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Experimental traumatic brain injury models in rats

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Abstract
Head traumas are high-mortality pathologies that can disable. Traumatic brain injury (TBI) is a heterogeneous disease containing brain damage caused by external effects. In the human brain injury after trauma, examinations cannot be made at histopathological and molecular levels, and the effect of a new drug on a head -trauma person cannot be examined. Human models are required to experimentally reveal the similarities of human TBI's biomechanical, cellular, and molecular events and to develop new treatments and show their effectiveness. Today, the most commonly used animals in TBI experiments are rats. Rats are preferred because their volumes are small and their costs are low, and the working groups can be enlarged. In this study, the commonly used rat TBI models and the restrictions of these models were compiled.

Keywords: *Rat, brain injury, injury models.*

1. Introduction

Head traumas are high-mortality pathologies in acute and chronic processes that are disabled and require long-term treatment and care. Head traumas and the risk of mortality and morbidity are increasing daily.[1] Traumatic brain injury (TBI) is a heterogeneous disease caused by brain damage caused by an external effect caused by a piercing instrument, a piercing tool, or an explosion. The source, density, direction, and duration of these effects determine the shape and results of the damage.[2]

Primary brain injury occurs first in the central nervous system after trauma. After many complex physiopathological events following primary brain injury, secondary brain injury occurs after hours or days.[3] In patients with TBI, secondary injury has been shown to affect prognosis in a poor direction. Secondary injury mechanisms include neurotransmitter release, free radical formation, calcium-dependent cell damage, gene activation, mitochondrial dysfunction, and inflammation.[4]

In human brain injury after trauma, examinations cannot be made at histopathological and molecular levels, and the effect of a new drug on a head trauma person cannot be examined. Therefore, animal models are required to experimentally reveal similar biomechanics and cellular and molecular events that cannot be handled in the clinical environment of Human TBI, develop new therapeutic interventions, and show their effectiveness. In the 1980s, various head trauma models were tried using cats, dogs, and external primates.[5] Although large animal models are still needed because the dimensions and physiology of TBI are closer to people, the use of rodents has become widespread since the 1990s.[6] Because we know many things about their physiological and behavioral features, and they are easily accessible to researchers, rats are used commonly.[7] Their volumes are small, their costs are low, and the working groups can be enlarged, and standardized result measurements are the main reason why researchers often prefer rat TBI models.

2. Rat traumatic brain injury models

There are four widely used unique models:
1. Head Impacts; Weight-Drop TBI model
2. Fluid Percussion Injury Model (FPI)
3. Controlled Cortical Impact Injury Model (CCII)
4. Penetrating Ballistic-Like Brain Injury Models

2.1. Head impacts; Weight-Drop TBI model

In weight reduction models, the skull (whether a craniotomy or not) is exposed to a free, directed weight with a pipe-shaped guide to create a large focal or diffuse TBI (Figure 1).

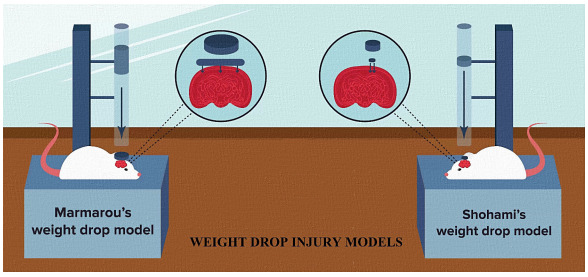

Figure 1. Weight drop injury models

In this model, an object weighing 450-500 grams is released from a distance between 1 and 2 meters, and a blow to the animal's head is created with the effect of gravity. The trauma formed varies according to the object's weight and the height at which it is left. The severity of the injury can be changed by adjusting the weight and height. It is a suitable model to investigate particularly

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moderate and severe diffuse head traumas. In head trauma, which is formed with 450 g weight left from 2 meters, the mortality rate was 44%, and the fracture rate in the skull was 12.5%.[8] In this model, to prevent skull fractures, the scalp is opened by making incisions in animals under anesthesia, the skull is seen, and a metal disk lambda and Bregma are fixed between Bregma. For focal trauma, the head is placed on a non-flexible platform. For creating diffuse TBI, the head is placed on a flexible platform-like platform.[9] Depending on the severity of the damage, diffuse head trauma can result in hemorrhage, death of neuronal cells, astrogliosis, diffuse axon damage, and brain edema. Various variants are available.

Marmarou weight-lowering model has been developed to typically drop or mimic the common TBI caused by motor vehicle accidents.[8] A craniotomy is not applied, the scalp is opened to prevent skull fractures, a disk is fixed to the skull, and the animal is put on the soft platform prepared using a flexible sponge or foam. As a result of trauma, the corpus callosum, optical nerve, internal capsule, and brain stem are damaged structures. Death is often caused by respiratory depression, and the application of mechanical ventilation after the impact significantly reduces the mortality rate after injury in animals.

In Feeney's weight-lowering model, unlike the Marmarou weight reduction model, rats are made craniotomy, and trauma is formed by applying weight on the disc on the disc. A cortical contusion occurs in this model.[10]

In Shohami's model, the head is placed on a hard surface, without protection with the disc, an impact of weight reduction is applied to one side of the skull, and a closed head injury is created.[11] The activation of neurobehavioral deficiencies, microglia, and astrocytes detected in this injury model, neuro-degeneration, and Morphological changes are similar to the clinical state of human closed head injury.[12-14]

Variances of weight reduction models are insufficient to form a wide range of front coups in motor vehicles and sports accidents. To investigate this type of injury, a new RAT closed head injury model called the Maryland model was developed by changing Marmarou's weight reduction model.[15] In this model, the impact force provided by the impact is applied to the anterior part of the cranium. TBI is formed by causing the brain's anterior-posterior and sagittal rotational acceleration in the intact cranium. Skull fracture, cortical contusion, long-term apnea, and mortality are characterized by being very low, and petechial bleeding may occur.

Recurrent Light TBI, a closed head trauma form, is common in contact sports such as boxing, hockey, football, and American football, child abuse victims, and military personnel. Increased evidence has shown that recurrent brain shakes can cause cumulative and long-term behavioral symptoms, neuropathological changes, and neurodegeneration. A different model has been defined in the scanning of new treatments for mild brain shock injuries. For this purpose, Marmarou's weight-lowering model was changed to allow recurrent head impacts in mild anesthesia.[16] In this method, incision and skull protective disk are not applied. Posttraumatic skull fractures and intracranial bleeding are rare. Minor deficiencies in motor coordination and locomotor hyperactivity improve over time. Mild astrocytic reactivity occurs without deterioration of the blood-brain barrier, without edema and microglial activation. This new animal model is used.[17] The high variability of weight-lowering in weight reduction models is a disadvantage of the high variability of injury.

2.2. Fluid percussion model (FPI)

In this model, the movement is created with a pendulum; after the pendulum hits a reservoir full of water, the piston at the end of the reservoir moves with the pressure effect in the water. A craniotomy is applied to a solid in the dura impact, thus creating a traumatic injury in the brain (Figure 2).[18]

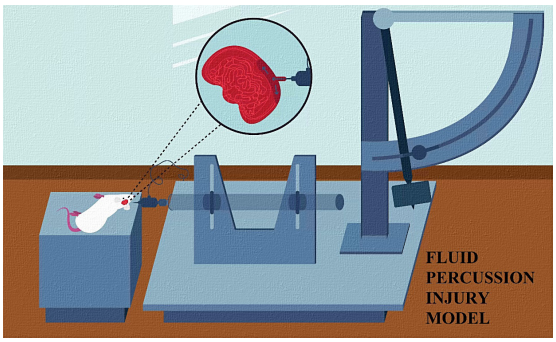

Figure 2. Fluid percussion injury model

The only adjustable mechanical parameter is a trauma intensity to be formed with the height of the pendant. According to the violence applied, pushing and deformation of the brain tissue occur. A combination of focal cortical contusion and diffuse subcortical neuronal damage (including hippocampus and injury in the thalamus) occurs. Intracranial bleeding and edema occur. Regardless of the application site of trauma, this model causes cognitive dysfunction, and thus, these models can also be used for posttraumatic dementia. Depending on the craniotomy's distance from the sulk suture, FPI models can be divided into moderate line (centered on the sagittal suture), parasagittal (moderate <3.5 mm lateral), and lateral models (moderate>3.5 mm lateral). The craniotomy location determines the scope and location of the produced tissue damage. In this model, the degree of adjustable liquid pressure and damage is proportional. The degree of cortical damage is largely dependent on both the craniotomy position and the seriousness of the injury.[19] This model shows higher morbidity than other models caused by apnea due to brain stem damage.[20] The disadvantage of the model is that it does not fully reflect the head trauma model in humans due to craniotomy administration.[21]

2.3. Controlled cortical impact injury model

Pulse is performed on the right-out dura that is directly exposed after a unilateral craniotomy between Bregma and Lambda. It uses a pneumatic or electromagnetic impact device to create an impact (Figure 3).[22]

Contact, hemorrhage, and blood-brain barrier due to the severity of the damage occur. This trauma model can see neuronal cell death, degeneration, astrogliosis, microglial activation, inflammatory events, axonal damage, cognitive disorders, excitotoxicity, and vasogenic and cytotoxic edema. This model is often more useful for studies that explain the pathophysiological processes and biomechanics of the secondary injuries of focal TBI.[23,24] The advantages of this method are the control

of the severity, velocity, and depth of the mechanical factor, and the disadvantage is similar to the FPI model.

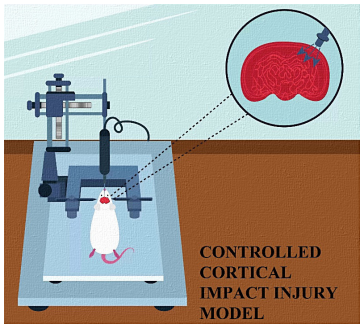

Figure 3. Controlled cortical impact injury model

2.4. Penetrating ballistic-lise brain injury models

Today, due to the prevalence of firearms, cranial injuries caused by such weapons are important community health problems. Fire-weapon injuries, most of the penetration brain injuries, have high mortality. 2/3 of the cases die as soon as the incident is. This type of injury is made with high-energy bullets or by creating a shock wave. The model formed with a shock wave is called Blast Injury Model (Figure 4).

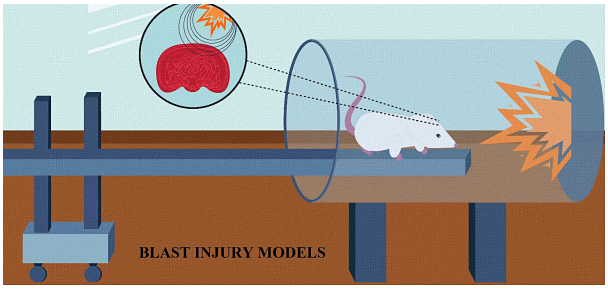

Figure 4. Blast injury models

The injury here is proportional to the intensity of the bullet and the path it travels. Compared to other TBI models, the amount of intracranial bleeding is high, and significant white and gray substance damage, brain swelling, neuroinflammation, and results in sensory-motor disorder.[25] Middle to severe brain trauma constitutes a similar condition.

The features of the injury models are given in Table 1.

Table 1. Features of injury models

Model		Type of injury	Advantage	Disadvantage	Skull fracture	Injury violence
Head Impacts; Weight-Drop TBI Model	Marmarou	diffuse	model is well characterized, the biomechanic of the injury mechanism is similar to human TBI*	usually not reproducible , high mortality rate	+/-	*high concussion high axonal injury low contusion low haemorrhage*
	Shohami	focal	the biomechanic of the injury mechanism is similar to human TBI	usually not reproducible	+/-	*high concussion high axonal injury low contusion low haemorrhage*
	Feeney	focal	the biomechanic of the injury mechanism is similar to human TBI	need for craniotomy, high mortality rate	-	*high contusion low axonal injury low concussion low haemorrhage*
	Maryland	diffuse	the biomechanic of the injury mechanism is similar to human TBI	there is a need for more work	-	*high axonal injury low concussion low haemorrhage*
	Repeated Light TBI	diffuse	low mortality rate	there is a need for more work	-	*low concussion low haemorrhage*
Fluid Percussion Injury Model		mixed	reproducible	need for craniotomy, high mortality rate	-	*high contusion low concussion low axonal injury low haemorrhage*
Controlled Cortical Impact Injury Model		focal	reproducible; low mortality rate	need for craniotomy	-	*high contusion high haemorrhage low concussion low axonal injury*
Penetrating Ballistic-Like Brain Injury Models		focal	the biomechanic of the injury mechanism is similar to human TBH	not standardize	+/-	*high contusion high haemorrhage low concussion low axonal injury*

**TBI: Traumatic brain injury*

3. Limitations of existing animal models

3.1. Physiological differences

Differences in the white-gray ratio in humans and animals. In addition, in animal TBI models, PCO_2, PO_2, PH, blood pressure, and brain temperature, including TBI before and after physiological variables, cannot be meticulously measured. These variables are very important in determining the physiopathological responses given to injury and treatment.[26]

3.2. Injury severity measurement

Evaluating trauma intensity as acute is critical for TBI's diagnosis, management, and prognosis.[27] Glasgow Coma Scale (GCS) is the primary tool for patient selection in TBI clinical studies, and the expanded version of the Glasgow Outcome Result Scale or Glasgow Outcome Result Scale is the primary method for evaluating the results.[28] However, a common scoring system, such as GCS, has yet to be created in animals for a short neurological examination.

3.3. Long-term and short-term studies

To date, most of the studies carried out in TBI's animal models have focused on short-term survival periods during the hours and days intervals, and little work has been covered by a month after the injury. Therefore, information about long-term pathophysiology and functional results.[29-31]

3.4. TBI models with comorbides

Multiple injuries, age, hypoxia, and hypotension are comorbidity factors that affect the results of TBI. Factors such as spine, abdominal, and thoracic trauma accompanying the head trauma encountered in real life cannot participate in the experiment, which makes the experiment similar to the realities. In addition, animal modeling is not a good example of childhood TBI modeling.[32]

4. Conclusion

As a result, different animal models developed to understand TBI physiopathology and apply potential treatments only partially reflect the complex events seen in the human brain. In addition, promising neuroprotective drugs, which were determined to be effective in animal TBI models, could not give the desired result in phase II or phase III clinical experiments. No model can reflect all the events in TBI.[23] Existing animal models can mimic some of them, although not all types of human brain damage. It is likely to achieve more positive results by selecting the appropriate model in the studies and decreasing restrictions.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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This situation does not exist.

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