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Weight Drop Models in Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is the leading cause of morbidity and mortality worldwide. TBI is often seen in people with loss of motor, cognitive and sensory function. TBI causes serious health problems such as death, disability and mental disorders. TBI continues to be an increasing health problem all over the world. It is estimated that approximately 1.7 million people suffer from head trauma each year and approximately 50,000 of these individuals die. Although TBI is seen in all ages and populations, the age population with the highest incidence is children and the elderly. Falls, sports activities and motor vehicle accidents are the biggest risk factors for TBI. To develop diagnosis and treatment methods for traumatic brain injury, the molecular and cellular mechanisms underlying neuropathology should be known. Therefore, different models of mild, moderate and severe experimental traumatic brain injury models are used. Animal models of traumatic brain injury are broadly classified as focal, diffuse, and mixed injury. Fluid percussion, controlled cortical effect, weight reduction and blast wave are the most preferred models in traumatic brain injury experimental research. This review describes the strengths and weaknesses of current rodent models for traumatic brain injury.

Key words: Experimental Traumatic Brain Injury Models, Weight Drop

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INTRODUCTION

1. Traumatic Brain Injury

Traumatic brain injury (TBI) is defined as brain injury caused by external mechanic force such as rapid acceleration or deceleration, blust waves, crush, impact or penetration of a bullet (1). TBI cause temporary or permanent disfunction of cognitive, physically and psychosocial (2). TBI is the leading cause of death and disability for people 75 and older (3). Around the world 10 million death and hospitalization happening in a year and an estimated 57 million people are estimated to suffer from this type of brain injury (4). Motorcycle and sporting accidents and blast wave diffuse injury are major causes of TBI (5). Most traumatic brain injury injuries cause cognitive/behavioral impairment, chronic encephalopathy, epileptic seizure and neurodegenerative Alzheimer's disease if not treated appropriately (6). Although there is no single animal model that can fully mimic human brain injury, animal models of TBI offer the best alternative for investigating the biomechanical, cellular, and molecular mechanisms as well as time-dependent effects of injury-related neuropathological progression (6, 7). Experimental models are so critical for assessment of injury severity and efficacy of therapeutic treatments after TBI (6). There are three types of experimental models for TBI: Focal, diffuse and mixed injury (8). Focal injuries causes are blow to the head, car accidents or localized tissue injury caused by violent attacks. Diffuse injury is caused by the acceleration or deceleration effect, including head movement, in motor vehicle accidents or blast wave propagation. Mixed injuries are seen after fall down or sport accidents.

2.Pathophysiology of Traumatic Brain Injury

TBI causes cognitive, motor, and sensorimotor dysfunction. Animal models are preferred to investigate the pathophysiology and treatment modalities of human TBI. TBI has mixed pathophysiology that include primary and secondary injury mechanism. This primary injury is the conclusion of moment mechanical brain tissue injury which happen by external force’s acceleration and deceleration (8). The primary injury includes confusion, hemorrhage and neuronal axonal injury. Secondary injury develops minutes to months after the primary injury. As a result of primary damage, secondary damage occurs, including molecular, cellular, metabolic and biochemical activation processes leading to neuroinflammation, neurodegeneration and atrophy (9). Primary injury can be preventable with seat belt or helmet. However, secondary damage provides a treatment opportunity for therapeutic intervention that can prevent and/or reduce brain damage and heal the patient. The first effect that making sudden cell death is not recoverable so the treatments are focusing on secondary injury path that increase the primary

injury. However, there is no proven effective neuroprotective treatment to date (10-13). The usage reason of animal model at TBI is understand the secondary injury process and develop new treatments (10). But for now there are no success treatment at clinical result which were succeed at animal models. To date, however, promising results from preclinical studies of possible TBI treatments have not translated into successful results in clinical trials (10). Pathophysiological heterogeneity, there is not enough pharmacokinetics analyses for determine the optimal dosage and compounds given outside the therapeutic window can cause the clinical failure for TBI patients (10, 14).

TBI animal models are include biochemical mechanism, oxidative stress, inflammation, apoptosis, necrose, diffuse axonal injury, neurodegeneration and cognitive dysfunction at injury place (Figure 1.) (6). Many biochemical cascades responsible for secondary damage such as glutamate excitotoxicity, disruption of cellular calcium homeostasis, increased free radical production, lipid peroxidation, mitochondrial dysfunction, inflammation, apoptosis, and diffuse axonal damage have been identified (15, 16). Secondary injury process ends with endothelial and glial cell death and white ore degeneration (17, 18). Cell death occurs within minutes after injury and continues for days to months (17, 19). Necrotic and apoptotic cell death is defined in damaged areas, injury border area and subcortical areas (19, 20). Apoptosis after TBI is seen with gray and white matter atrophy. Acute cell death and delayed cell death have important role for functional disorder after TBI (18). With this low effect TBIs can cause diffuse axonal injury with cognitive dysfunction (16).

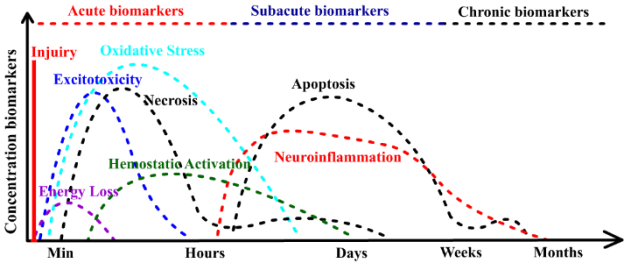

Figure 1. Pathophysiology of Traumatic Brain Injury

2. Experimental Traumatic Brain Injury Models

Pathophysiological heterogeneity at TBI patients are affected with primary injury zone, type and age, health, gender, medicine, alcohol and drugs and genetic etc. (21). TBI animal models design for well controlled and relatively homogeny parameters like age, gender, genetic and injury (10). For this reason animal model cannot summarize all part of secondary injury and this explain why at the clinical trial is not successful (22). With this animal models are necessary for develop new therapeutic treatments and make them characterize also necessary for research biomechanical, cellular and molecular sides which you cannot work at clinical trials (16). For develop new therapeutic strategies and exceed the space between

preclinic and therapeutic the animal models need to develop and change.

There are different animal models are using for understanding the TBI's pathological feature and develop possible therapeutic treatment. Animal models aim to mimic the clinical type of TBI. For the clinical heterogeneity status of TBI many animal models developed. Although larger animals are closer to humans in size and physiology, rodents are often preferred for TBI research due to their small size, low cost, and standardized outcome measures (16). At the Table 1 advantages and disadvantages of most used weight drop models in traumatic brain injury models are shown.

Table 1. Animal Weight Drop Models of Traumatic Brain Injury and Assessment of Injury Severity

Injury model	Injury	Clinical relevance	Strength	Weakness	Animals
Weight Drop Models		Hemorrhage and diffuse axonal injury. Example: falling down, motor vehicle accidents	Mechanism is similar to human TBI, severity of injury can be adjusted; well-characterized neuroscoring post-injury; inexpensive, easy and convenient	High mortality rate due to apnea and skull fractures, possibility of rebound injury, chance of inaccuracy	Mouse, Rat
Marmarou	Mainly diffuse		Damage mechanism close to human TBI; well characterized	Not highly reproducible, high mortality without ventilation	Mouse, Rat
Feeney	Mainly focal		Damage mechanism close to human TBI,	Craniotomy requirement; high death rate	Rat
Shohami	Mainly focal		Easy to use with instant neurological severity scoring in 1 hour	Not highly reproducible	Mouse, Rat
Marmarou Weight Drop Model	**Injury severity**	**Weight (gr)**	**Height (m)**	**Mortality rate**	
	Mild	450	1.0	0%	
	Middle		1.May	12.5 %	
	Severe		2.0	50%	

3.1. Weight Drop Injury Model

At the weight drop model the skull (with or without craniotomy) subjected to free falling and directed weight (23). At these models severity of damage can controlled with mass of weight and height of mass. Weight drop model is cheap, repeatable and easy to make for focal and diffuse clinical situations (6).

Recoil affect and speeds causes different injury severity these are the disadvantages of this model (6).

3.1.1. Marmarou Weight Drop Model

Marmarou model is the most common used model for diffuse axonal TBI (24, 25). Marmarou model is used for model the fall injury and motor vehicle accidents for humans. Adult and 350-400 grams rats are prefer for this model (25). This model are designed as place a foam/sponge under the rat then fall a weight at the rat's head (24). The experimental setup consists of gravity and a freely falling metal weight column in a plexiglass tube (Figure 2.). After the animal is anesthetized, a midline incision is made to expose the skull. The stainless-steel disc is then rigidly attached to the skull with dental cement in a central position between bregma and lambda. Then the animals are placed at foam/sponge. The impact is generated by freely falling weights directly onto the cemented stainless-steel disc (26). In this model, diffuse neuronal and axonal damage occurs throughout the cerebrum and brainstem. Damage triggers a significant neuroinflammatory response in the intrathecal region. This damage leads to neurological deterioration and disruption of the blood-brain barrier (27). In the first 4 hours after the injury, a decrease in cerebral blood flow and an increase in intracranial pressure result in secondary autoregulation. Vasogenic edema occurs in the first hours, then diffuse cellular swelling occurs. Brain edema occurs in the first 20 minutes and continues for up to 24 hours. After the first 4 hours, it has been shown that blood-brain barrier permeability is impaired in relation to edema (26). Changing the mass of weight or altitude of weight causes the TBI models severity as mild/moderate/severe (28). The advantages of Marmarou's model are modeling the diffuse TBI types, usage and manipulation ease, repeatability and modelling the neuropathology very well (24). The disadvantage of Marmarou's model are strikes again (29), skull fixation (24) and the need for the use of anesthesia (3, 30).

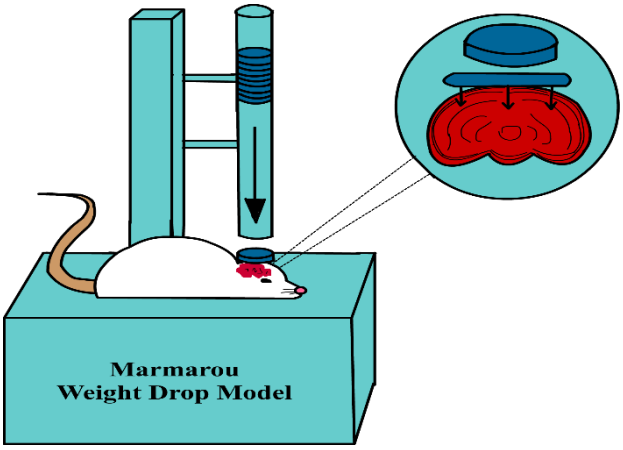

Figure 2. Marmarou weight drop experimental setup

3.1.2. Feeney's Weight Drop Model

Feeney's weight drop model happens as same Marmarou's (Figure 3.). Weight is transmitted to the dura via the craniotomy and causes cortical contusion (31). This model ends with cortical contusion which seen with hemorrhage and blood-brain barrier injury (32). Inflammatory periods cause microglia, astrocyte, neutrophil and macrophages activation (32). As morphological the injury seen in the first hours as bleedings at the white ore at 24th hour it causes necrotic cavity formation (32). Moreover this model causes delayed microcirculatory disorders and cortical spreading depression (33). Cell death after trauma depend on severity of effect (34). Primer injury is more about focal but at the cortical lesion diffuse axonal injury seen (23).

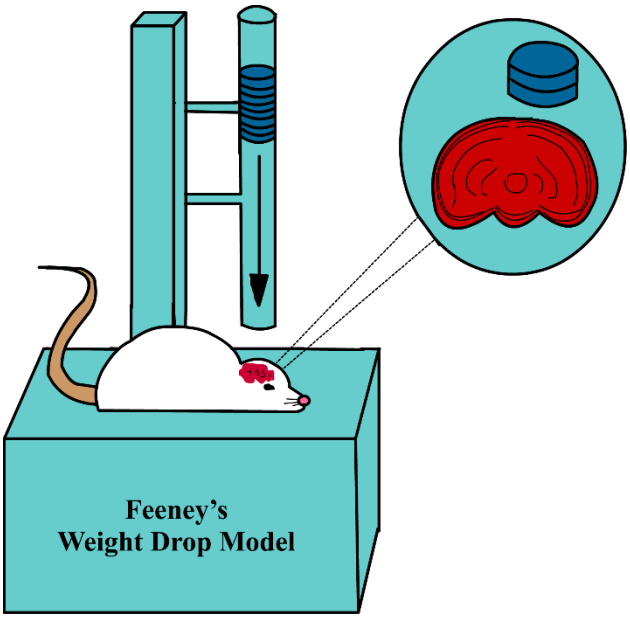

Figure 3. Feeney's weight drop experimental setup

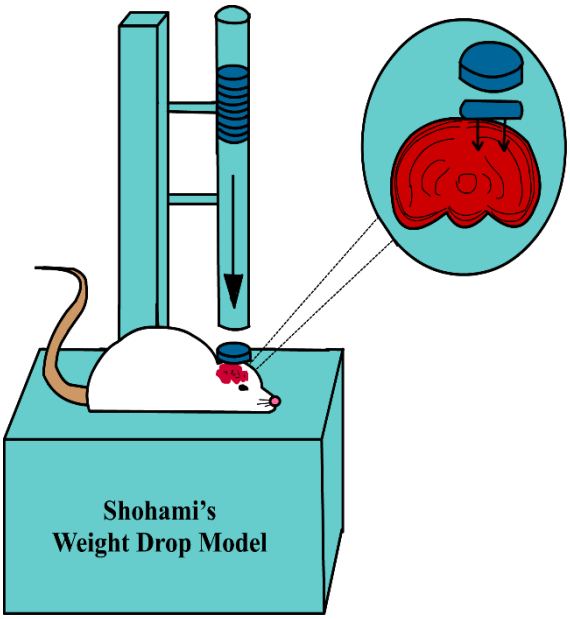

Figure 4. Shohami's weight drop experimental setup

3.1.3. Shohami's Weight Drop Model

The Shohami model is the method used in closed head injury using a weight-dropping blow to one side of the skull in rat (35) and mouse (27, 36) (Figure 4). The severity of injury in this model depends on mass of the weight and height of the fall. Therefore, heavier masses and/or increased fall height cause brain edema, cell death from the contusion site and activation of inflammatory cells over time following ipsilateral cortical brain contusion and disruption of the blood-brain barrier (32). Models using lighter masses and/or shorter fall heights show concussion-like brain injury, bilateral cell loss, short-term cerebral edema, and long-term cognitive impairment (23). Generally light weight drop injuries associates with diffuse injury beside heavy weight drop injuries causes focal contusion. This model's important advantage is under the gas anesthesia it could apply fast so shortly after the injury the neurological scoring can make (27, 36). Weight drop model disadvantage is the big differences between injury severities.

4. Limitations of Current Animal Models

4.1. Physiological differences

As physiological the human brain and other mammals brain have important similarity but as brain geometry, craniospinal angle, gyral complexity and ratio of white and gray ore there are important differences (10).

For treatment after TBI there are important differences between the gender human and animal (10). For women there are less comorbidity and complication seen after TBI (10). Experimental animal research shows us female sex hormones have neuroprotective effect (10). Current clinical evidence shows us progesterone, which female hormone is getting better the neurological results for TBI patients (10). In addition to sex hormones, many other gender differences affect outcome, including pre-injury comorbidities, brain function, and metabolism (10). Physiological variables before and after TBI, including PCO_2, PO_2, pH, blood pressure, and brain temperature, are also important in determining

pathophysiological responses to injury and treatment in TBI model studies (10).

4.2. Long- and short-term therapeutic treatments in animal TBI models

Most studies in animal models of TBI focus on short-term survival times ranging from hours to days and rarely exceeding one month after injury (37). These short-term studies provide us a lot of information about pathophysiologic and functional results at the acute time after TBI. Histological and behavioral data obtained at early post-injury time points may not provide a robust assessment of long-term outcomes and cannot be used to evaluate clinical treatments for long-term efficacy (10). More studies evaluating injury response and functional impairments over longer time periods (3 months to 1 year after TBI) are needed to confirm whether early changes can predict long-term outcome (10). Long-term functional and structural change can be happen until 1 year later from the TBI (10). These findings show therapeutic treatment is not limited with a couple hours after TBI, it could be more and more long time. Also, delayed progression of brain damage over months or even years suggests that early treatment is necessary to reduce brain damage, but not enough to support long-term recovery. Delayed treatment may benefit to TBI patients which missing the early phase of neuroprotection therapy (10). In an animal study functional recovery reported after delayed neurorestorative treatment to TBI patients which applied after 24 hours or more late. Although long-term behavioral disorders can be detected in rodent TBI models, it is known that cognitive disorders are more persistent than sensorimotor disorders (10). In animal models of TBI, it is necessary to test clinically relevant physiological parameters, long-term functional and cognitive outcomes, and the efficacy of new treatments.

4.3. TBI models comorbidities

Age is an important affect for TBI treatment. TBI is prominent death reason for children. Recovered people from the TBI when they were child is a big candidate for having behavioral disfunction (38). Clinical and experimental studies show the developing brains can be more sensitive to TBI (16, 39). TBI severity is an important risk with increasing age. The risk of TBI injury severity increases with increasing age. Elderly individuals with TBI differ from younger adults with TBI, including incidence rates, etiology of injury, nature of complications, length of hospital stay, functional outcomes, and mortality (16). Older than 75 ages adults are group with the highest hospitalization and death rates and falling is the prominent reason for TBI (16). Moreover the treatment dosage of therapeutic for youth rats may not be treat the old rats (16). This situation shows for old rats population need new treatments. Given the high incidence of TBI in the elderly population, much more preclinical research is needed in this area.

3. Neurobehavioral Assessment of Traumatic Brain Injury

5.1.Traumatic Brain Injury Behavior Experiments

At the Traumatic brain injury the motor, cognition, depression and anxiety like functional behaviors are generally evaluate. While motor tests measure the animal's motor coordination and balance, cognitive tests examine working memory and learning in rats with the help of visual cues (6). Tests that measure anxiety and depression generally examine the exploratory and anxiety behaviors of animals.

Behavioral disorders caused by TBI are mostly observed early after injury and gradually improve over time, depending on the severity of the injury. A similar pattern of improvement in cognitive impairment is observed over time in human TBI cases (40). Motor dysfunction after experimental traumatic brain injury is usually evaluated with open field, rotarod, balance beam, rod and rope grip tests (6). Cognitive dysfunctions are evaluated using Morris water maze test, radial arm maze, novel object recognition, object localization, Y and T maze tests (6).

5.2. Evaluation of Experimental Mild, Moderate and Severe Traumatic Brain Injury

With the Glasgow Coma Scale (GCS) which is a clinical evaluate method is not possible the evaluate of severity of injury because the severity of TBI in humans is assessed in the verbal response to the state of consciousness immediately after injury (6, 10). Also it is hard to evaluate an animal with anesthesia after injury. Neurological severity score (NSS) is generally used method for evaluate the injury severity for animal models (6, 10). The NSS scale evaluates loss of movement, straight walking, righting reflex, eye reflexes, limb reflexes, walking and balancing in the beam, and searching behavior (6, 10).

5.2.1. Glasgow Coma Scale (GCS)

GCS is a standard scale used for measuring the consciousness level, degree of cognitive impairment and severity of injury (10). Scoring is determined by summing up the ratings assigned to three factors based on whether and how the patient responds to certain standard stimuli by opening their eyes, verbally responding, and motor responding. A high score of 13 to 15 indicates mild brain damage, a score of 9 to 12 indicates moderate brain damage, and a score of 3 to 8 indicates severe brain damage.

5.2.2. Neurological Severity Score (NSS)

NSS is a trustworthy scale used for measuring the neurological injury, motor function and behavior after head trauma for mice and rats. NSS is combination of motor, behavior, reflex and balance tests for rats. It is rated from 0 to 18 (normal score, 0; maximum damage/impairment score, 18). A score is awarded for failure to perform tasks or tested reflex impairment: 13–18, damage severity; 7–12, medium moderate damage; 1-6, slight damage. In experimental studies, behavioral changes such as neurological severity score and motor function tests were evaluated, as well as physiological changes such as weight loss and increased intracranial pressure; Histological changes such as infarct volume and neuronal loss are also used (26, 41, 42).

CONCLUSION

Traumatic brain injury is one of the leading causes of death and disability. TBI is the result of external force causing mechanical disruption of brain tissue and delayed pathogenic events that exacerbate the damage. These pathogenic injury processes are poorly understood and thus no effective neuroprotective therapy is available so far. Experimental models, animal models are necessary to investigate the physiological and pathophysiological mechanisms of TBI, to test new therapeutic agents, and to ensure that clinical trials are safe and successful. Various rodent TBI models have been developed to model the different injury mechanisms associated with human TBI. The most commonly

used rodent models of traumatic brain injury are fluid percussion, cortical contusion effect, weight reduction and blast wave models. The design and selection of a particular model poses a major challenge for neuroscientists, as not all events that can occur in traumatic brain injury can be covered by a single rodent model. This section describes the strengths and weaknesses of current rodent models for traumatic brain injury.

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