular dysfunction, BBB disruption, and oxidative stress. Mitochondrial dysfunction leads to the overproduction of ROS and RNS, resulting in oxidative stress. This leads to the activation of microglia cells and astrocytes in neurons, initiating inflammatory cascade of events. The detrimental cycle of inflammation can be initiated by reduced blood flow from BBB disruption, leading to an excessive influx of calcium ions into cells and cell death.

ANIMAL MODELS FOR TBI

Animal models of TBI have proven invaluable. These models have been employed to comprehend the pathological mechanisms underlying the evolution of varying degrees of TBI. They have facilitated the development of potential therapies to mitigate the effect of secondary brain damage. They have been used to study neurological changes, behavioral impairments, and cognitive deficits associated with TBI.[2,5] Many models have been created due to the heterogeneous nature of clinical TBI and divided into three main groups based on the three main types of TBI clinical presentations: focal, diffuse, and non-impact injuries. The most popular animal models for TBI research are rodents: rats and mice. There are benefits to using mice and rat models, including cost-effectiveness, ease of use, and strong repeatability and controllability.[2] Importantly, they make it possible for researchers to carry out a study without putting people in danger or causing them discomfort.[2,4] In rodents, researchers can modify a variety of characteristics, including pre-existing comorbidities like age, gender, and genetics, as well as the type, severity, and location of the injury. Because of this degree of control, researchers can focus on particular factors and examine how they affect the healing and damage processes in TBI.[2, 5] The constraints inherent in rodent models, including variations in cerebral structure, the intricacy of cortical folding, and the proportion of white matter to gray matter have prompted a surge in the use of larger animal species and nonrodent models for TBI research. Although rats and mice are the most widely used models for TBI, there have always been worries about how well these models translate to humans.[2,4] This is mainly because rodents have a lissencephalic cortex, as opposed to higher species' gyrencephalic brains, such as primates which include humans. Therefore, pigs, sheep, and animals, with gyrencephalic brains have all been used as large animal models of TBI.[17]

Methods of TBI induction in animal models

Researchers employ various methods to induce TBI in animal models. These methods include the weight-drop model, where an anesthetized animal has a weight dropped on its exposed skull to cause a focal or diffuse injury. This model allows for easy adjustment of mechanical variables such as impact depth, velocity, and time.[4,17] Another method is the fluid percussion model, which produces diffuse injury by applying a fluid pulse to the exposed brain surface. This model is particularly useful in simulating TBI comparable to human cases.[18,19] The cortical impact model, on the other hand, generates a focal injury similar to TBI in humans by using a pneumatic piston to apply a controlled impact to the exposed brain surface.[20,21] Lastly, the blast injury model aims to replicate the effects of blast injuries on animals by subjecting them to a blast wave. This model is valuable in studying TBI resulting from explosion-related injuries that military personnel often experience.[22] These models have been used to evaluate possible treatments and investigate the underlying pathophysiology of TBI. We go into great detail about these models in the upcoming sections, including their benefits, drawbacks, and appropriate applications in TBI research.

WEIGHT DROP MODEL

This model involves dropping a brass load with specific parameters onto the animal’s head through a plexiglass tube from a specified height. The different types of weight-drop models are due to differences in parameters used such as weight, height, and head movement-either fixed or rotating. Other important differences are in the use of anesthesia or not, whether craniectomy is performed or not, and whether the impact is directly or indirectly to the skull. This model also has the drawback of being unable to adequately simulate the intricate and varied nature of TBI in humans. While TBI is typically caused by a mix of factors (both focal and diffused forces), the weight drop model only considers one kind of physical force (either focal or diffuse) that is applied to the head.[2,4,5]

These are the most popular weight-drop models we will look at in the current review.

Feeney's weight drop model

This model involves weight being dropped onto a particular spot on the exposed skull of an anesthetized animal, resulting in localized injury. It is mostly used to cause focal TBI or injury to a specific region of the brain (Table 1).[4,5] In Feeney's model, an incision is made in the midline of the head, allowing clear access to the skull below to inflict a direct cortical injury. The immediate impact causes hemorrhages in the white matter just beneath the deformed cortex which persist for the next 24 hours. Over the next two weeks, the degeneration of the white matter worsened. In rats with severe contusions, deficiencies in metabolism, primarily, the diminished N-acetyl aspartate worsen injury severity and functional impairments that last longer than 90 days following trauma.[2,5] The severity of the injury caused by Feeney's model can be adjusted by changing the weight of the object dropped and the height from which it is dropped. Feeney's model is exceptionally reproducible, making it an invaluable tool for researching the impacts of TBI.[23,24] Feeney's model possesses notable strengths, predominantly its simplistic design. Moreover, it effectively mimics the biomechanics of injury observed in moderate to severe cases of human TBI, such as the forceful acceleration of objects against the skull. However, increased rates of mortality may arise due to the use of heavier weights to produce severe TBI, which diminishes the model's repeatability.[6]

Table 1: The differences, similarities, advantages, and disadvantages between Feeney's, Shohami's and Marmarou's weight drop TBI models.

Model	Injury mechanism	Injury severity	Injury location	Advantages	Disadvantages
Feeney's weight drop model.[4,5]	A weight is dropped onto the exposed dura after a craniectomy	Variable, depending on the weight and height	Focal, affecting the underlying cortex	Reproduces the focal injury and contusion seen in human TBI	Requires anesthesia and surgery; does not produce diffuse injury or axonal damage
Shohami's weight drop model[2,5]	A weight is dropped onto the intact skull after a small incision in the scalp	Moderate to severe, depending on the weight and height	Focal, affecting the underlying cortex and hippocampus	Reproduces the focal injury, contusion, and hippocampal damage seen in human TBI	Does not require anesthesia or surgery; does not produce diffuse injury or axonal damage
Marmarou's weight drop model[2,5,26]	A weight is dropped onto a metal disc placed on the intact skull	Variable, depending on the weight and height	Diffuse, affecting the whole brain	Reproduces the global diffuse injury seen in human TBI	Requires anesthesia and surgery; does not produce focal injury or contusion

Shohami's weight drop model

This model is similar to Feeney's model in that it similarly includes dropping a weight onto a certain section of the skull, but it may target different brain regions or use different impact parameters and is used to produce a focal injury (Table 1). An incision is made through the scalp's midline, much like in Feeney's model, to provide easy access to the skull below.[4] This model, in contrast to Feeney's techniques, does not necessitate direct access to the brain by craniectomy, which can be advantageous for totally lowering the chance of harming the dura before the damage. Further, this model differs from Feeney's model in that it depicts a blunt impact to an exposed skull rather than a penetrating mechanism of injury due to changes made to the tip and the absence of a craniectomy.[2,5,25] Shohami's injury has physical abnormalities, such as disruption of the BBB, cerebral edema, localized contusions, and cerebral hemorrhage. In this model, changes to the BBB persisted for up to 30 days in rats, whereas cerebral edema and BBB permeability increased in the ipsilateral region at 4 and 24 hours. Furthermore, 18 hours after injury, rats' levels of cerebral edema heightened.[2,5,25] Overall, Shohami's TBI model is very reproducible, and by varying the height and weight of the object dropped, degree of harm caused can be varied.[4,5]

Marmarou's weight drop model

The Marmarou weight drop model is a popular animal model of TBI in which a weight is dropped against the exposed skull of an anesthetized animal to cause diffuse TBI. The Marmarou's model is mostly used to cause diffuse TBI, which is a damage to myriad areas of the brain. It is intended to cause closed-head TBI, which is brain damage without the additional complications of open-head injuries.[17,26] In the Marmarou model, an incision is created through the scalp's midline, allowing clear access to the skull below. The animal is placed on a thick form and a metal disc is positioned atop the skull to cushion bone fractures and distribute the force across a sizable portion of the brain (Table 1).[26] By varying the object's weight and the height from which it is dropped, Marmarou's model produces highly reproducible injuries that can vary in severity.[4,23] Neuronal injury in both ipsilateral and contralateral cortices, as well as DAI in the cerebral and cerebellar peduncles, has been observed in this model. Marmarou's model has been well-

characterized in the literature because it produces DAI after impact; nonetheless, it has been linked to a significant mortality rate.[5] However, investigators can limit the mortality rate in the model by using mechanical ventilation to ease the respiratory depression seen in the rats after damage.

Conclusively, animal models of TBI are frequently induced using weight-drop models, such as Feeney's model, Shohami's model, and Marmarou's model. Both focal cerebral contusions and severe diffuse brain injury marked by axonal damage can been replicated using weight-drop models. These models give researchers studying TBI controlled and reproducible ways to examine possible therapies. Each model has its limits, as illustrated in Table 1, and none of them can fully simulate all the features seen in human TBI. It is crucial to select the right model in light of the research question and the result measurements. To more accurately simulate the whole intricacy of a TBI in humans, additional improvements in these models are required.

Modification of weight drop models

Researchers can modify the weight drop model to explore different aspects of TBI. The weight drop model can be altered by researchers through adjustments to the experiment's overall design, allowing for the investigation of various aspects of TBI. There are several examples of how scientists have modified the weight drop model. Firstly, researchers can target a specific region of the skull by dropping the weight to induce a focal injury. This approach facilitates the examination of TBI's impact on specific brain regions. Secondly, by placing the weight on the intact skull, researchers can induce a diffuse injury, enabling them to study how TBI affects the entire brain. Additionally, researchers can adjust the weight or height of impact to create mild TBI or concussion-like injuries, which allows for the analysis of the consequences of repetitive mild TBI, a common type of TBI in sports-related injuries.[2,4,5,27] Lastly, researchers can modify the weight drop model to create combined injuries, such as a TBI along with hypoxia or diseases such as diabetes or hypertension, providing insight into the consequences of TBI in relation to other disorders.[28,29]

FLUID PERCUSSION MODEL

The fluid percussion model (FPI) is a popular experimental technique for researching TBI in rats, ferrets, pigs, and other animals. The FPI causes an injury during a craniectomy by delivering a brief fluid pressure pulse to the intact dura. The skull is cut either laterally over the parietal bone, between the lambda and bregma, or centrally around the midline. A pendulum strikes the piston of a fluid reservoir, resulting in a pressure wave that is sent to the brain.[18,19] FPI models are classified as midline (centered on the sagittal suture), parasagittal (<3.5 mm lateral to midline), and lateral (>3.5 mm lateral to midline; LFPI) depending on the position of the craniectomy away from the sagittal suture.[2,30] Originally, FPI models were created for use in cats and rabbits, the midline FPI model of TBI was then refined to create the LFPI model in rodents.[2,31-32] Additionally, for over three decades, FPI TBI models have been used extensively to study TBI pathophysiology and test potential treatments in cats, rabbits, dogs, sheep, and pigs.[2,17,30,32] This might explain why FPI is the most popular and well-characterized model of experimental TBI nowadays.

The adapted lateral FPI can be used to recreate the features of moderate to severe TBI with cerebral bleeding, brain edema, and progressive gray matter damage-all pathophysiological features of TBI.[2,5] An excellent advantage of the LFPI model is that it accurately replicates the etiological processes of TBI in humans as it produces a combination of focal injury and diffuse axonal injury which allows researchers to validate their results. Further, within minutes of the impact, LFPI causes neuronal injury, which develops into a loss of neurons within 12 hours. Then, over the next several days to months, there are deficiencies in neurobehavioral and cognitive functions, and over time, there are neurological impairments and cognitive dysfunction.[33] The FPI has been used widely, yet there may be issues with its reproducibility and variability in the location and intensity of injury.[34]

CORTICAL IMPACT MODEL

The cortical impact model, or CCI, is a widely used experimental method for studying TBI in animal models. In CCI, a controlled impact is applied via a pneumatic piston attached to a rod to the exposed brain surface which causes focal damage. The size and shape of the rod's tip can be changed to allow for scalability to other species. CCI devices can regulate the impact's velocity, depth, duration, and site. The CCI generate both morphological and cerebrovascular damage that closely resemble human TBI.[20,21] In CCI model, a unilateral craniectomy, usually between the bregma and lambda, delivers the controlled impact to the intact dura, producing deformation of the underlying cortex. The impacts of the CCI model include hemorrhage, concussion, loss of cortical tissue, and disruption of the BBB.[2] In CCI, the proper depths to cause mild, moderate, and severe TBIs have been determined by prior research to be 0.0-0.2 mm, 0.5-1.0 mm, and 1.2-2.0 mm, respectively. Cortical tissue loss in the ipsilateral is observed six weeks and twenty-four hours following a moderate injury using a velocity of 3.0 m/s, tip diameter of 3 mm, and depth of 1 mm. The CCI model also produces neurobehavioral and cognitive impairments similar to those observed in clinical TBI.[2,5]

Compared to other models like FPI, CCI has the advantage of being able to inflict injuries of different intensities and applying the impact at different depths and velocities. The degree of histopathological severity in

CCI increases as cortical deformation and impact velocity increase, allowing for adjustment of injury severity based on specific experimental needs.[20,21] Further, cognitive impairments in mice and rats were strongly linked to the depth of deformation and impact velocity in CCI.[2] Because of the ability to change depth and velocity, a modified version of the CCI has been used to cause mild TBI or symptoms associated with concussions in mice. With this change and control, researchers can examine the consequences of mild TBI, which is a prevalent type of TBI in sports-related injuries.[35]

Some of the differences in injury mechanisms between the controlled cortical impact model and the fluid percussion model

The CCI model and the FPI model are two commonly used models for studying TBI in animals. To assist researchers in selecting the best model for their work, we have detailed some of the differences in the processes of injury between these two models in Table 2. Picking these models for TBI research, researchers should take these variations in the processes of the injury into account.

Table 2: Some of the differences in the mechanisms of injury between the controlled cortical impact model and the fluid percussion model.

Controlled cortical impact model	Fluid percussion model
The CCI model involves the use of a pneumatic piston to deliver a controlled impact to the exposed brain surface, causing a focal injury.[20,21]	The FPI involves the delivery of a fluid pulse to the exposed brain surface, causing a diffuse injury.[33,36]
The CCI model produces a direct mechanical deformation of the brain tissue, resulting in a focal injury.[36]	The FPI produces a pressure wave that is transmitted through the brain tissue, resulting in a diffuse injury.[21,36]
The CCI model produces a more localized injury than the FPI.[21]	The FPI produces a more widespread injury than the CCI model.[21]
The CCI model mimics several features of human TBI in terms of morphologic and cerebrovascular damage responses.[20]	Depending on the position and strength of the pressure wave, the FPI could result in either focal or diffuse injury.[21,33]
The CCI model was adapted to cause mild TBI or concussion-like injuries in mice. This alteration enables researchers to investigate the impact of repetitive mild TBI, a prevalent kind of TBI in sports-related injuries.[35]	When compared to the CCI model, the FPI results in a more widespread injury and primarily causes moderate to severe TBI. To research diffuse injuries, the FPI would therefore be more appropriate.[21,34]

BLAST INJURY MODEL

An explosion can cause blast injury, a complicated kind of physical injury that can happen either directly or indirectly. Blast injuries fall into four broad categories: primary, secondary, tertiary, and quaternary. There are two ways that a blast can affect the brain: firstly, either directly through the blast wave passing through the skull (primary blast), which causes the head to accelerate or rotate (tertiary blast), or indirectly through the impact of particles that have been accelerated by the energy released during the explosion (secondary blast).[37] The second way is through the transfer of kinetic energy of the primary blast wave to organs such as lungs, ears, eyes, and gastrointestinal tracts, and organ systemic blood, ultimately reaching the central nervous system (CNS).[38]

One tool that's frequently used to simulate blast injuries is the shock tube developed in rodents. It makes it possible to simulate shock waves for extended periods in an affordable and reproducible manner.[22,39] Experimental blast models have also been developed in larger animals mainly pigs, as well as in non-primates.[40] In several animal models, primary blast results in significant behavioral difficulties and cognitive deficiencies. The behavioral deficits and cognitive impairments correlate positively with the intensity of primary blast. In the early hours, there is in addition to axonal damage in the cerebellum and brainstem, hemorrhage, laceration, and brain contusion. Furthermore, axonal degradation was observed 24 hours, 72 hours, and two weeks in rats exposed to a single blast wave.[5,41] The biochemical changes begin early with metabolic impairments primarily in glucose metabolism, then a decline in energy reserve followed by the development of oxidative stress. The latter mechanisms include impaired blood flow and ischemia, onset of inflammation, diffuse axonal injury, and apoptotic and non-apoptotic cascades that lead to neurodegeneration.[39,42]

Blast injuries involve a very complicated mechanism of injury; hence, a suitable and clinically relevant blast-injury model should be founded on a sufficient understanding of shock-wave physics, the features of the injurious environment created by an explosion, and the clinical signs of the resulting injuries. In experimental blast research, the purpose of the study and the aspect of a clinical CNS injury that the researcher wants to imitate determine the design and selection of a particular blast injury model. Because blast injuries are complicated, a rigorous definition of the conditions in a model that

replicates some elements of blast injuries is necessary; otherwise, the results obtained can be dangerously deceptive and lack clinical and military value. For instance, the researchers should first clearly state the explosion effects that are to be replicated. In the event that the primary blast is chosen, the investigator must ensure that the animals are restrained to avoid the tertiary blast's typical acceleration of the head and body during exposure.[39,43]

APPLICATIONS OF THE CURRENT ANIMAL MODELS OF TBI

The heterogeneous nature of human TBI has led to the development of various animal models of TBI. The weight drop model is often used to simulate blunt-force trauma, akin to the impact of falling objects or vehicular accidents. For example, researchers may use weight drop model to study the effects of repetitive mild TBI by subjecting rodents to multiple impacts over time, making it suitable for investigating chronic traumatic encephalopathy (CTE) in sports-related injuries or military settings.[44,45] The fluid percussion is used to study diffuse brain injury. Researchers may use FLP to study post traumatic neuroinflammation by accessing microglial activation and cytokine expression in the brain following injury. This helps to elucidate the role of neuroinflammation in TBI pathology and identify potential targets for anti-inflammatory therapies.[46] The cortical impact induces focal brain injury and allows researchers to study localized damage and its effects, making it valuable for assessing interventions targeting specific brain regions or pathways. For example, investigators may use CCI to explore the efficacy of neuroprotective compounds in reducing neuronal cell death and tissue damage post-TBI. By administering candidate drugs before and after injury induction, researchers can test their potential therapeutic benefits in mitigating TBI-related pathology.[47] The blast injury model is mainly used to study the effects of explosive blasts on the brain. Researchers may use the blast injury model to investigate mechanisms underlying blast-induced neurobehavioral deficits, such as anxiety and cognitive impairment. By accessing behavioral outcomes and neurobiological changes post-blast exposure, researchers may identify novel therapeutic targets for managing blast-related TBI complications.[41] It is important to point out that, while these models may have unique injury mechanisms and applications, they may share similar research objectives in certain contexts, particularly regarding the assessment of therapeutic interventions and long-term outcomes post-TBI. For example, both weight drop and cortical impact models can be used to assess the efficacy of neuroprotective compounds in reducing neuronal cell death and tissue damage post-TBI. Additionally, researchers may use either model to study the long-term effects of repetitive mild head trauma and potential interventions for mitigating chronic neurodegeneration.[44,45]

The limitations of the current animal models of TBI and the need for further refinements

The current animal TBI models face significant limitations, including their oversimplification of injury mechanisms, failure to capture the heterogeneity observed in human TBI, and imitations in replicating chronic and long-term effects. For example, while models like the weight drop and fluid percussion focus on specific injury mechanisms such as blunt-force trauma or diffuse brain injury, they often fail to mimic the combined injury mechanism seen in human TBI. Moreover, the individual variability present in human TBI, influenced by genetic factors, pre-existing health conditions, and lifestyle, is often overlooked in animal studies, limiting the generalizability of findings. Additionally, many animal models primarily asses acute-phase outcomes, neglecting the chronic and long-term consequences that characterize human TBI recovery. Future refinements of TBI models should aim to address these limitations by incorporating factors such as individual variability (genetic variations, sex, or age), comorbidities (introducing pre-existing health conditions e.g. diabetes, hypertension), chronic effects (extending study duration to investigate long-term effects), advanced imaging techniques (such as functional MRI, diffuse tensor imaging or positron emission tomography), and biomarkers assessments (neuroinflammatory markers or specific proteins).[2,28,29,48-54] By doing so, researchers can enhance the translational relevance and predictive validity of animal models, facilitating the development of more effective therapeutic interventions for TBI.

Moving forward, researchers must continue to refine and innovate TBI models to better mimic the complexity of human TBI, incorporating factors such as individual variability, comorbidities, and chronic effects. Integration of advanced imaging techniques, biomarkers assessments, and multidisciplinary collaborations will enhance the translational potential of preclinical TBI research, ultimately leading to improved clinical outcomes for TBI patients.

CONCLUSION

The selection of an appropriate model is paramount for advancing our understanding of TBI and developing effective therapeutic interventions. Each model, whether it is the weight drop, fluid percussion, cortical impact, or blast injury model, offers unique advantages and limitations that must be carefully considered in alignment with specific research questions and outcome measures. While the weight drop model provides simplicity and reproducibility, the fluid percussion model offers control over injury parameters and mimics diffuse brain injury. The cortical impact model allows for the induction of focal injury with reproducible parameters, while the blast injury model is relevant to the military TBI context, albeit with challenges with standardization.

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