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A Review Article on Changes in Neurological Behaviour in Rodents after Traumatic Brain Injury

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Abstract: Traumatic brain injury (TBI) is presently the leading cause of injury- related morbidity and mortality worldwide, with an estimated global cost of USD 400 billion annually. Traumatic brain injury (TBI) has been constantly linked to affective diseases similar as anxiety and depression. Traumatic brain injury is acquired from an external force, which can induce ruinous goods to the brain vasculature and neighbouring neuronal cells. Disruption of vasculature is a primary effect that can lead to a host of secondary injury falls. In this review we bandy the part of behavioural tasks in assessing issues associated with TBI. Animal models and behavioural assessments give varying strengths and weakness depending on the medium of injury and associated cognitive deficits in both acute and chronic stages of injury progression. Thus, this review aims to give guidelines for assessing rectifiers by probing the part of animal models and behavioural tasks for assessing TBI.

Key Words: neurotrauma; neurobehavioral; Traumatic brain injury; Animal models.

1. Introduction

Traumatic brain injury (TBI) is currently the leading cause of injury-related morbidity and mortality worldwide, with an estimated global cost of USD 400 billion annually [1]. Behavioural outcomes associated with TBI begin with primary injury to the brain resulting from an externally applied force [2]. These external forces can originate from direct contact between the brain and an object or through non-impact situations including rotational acceleration and the energy waves produced from blasts [3, 4]. Survivors of TBI are at increased risk for the development of severe, long-term psychiatric disorders. Prevalence of any psychiatric illness in the first year after the injury has been observed at a rate of 49% following moderate to severe TBI and 34% following mild TBI, compared to 18% in those without TBI [5]. TBI sufferers are particularly susceptible to major depression [6, 7], generalized anxiety disorder [8], post-traumatic stress disorder [9, 10], social withdrawal [11], apathy [12, 13], or aggression [14, 15]. These conditions can persist for decades after brain injury [16, 17] and delay rehabilitation and resumption of employment [18, 19].

Behavioural changes following TBI are reported at rates of 25–88% in people with moderate or severe TBI, with higher prevalence associated with more severe TBI [20–21]. These changes in emotional and social behaviour can include indifference, egocentric behaviour, emotional liability, poor social judgement and communication, aggression, apathy, impulsive, disinherited or irritable behaviour [22, 23]. Another common neurobehavioral effect after TBI is apathy, with estimates on its prevalence varying from 20% to 71% [24], which can impair cognitive function, psychosocial outcome, and rehabilitation efforts. Apathy presents as both a sign and a symptom, and may be considered a diagnosis by itself, in addition to a secondary condition from another underlying condition [25]. This research has determined that submissive behaviour can inhibit aggression and assist in ending disputes before they escalate into violence. Subordination and submission, in addition to the avoidance of inferiority and submission, are associated with anxiety and depression. Models of dominant and submissive behaviour have been supported as methods in both human and animal research through self reporting, observational and behavioural techniques, as well as natural and experimental approaches [26, 27]. Between anxieties after TBI, depression after TBI and changes in social behaviour after TBI is to use multivariate statistical methods to analyze behaviour. Due to ethical considerations, it is very difficult to establish a causal relationship in the human population. Therefore, preclinical studies using laboratory animals provide a useful solution. The high rates of depression and anxiety in people who suffer from TBI, rodent models of TBI have also shown increased depressive-like and anxiety-like behaviour [28]. Rats and mice have a wide expression of social behaviours that can be objectively measured. Study on this topic would have important implications for the treatment of anxiety, depression, social changes, and functional limitations following TBI.

2. Classification of TBI Injury Severity

The severity of a patient's TBI is primarily affiliated with the mechanism of injury in which the initial applied force is delivered to the head.

2.1. Glasgow Coma Scale

Initial analysis for categorizing the behavioural deficits following TBI in a clinical setting is based on the Glasgow Coma Scale (GCS), originally developed in 1974 [29, 30]. Although the classification criteria for this system were developed nearly 50 years ago, the system is

still regularly used by medical professionals to evaluate the degree of injury immediately following head trauma.

2.2. Mayo Classification of TBI

Mayo Classification of TBI In order to build upon the GCS method and provide a more complete classification system for the evaluation of TBI injuries, in 2007, the Mayo Clinic developed a model incorporating a variety of variables, including death, LOC, post-traumatic anterograde amnesia (PTA), and computed tomography (CT) imaging [31].

3. Categories of TBI

TBI can often be used to describe a broad condition with varying degrees of damage, but the causal injuries associated with TBI are categorized into three distinct forms: focal, diffuse, and non-impact. Focal injuries in a human population are created through direct impact forces acting on the skull, which causes compression of the underlying tissue. Focal injuries include skull fractures, contusions, lacerations, haemorrhages, and subdural, epidural, and intraparenchymal hematomas [32].

4. TBI Animal Models

Animal models are valuable tools used for providing an effective comparison to a variety of human conditions. Understanding the mechanism for the progression of various diseases allows researchers to develop treatment protocols which can be modified prior to human testing for optimal results. These models have been created for a multitude of ailments affecting the brain, including TBI [33]. TBI animal models have aided in the development of potential treatments for the reduction of oxidative stress, improving permeability and other various biochemical impairments following TBI [34]. Several models have been developed, sectioned into three distinct categories as seen in clinical Presentations of TBI: focal, diffuse, and non-impact injury [35].

4.1 **Focal TBI**

4.1.1 Weight Drop

The weight drop model is one of the original methods used for assessing TBI and has

several variations for modifying the overall design of the experiment. These variations are effective in differentiating between the various mechanisms of injury caused by a force impacting the animal's head.

(B) Feeney's Weight Drop Model

In Feeney's weight drop model, an incision is made through the midline of the scalp to create clear accessibility to the skull below. A portion of the skull is removed through craniectomy to allow for a direct impact between the free-falling weight and the animal's brain covered by the dura mater. The hole created from the removal of the skull is directly related to the diameter of the weight, reducing the risk of skull fracture from the weight colliding with the outer edges of the hole.[35]

(C) Shohami's Weight Drop Model

In Shohami's weight drop model, the mechanism of impact is shifted to represent trauma in a closed head injury (CHI) experiment. Prior to injury, an incision is made through the midline of the animal's scalp to gain accessibility to the skull.

(D). Fluid Percussion Injury

Fluid percussion injury (FPI) models provide a mechanism of impact that has been shown to produce variable TBIs with a focal injury and characteristics of both focal and diffuse brain injuries.

(E). Lateral Fluid Percussion Injury

Lateral FPI models are classified into mild (26–32 psi), moderate (35–41 psi), and severe (>41 psi) injuries based on the pressure pulse of the fluid. For lateral FPI, the centre of the craniectomy is positioned <3.5 mm or >3.5 mm laterally from the midline for parasagittal and lateral injuries, respectively.

(F) Penetrating Ballistic-Like Brain Injury

The penetrating ballistic-like brain injury (PBBI) model represents an injury consistent with severe TBI with a mechanism of injury similar to a gunshot wound. PBBI models produce an impact through the acceleration of a high-energy projectile into an impactor probe placed inside a cranial window, creating a temporary brain cavity in the animal model.

(G) Controlled Cortical Impact

The controlled cortical impact (CCI) model is currently one of the most used and wellcharacterized models of TBI due to the model's reproducibility and specificity regarding mechanical parameters.Originally developed in ferrets, the CCI model has been adapted for a variety of species, including mice, rats, swine, and monkeys**.** Features of injury include subdural hematoma, subarachnoid hemorrhage, and axonal injury, in addition to cortical

contusions and cortical tissue loss, which have been shown in clinical presentations of TBI.[35]

4.1.2 Non-Impact TBI

Non-impact TBI animal models provide an alternative mechanism for clinical presentations of injury that are not produced directly from mechanical impact. The previous injury models have all been representative of a human TBI developed from an initial mechanical force delivered to the head.

(A) Closed-Head Impact Model of Engineered Rotational Acceleration (CHIMERA)

The CHIMERA model was designed to produce a repeatable CHI in rodents through frontal rotational acceleration of the head without the need for surgical intervention.

(B) Blast Injury Model

Blast injury models have been extensively characterized for understanding the mechanism of injury relevant to military combat. While clinical a presentation of blast-induced TBI typically includes multiple levels of injury, the pathophysiology following primary blast injury requires its own individual model and experimentation. These models produce energy waves by releasing compressed gas through a tube to simulate blast effects in an animal without the need to expose the skull.[36]

5. Behavioural Analysis

Animal behaviour is a common method of determining deficits post-TBI. The model used for testing is crucial for behaviour as severity, phase of secondary injury, number of injuries, area of impact, and type of injury have been shown to show differences in behaviour post-TBI [36,37–39]. Thus, anyone looking to utilize behavioural analyses must be aware of any potentially confounding issues that may result from motor deficits, visual impairment, animal strain, sex differences, or other issues that may arise during testing. There are various forms of behavioural analyses one could benefit from using that are categorized into four groups of tasks: spatial learning and memory, nonspatial learning and memory, emotional, and motor coordination.

1. Spatial Learning and Memory Tasks

Spatial learning and memory are governed by the ability to navigate with two forms, allocentric and egocentric navigation. Allocentric navigation is generally described as using distal spatial cues to guide the direction of movement while egocentric navigation relies more heavily on internal cues such as remembered sequence, speed, the direction of movement, and utilizing closer cues referred to as “signposts”. Important in the discussion of egocentric

versus allocentric navigation is distinguishing between “signposts” and “landmarks”. While they provide information for egocentric and allocentric navigation, respectively, signposts do not provide any relational information. Signposts simply convey where to change direction and do not aid in understanding where one is in comparison to other signposts. In contrast, landmarks do not inherently tell you where to change direction, but can provide key information regarding one’s placement in relation to other landmarks [40]. To better understand, think of signposts as a particular intersection where you know to turn right to reach your location. Inversely, one could also use the landmark of the street sign and the knowledge of the direction they are approaching from to know to turn right in that situation.

2. Nonspatial Learning and Memory

As opposed to allocentric navigation, as described above, egocentric navigation is a method of determining how to travel similarly to how one might go about a traditional maze, using memory of motions made in conjunction with interior focal points to map out the area mentally. This kind of navigation can be seen in patterns such as the serial and non-spatial navigation while this can occur in many spatial learning tasks such as the RAM, certain variations of spatial learning tasks can be altered to examine nonspatial learning and memory specifically. While the overall administration of these tasks changes for the preclinical models, clinical delayed non-match to sample and VR tasks can also be adjusted to similar specifications to test nonspatial learning and memory. Some test conducted in Nonspatial Learning and Memory like In the Novel Object Location test rodents are allowed to explore an empty open field for 5 min. Animals are then given a 5 min trial one hour later with the objects placed in the open field and then another 5 min trial one hour later with one object in the same place and another object in a new place within the field. The one-hour inter-trial interval forces the animal to rely on the long-term memory rather than short-term memory or luck. Rodents are expected to use their natural curiosity to spend more time examining the object in a novel location as opposed to the object which had not moved.

3. Emotional Tests

Emotional changes in human TBI have been well documented. Despite this, many of the emotional tests used to determine emotional deficits, such as anxiety-like behaviors, lead to directly conflicting results depending entirely upon the paradigm, even within the same procedures. These differences have yielded results determining both high and low levels of

anxiety in the same open field test along with equal anxiety when compared to uninjured counterparts [41]. Many of these tests yield similar conflicts in TBI research. Additionally, human patients have reported near day-to-day variability in their levels of anxiety, depression, and other emotional markers [42]. This may influence attempts to find correlations between preclinical studies of TBI and clinical studies. However, many of these models have been used for drug exploration in other realms such as antidepressants, antianxiety, and other various psychopharmacological drugs. This may redeem some of the criticisms these tasks have been given in the realm of TBI research, though the innate variability of emotional deficits in TBI could also account for that difference.

3.1. Forced Swim Test

The forced swim test was designed originally for testing of antidepressant drugs and is accepted as a preclinical model of depression because of its usage in testing for antidepressant medication [43].

3.2. Dark/Light Avoidance Test

The light/dark avoidance test is used to quantify anxiety-like behaviours. Rodents have a natural aversion to well-lit areas, as referenced when discussing the BM. The light/dark test utilizes this as a way to determine anxiety-like behaviours by defining the light area as an anxiolytic zone and measuring time spent in the light and dark zones along with path length in each zone over a 15 min period [44].

3.3. Open Field Test

The open field test is useful for measuring both locomotion and anxiety-like behaviours in rodents and is one of the most commonly used methods of behavioural testing, especially in rodents. The field consists of a walled area with a light focused directly above the area with a 10 min limit to the test. For anxiety testing, measurements of time spent in the outside area of the maze, known as thigmotaxis, are considered to be a marker of anxiety-like behaviour. The more time an animal spends in the centre of the arena, the less anxiety-like the animal's behaviour. Additionally, movement can be measured with higher amounts of distances travelled being considered as an anxiety-like reaction [45].

3.4. Resident Intruder Test

The resident intruder test is a common test for aggression. Much of the data gathered from this test are specifically behavioural, relying heavily upon noticing differences, frequency and duration of offensive aggression, defensive aggression, and violence. During the test, the female is replaced with a novel male into the cage and observed to determine a battery of

scoring measuring two opposites of behaviour, aggression and sociability/anxiety, measured by the Total Offense Score and the Social Exploration Score, respectively [46].

Conclusions

In summary, we demonstrate the effects on anxiety outcomes after traumatic brain injury may be the result of the variability in injury models used, behavioural assays of anxiety chosen and time-points at which assessments were made. Categorizing the animal models based on previously established classification systems would provide additional framework for researchers to compare between the different models. Additionally, classifying the animal models creates an additional comparison to human TBI, ultimately benefiting diagnostic and treatment methods. In the future, effort should be placed towards establishing a standardized behavioural assessment for comparing animal models, in the hopes of effective translation between cognitive deficits seen in animals and humans. Including behavioural analysis would further strengthen the comparison between animal models and human TBI, leading to increased success in clinical trials.

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