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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 neighbouringneuronal cells. Disruption of vasculature is a primary effect that can lead to a host of secondaryinjuryfalls.Inthisreviewwebandythepartofbehaviouraltasksin assessing issues associated with TBI. Animal models and behavioural assessments give varying strengths and weakness depending on the medium of injury and associated cognitivedeficitsinbothacuteandchronicstagesofinjuryprogression.Thus,this review aims to give guidelines for assessing rectifiers by probing the part of animalmodels and behavioural tasks for assessing TBI.

KeyWords:neurotrauma;neurobehavioral;Traumaticbraininjury;Animalmodels.

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 resultingfrom 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 atincreased riskforthe development of severe, long-termpsychiatric 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], generalizedanxietydisorder[8],post-traumaticstressdisorder[9,10],socialwithdrawal [11],apathy[12,13],oraggression[14,15].Theseconditionscanpersistfordecadesafter braininjury[16,17]anddelayrehabilitationandresumptionofemployment[18,19].

BehaviouralchangesfollowingTBIarereportedatratesof25–88%inpeoplewithmoderate orsevereTBI,withhigherprevalenceassociatedwithmoresevereTBI[20–21].These changes in emotional and social behaviour can include indifference, egocentric behaviour, emotional liability, poor social judgement and communication, aggression, apathy, impulsive, disinheritedorirritablebehaviour[22,23].Anothercommonneurobehavioraleffectafter TBI is apathy, with estimates on its prevalence varying from 20% to 71% [24], which canimpaircognitivefunction,psychosocialoutcome,andrehabilitationefforts.Apathypresents as both a sign and a symptom, and may be considered a diagnosis by itself, in addition to a secondaryconditionfromanotherunderlyingcondition[25].Thisresearchhasdetermined that submissive behaviour can inhibit aggression and assist in ending disputes before they escalateintoviolence.Subordinationandsubmission,inadditiontotheavoidanceof inferiorityandsubmission, are associatedwithanxietyanddepression.Modelsofdominant andsubmissivebehaviourhavebeensupportedasmethodsinbothhumanandanimal research through self reporting, observational and behavioural techniques, as well as naturaland 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.Duetoethicalconsiderations,itisverydifficulttoestablishacausalrelationship in the human population. Therefore, preclinical studies using laboratory animals provide ausefulsolution.Thehighratesofdepressionandanxietyinpeoplewhosufferfrom 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. ClassificationofTBIInjurySeverity

Theseverityofapatient'sTBI isprimarilyaffiliatedwiththemechanismof injuryinwhich the initial applied force is delivered to the head.

2.1. GlasgowComaScale

Initial analysis for categorizing the behavioural deficits following TBI in a clinical setting is basedontheGlasgowComaScale(GCS),originallydevelopedin1974[29,30].Although theclassificationcriteriaforthissystemweredevelopednearly50yearsago,thesystemis

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

2.2. MayoClassificationofTBI

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. CategoriesofTBI

TBI can often be used to describe a broad condition with varying degrees of damage, but the causalinjuriesassociatedwithTBIarecategorizedintothreedistinctforms: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. TBIAnimalModels

Animal models are valuable tools used for providing an effective comparison to a variety of humanconditions.Understandingthemechanismfortheprogressionofvariousdiseases allowsresearcherstodevelop treatmentprotocolswhichcanbemodifiedprior tohuman testing for optimal results. These models have been created for a multitude of ailmentsaffecting 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 **FocalTBI**

4.1.1 WeightDrop

Theweightdropmodelisoneoftheoriginalmethodsusedforassessing TBIandhas

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'sWeightDropModel

In Feeney's weight drop model, an incision is made through the midline of the scalp to create clearaccessibilitytotheskullbelow.Aportionoftheskullisremovedthroughcraniectomy to allow for a direct impact between the free-falling weight and the animal's brain covered by theduramater.Theholecreated fromtheremoval ofthe skullisdirectlyrelated tothe diameter of the weight, reducing the risk of skull fracture from the weight colliding with the outer edges of the hole.[35]

(C) Shohami'sWeightDropModel

In Shohami's weight drop model, the mechanism of impact is shifted to represent trauma in a closedheadinjury (CHI)experiment.Prior toinjury, anincision ismadethroughthemidline of the animal's scalp to gain accessibility to the skull.

(D). FluidPercussionInjury

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). LateralFluidPercussionInjury

LateralFPImodelsareclassifiedintomild(26–32psi),moderate(35–41psi),andsevere (>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) PenetratingBallistic-LikeBrainInjury

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 impactthrough the accelerationof a high-energyprojectile intoanimpactor probe placed inside a cranial window, creating a temporary brain cavity in the animal model.

(G) ControlledCorticalImpact

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 includesubduralhematoma,subarachnoidhemorrhage,andaxonalinjury,inadditiontocortical

contusionsandcorticaltissueloss,whichhavebeenshowninclinicalpresentationsof TBI.[35]

4.1.2 Non-ImpactTBI

Non-impactTBIanimalmodelsprovideanalternativemechanismforclinicalpresentations 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-HeadImpactModelofEngineeredRotationalAcceleration(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) BlastInjuryModel

Blast injury models have been extensively characterized for understanding the mechanism of injuryrelevanttomilitarycombat.WhileclinicalapresentationofblastinducedTBI 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. BehaviouralAnalysis

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, areaof 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,sexdifferences,orotherissuesthatmayariseduringtesting.Therearevariousforms 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. SpatialLearningandMemoryTasks

Spatiallearningand memoryaregovernedbythe abilitytonavigatewithtwoforms, 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 heavilyoninternalcuessuchasrememberedsequence,speed,thedirectionofmovement, andutilizingclosercuesreferredtoas“signposts”.Importantinthediscussionofegocentric

versus allocentric navigation is distinguishing between “signposts” and “landmarks”. Whilethey provide information for egocentric and allocentric navigation, respectively, signposts do notprovideanyrelationalinformation.Signpostssimplyconveywheretochangedirection 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 keyinformation regarding one’s placement in relation to other landmarks [40]. To betterunderstand,thinkofsignpostsasaparticularintersectionwhereyouknowtoturnrightto reach your location. Inversely, one could also use the landmark of the street sign and the knowledge of the direction they are approaching fromtoknow toturnrightinthatsituation.

2. NonspatialLearningandMemory

Asopposedtoallocentricnavigation,asdescribedabove,egocentricnavigationisamethod of determining how to travel similarly to how one might go about a traditional maze, using memory of motionsmade in conjunction with interior focalpointstomap outthe 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.Whiletheoveralladministrationofthesetaskschangesforthepreclinical 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 LearningandMemorylikeIntheNovelObjectLocationtestrodentsareallowedtoexplore 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 another5 min trial one hour later with one object inthe 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. EmotionalTests

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.Thesedifferenceshaveyieldedresultsdeterminingbothhighandlowlevelsof

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, humanpatientshavereportednearday-to-dayvariabilityintheirlevelsofanxiety, depression,andotheremotionalmarkers[42].Thismayinfluenceattemptstofind 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 innatevariability of emotional deficits in TBI could also account for that difference.

3.1. ForcedSwimTest

The forced swimtestwas designed originallyfor testing of antidepressant drugs and is acceptedasapreclinicalmodelofdepressionbecauseofitsusageintestingfor antidepressant medication [43].

3.2. Dark/LightAvoidanceTest

The light/dark avoidance test is used to quantify anxiety-like behaviours. Rodents have anatural 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 anxiolyticzoneandmeasuringtimespentinthelightanddarkzonesalongwithpathlength in each zone over a 15 min period [44].

3.3. OpenFieldTest

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 a10 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 distancestravelled being considered as an anxiety-like reaction [45].

3.4. ResidentIntruderTest

Theresidentintrudertestisacommontestforaggression.Muchofthedatagatheredfrom this test are specifically behavioural, relying heavily upon noticing differences, frequency and duration of offensive aggression, defensive aggression, and violence. During the test, thefemaleisreplacedwithanovelmaleintothecageandobservedtodetermineabatteryof

scoringmeasuringtwooppositesofbehaviour,aggressionandsociability/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 maybetheresultofthevariabilityininjurymodelsused,behaviouralassaysofanxietychosen 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 furtherstrengthenthecomparisonbetweenanimalmodelsandhumanTBI,leadingto increased success in clinical trials.

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