Traumatic Brain Injury: The Therapeutics Approaches of Brain Injury and Different Animal Models

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Abstract

Traumatic brain injury is one of leading causes of indisposition and impermanence across allages of people in world, According to CDC (centers for disease control and prevention) approximately 2.5 million patient are affected to traumatic brain injury such patients are hospitalized and another patient are died. Primary and secondary are two type of pathophysiology of traumatic brain injury primary brain injury is focal or mechanical brain injury and secondary brain injury is a diffused brain injury, secondary brain injury cause different therapeutics approaches such as blood brain barrier ,edema, inflammation, mitochondrial dysfunction , ecotoxicity, oxidative stress, apoptosis and cell death. We use the different animal model to determine the mild, moderate and severity of traumatic brain injury. Two types of animal model:A. Focal brain injury such as Controlled cortical injury (CCI), Fluid percussion injury (FPI), penetrating ballistic like brain injury, abusive head trauma B. Diffuse brain injury animal models such as Feeney's weight drop model, Marmarou's weight drop, and Blast injury.

1. INTRODUCTION

Traumatic brain injury (TBI) is a one of leading causes of casualty and disability in most commonly in adults ages in the world, is frequently caused by mechanical shock, resulting in focal and neuronal dysfunction. TBI refers to exterior or interior force that leads to a temporary or permanent impairment of physical, psychological, and cognitive function along with an altered state of consciousness.[1,2]Depending on the extent the damage, the clinical manifestations of this pathological condition of the brain might take the form of a concussion, a contusion of variables severity compression of the brain brought on by diffuse axonal injury . TBI should be acknowledge as it raises the danger of diseases of the nervous and psychiatric system, as well as illnesses of the circulatory respiratory, motor and digestive system.[3]The world health organization predicts that TBI will be a serious health issue and the cause of disability. Permanent brain dysfunction as result of secondary brain injury such as major therapeutics approaches are involve like as excitotoxicity, mitochondrial dysfunction ,axonal dysfunction, cell degradation ,apoptosis, inflammatory . It can result various neurological dysfunction such as Parkinson, Alzheimer, epilepsy, and traumatic brain injury.[4]

2. EPIDEMIOLOGY

According to the Centers for Disease control and prevention (CDC), 2.5 million individuals worldwide experienced traumatic brain injury in 2010, with many of these patients hospitalized and some passing away.[5] By,2014, these numbers had increase to 2.53 million cases worldwide, Hospitals treat 288,000 traumatic brain injury patients, and 56,800 of these patients die as a result of their injuries. These data cover patients who as athletes, military personnel, and victims of accidents.[6]

3. THERAPEUTICS APPROACHES OFTRAUMATIC BRAIN INJURY

Traumatic brain injury causes brain damage, there are involves in twotypesinjury, primary and secondary injury. Primary brain injury causes focal brain injury and while secondary brain injurycauses diffuse brain injury such as blood -brain barrier (BBB), brain edema,peripheral blood cells infiltration, axonal damage, mitochondrial dysfunction, oxidative stress, apoptosis and cell death.[7]

Excitotoxicity

Traumatic brain injury destruction of the blood brain barrier(BBB), excess neurotransmitters are released and glutamate transporters that are normally responsible for the reuptake of glutamate are unable to function properly. Both ionotropic and metabotropic glutamate receptors are activated when glutamate and its various metabolites bind to them. Ionotropic glutamate receptors include the NMDA and AMPA receptors, which allow sodium,

potassium, and calcium ions to ether the membrane for depolarization. In Traumatic brain injury excessive glutamate release allow extracellular Ca^{2+} and Na^{+} ions to enter the cell, altering ions homeostasis and leading to overexpression of these receptors. It has been demonstrated that the excitotoxic response is mediated by GluN2B, which is found in synaptic cytosol. Numerous downstream signaling molecules, including Ca^{2+}/ calmodulin-dependent protein kinase II, protein kinase C, mitogen- activated protein kinases (MAPK),and protein phosphates, are triggeredby excess intracellular Ca^{2+}. Ca^{2+} overproduction in the cytosol causes caspases, calpain, andother apoptotic proteins to be activated, resulting in cell death. The accumulation of reactive oxygen species (ROS) also impairs mitochondrial function.[8,9]Excitotoxicity results in cell death, and excitotransmitters causes cells to die from oxidative stress. NMDA receptors activation is used to initiate glutamate independent excitotoxicity immediately following a head injury's shear and stretch forces. One study also showed that NMDA receptors are mechanosensitive to specific subunits and signaling cascades that control how NMDA receptors respond to mechanical stimuli. The mechanosensitive response was mediated by the GluN2B subunit.[2,3,9]

Mitochondrial dysfunction

Traumatic brain injury is considered by mitochondrial diminishing, which modifies physiological and metabolic function andcausesof cell death. ROS production and mitochondrial membrane depolarization without ATP synthesis may result from an excessive Ca^{2+} infiltration. ROS production, depolarization of the mitochondrial membrane, and inhibition of ATP synthesis are all consequences of the invasion of excess ions into mitochondria.[10]Electron transport chain and oxidative phosphorylation processes are compromised as a result, causing calcium regulation and metabolic function to be disrupted. The mitochondrial permeability transition pore (mPTP) is activated when there is stress. Upon binding with cyclophilin D, mitochondrial dysfunction also causes a structural change in the adenine nucleotide translocator protein, resulting in mPTPopening and increased inner membrane permeability.[11] A key role in apoptotic cell death is played by additional mitochondrial proteins like cytochrome C and apoptosis inducing factor (AIF).[12,13]

Neuroinflammation

TBI causes a wide range of immunological and inflammatory responses in the tissues. Prostaglandins, pro-inflammatory cytokines, and free radicals are cellular mediators that are individually activated by primary and secondary processes. Polymorphonuclear leukocytes and cytokines released inflammatorymediators such as IL-6,IL-1,and TNF-24 hours after the trauma, as determined by examinationof TBI patient's post-mortem, cerebrospinal fluid, and a rodent model. The prolonged release of cytokines demonstrated that the BBB's permeability was altered, resulting in edema and neurological impairments. TNF- activates caspases for programmed cell death and interacts strongly with ligand. Chemokines like IL-8 (CXCL8),MIP-1 and MCP-1, which attract leukocytes to the injury site, have been found in traumatized areas. By interacting with the endothelium, endothelial and leukocyte cell adhesion molecules like ICAM-1 and VCAM-1 also make it easier for leukocytes and immune cells to get to the injured area. Macrophages activate microglial cells during prolonged neuroinflammation, resulting an increase in the release of astrocytes, as has been observed in TBI survivors many years after the injury. At the cellular and behavioural levels, the function of GSK-3 in the physiological model of mild traumatic brain injury (mTBI) was investigated. In addition to controlling cell apoptosis, GSK-3 has been linked to depressive behaviour. L803-MTS or the GSK-3 inhibitor improved mTBIinduced depression.[14]

Axonal degeneration

Diffuse axonal injury (DAI) is the result of a sudden mechanical injury to neurons that destroys the axonal cytoskeletal, which includes neurofilaments and microtubules. Myelin sheath degradation, axonal transport damage, and a build up of axonal transport proteins distinguish acute trauma- induced axonal damage from persistent calcium-mediated proteolysis. Long term axon swelling band cell and oligodendrocyte apoptosis occur when axonal transport protein is overexpressed. Retraction bulbs were primarily observed in the

corpus collosum and pyramidal tracts of the brain stem. They have been found in the cortex, cingulum, and hippocampus, according to reports.[14,15]

Apoptotic cell death

Apoptosis and cell death is main cause of causes of secondary brain injury. Molecular pathways, such as extracellular signal- regulated kinase (ERK), kinase/signal transducer and activator of transcription (JAK/STAT), and p38 MAPK, activate a number of downstream protease, including calpain and caspases. The extrinsic pathway (EP) and the intrinsic pathways (IP) are the two pathways the control apoptosis downstream caspase 3 through caspase 8 and 9 modulation, whereas EP incorporates TNF inte4ractions with their respective cell receptors. However, in TBI caspase independent apoptosis causes mitochondrial proteins, like AIF, DIABLO, endonuclease G, and polymerase-1 to be released into the nucleus. This further activates upstream signaling molecules that causes damage to neuronal and glial cells.[16,17]

4. ANIMAL MODEL

In situation of pre-clinical trial in TBI, we use animal models for such injury has been developed. Although larger animals are closer in size and physiology then we used to rodent is smaller in size and physiologically similar to human. [15]Rodent are mostly used to research in traumatic brain injury for measurements and standardized the among parameters and reasons which caused different-2 types of traumatic brain injury.[18]Animals models are best offer the alternative examines of biochemical, cellular, and molecular mechanism of TBI. It is associated to neurological pathology progression and its effects. Recent more specific animals models are used in research such as: 1.Abusive head trauma (AHT) 2.Fluidpercussion injury (FPI)3. Controlled cortical impact (CCI) 4. Feeney's weight drop model 5. Feeney's weight drop model 6. Marmarou's weight drop model, and other animals modelsare used in TBI such as: 1. Blast injury, 2. PBBI (Penetrating ballistic brain injury).[19-21]

4.1 Abusive head trauma (AHT)

Abusive head injury is non accident trauma. One of the prevalent types of traumatic brain injury is abusive head trauma (AHT), commonly known as "Shaken baby syndrome".It results from physical acceleration and deceleration that occurs during a road accident (typically a car accident). If can have a long -lasting effect on the victim's life. If the victim survives, it may also result in hearing loss, poor vision or blindness, memory loss and other problems.In animal model to identifies the pathogenesis and changements of physical and biomechanical mechanism of the pathologic, AHT can causes permanent brain damage, it can lead to neurological injury.[19,20]

4.2 Controlled cortical injury model (CCI)

CCI is the focal injury model which cause direct injury in brain such as ballistic injury, contusion is best model of laboratory experimental condition by animal model.[24] In the CCI model surgically impact on dura by rapid acceleration rod which is computer guided software and control depth of impacts and pneumatic position 3.5mm diameter. The rod size and shapes are varied for different species. The rod hits directly and exposed to the brain tissue which cause cortical injury and loss of cortical tissue, blood brain barrier damage. In this model appear take the advantage to controlled tissue deformation, controlled time, velocity, and depth of impact without causing of risks.[22,23]

4.3 Fluid percussion injury model (FPI)

FPI was performed using a fluid percussion device. The injury delivered to the dura meter previously to maintain anaesthesia during FPI and anesthetized rodent were fixed in a stereotactic device.The scalp was incised at the midline and the skull was exposed. A hole 3mm in diameter was made in the skull of the left hemisphere 2.5nm posterior and 2.5nm left lateral from the bregma.[23]After opening the skull fixed and fitted the fluid percussion device's polyethylene tube was connected to the lure fitting, which was then filled with sterilized saline.[24]

4.4 Penetrating ballistic like brain injury

Penetrating ballistic-like injury (PBBI) occurs when projectiles are transmitted with a leading shockwave and high energy.[23]This creates a temporary cavity in the brain that is many times larger than the projectile itself. In this model, the outcome is directly related to the projectile's anatomical path and the amount of energy transferred. Previously, experiment PBBI studies using a penetrating missile model on mice were the most relevant to gunshot wounds. It has been established that a rodent model of penetrating brain injury results in cognitive impairment. It causes significant damage to the while and grey matter, seizures, cortical spreading depression, neuroinflammation, and sensorimotor impairment.[25,26]

4.5 Marmarou's weight drop model

Diffuse axonal injury (DAI), which affects the entire head, is the most common type of traumatic brain injury in humans and experimental animal models and is caused by falls from heights or car accidents. Marmarou's model was developed to simulate DAI.[23]The selected brass weight in these models falls freely from the Plexiglas tube. To prevent skull fracture, the anesthetized rodent skull is covered with a stainless steel disc or helmet mounted midway between the lambda and bregma.[26] The brass weight is dropped by rodents onto the bed and onto a stainless steel disc. This model is characterized by diffuse axonal injury as well as widespread bilateral damage to neurons, axons, and dendrites. It also affects the respiratory tract, optical tract, cerebral and cerebellar peduncle's and the brain stem over time.[27]

4.6 Feeney's weight drop model

The closed head injury model is also known as Feeney's weight drop model. The rodent was anesthetized in intraperitoneal routes, and a craniotomy was performed on the right peritoneal lobe of the skull with the aid of a drill to open the dura muscles that protect the brain. Following the craniotomy, the rodent was placed in a bed, set to work, and delivered suitable weight, which resulted in a cortical contusion. Within 24 hours, this necrotic cavity injury developed, and the cavitation appears to last for two weeks.[28,29]

4.7 Blast injury

TBI has been identified in a large number of military personnelwho have been exposed to a blast but have not sustained any external injuries. The physiological, neuropathological, and neurobehavioral consequences of blast exposure were evaluated using a compression-driven shock tube to simulate blast effects, and the effect of a Kevlar thoracic protective vest on acute mortality in rats as well as on the frequency of TBI and DAI in those animals that survived was also evaluated.[28]Various animal models of blast TBI have been established, primarily in rodents, to elucidate the effects of primary blast waves on the CNS. Diffuse cerebral oedema, DAI, extreme hyperemia, and delayed vasospasm were all brought on by the induced TBI model, which simulated actual blast induced mild TBI.[29]

5. REFERENCE

1. Komal Thapa, Heena Khan, "Thakur Gurjeet singh, Amarjot kaur, Traumatic brain injury: Mechanistic insight on pathophysiology and potential therapeutic targets," Journal of molecular neuroscience, 2021.https://doi.org/10.1007/s12031-021-01841-7.
2. Si Yung Ng, Alan Yiu Wah lee, "Traumatic brain injury : Pathophysiology and potential therapeutic targets", Frontiers in cellular neuroscience,2019. DOI: 10.3389/fncel.2019.00528.
3. Chen Chen, Jiawei Hou, Junfeng Lu, Zeyu Zhu, Yang Yang, Weijia Peng, Rongbiao Pi, "A novel simple gtraumatic brain injury mouse model", Chinese neurosurgical journal, 2020.https://doi.org/10.1186/s41016-022-00273-5.
4. Baoqi Dang, Wenlin Chen, Weichum He, and Gang Chen, "Rehabilitation treatment and progress of traumatic brain injury dysfunction", Hindawi Neural plasticity,2017.https://doi.org/10.1155/2017/1582182.
5. Arti Rana, Shamsher Singh, Shamsher Singh, Ruchika Sharma, Anoop Kumar, "Traumatic brain injury altered normal brain signaling Pathways: Implication for novel therapeutic approaches", Current neuropharmacology, 2019, 17.614-629.
6. Allison Capizzi, Jean Woo, Monica Verduzco- Gutierrez, "Traumatic brain injury An overview of epidemiology, pathophysiology and medical management.
7. Rosalia Paterno, Kaitlin A. Folweiler, Akiva S.Cohen, "Pathophysiology and treatment of memory dysfunction after traumatic brain injury," Springer science+ business media new York,2017. DOI: 10.1007/s11910-017-0762-x.
8. Tae Yeon Kim, Kimle Niimi, Eiki Takahasi, "Role of Cav2.1 Channel signaling in Glutamate- related brain injury", Brain disorder and therapy, 2016. DOI:10.4172/2168-975X.10000226.

9. Daniela Baracaldo-Santamaria, Daniel Felipe Ariza-Salamanca, Maria Gabriela Corrales- Hernandez, Maria Jose Pachon-Londono, Isabella Hernandez- Duarte, Carlos-Alberto Calderon-Ospina, " Revisiting Excitotoxicity in Traumatic Brain Injury: From Bench to Bedside" 2020, Pharmaceutics, MDPI https://doi.org/10.3390/pharmaceutics14010152.
10. John B. Hiebert, Qiuhua Shen, Amanda R. Thimmesch, Janet D. Pierce, "Traumaticbrain injury and mitochondrial dysfunction",2015 ,DOI:10.1097/MAJ.0000000000000506.
11. Gang Cheng, Rong-hua Kong, Lei-ming Zhang, Jian-ning Zhang, " Mitochondria in traumatic brain injury and mitochondrial-targeted multipotential therapeutic strategies", British journal of pharmacology,2012, DOI:10.1111/J.1476-5381.2012.02025.x.
12. Susan Kim, Steve C Han, Alexander J Gallan, Jasmeet P Hayes, "Neurometabolic indicators of mitrocondrial dysfunction in repetitive mild traumatic brain injury", Concussion,2017, DOI: 10.2217/cnc-2017-0013.
13. Yihao Zhu, Handong Wang, Jiang Zhou, Xialiang Wang, Menliang Zhou, "SS-31 Provides neuroprotection by reversing mitochondrial dysfunction after traumatic brain injury", Hindawi, 2018, https://doi.org/10.1155/2018/4783602.
14. Chong-Chi Chiu, Yi-En Liao, Ling-Yu Yang, Jing- Ya Wang, David Tweedie, Hanuma K. Karnati, Nigel H. Gregi, Jia-Yi Wang, "Neuroinflammation in animal models of traumatic brain injury", Journal of neuroscience methods,2016.
15. W.Brad Hubbard, Binoy Joseph, Malinda Spry, Hemendra Vekaria, Kathryn E. Saatman, Patrick G. Sullivan, "Acute mitochondrial impairment underlies prolonged cellular dysfunction after repeated mild traumatic brain injury", Journal of neurotrauma,2018, DOI: 10.1089/neu.2018.5990.
16. Bogdan A. Stoica and Alan I. Faden, "Cell death mechanisms and modulation in traumatic brain injury", Neurotherapeutics: The journal of the American society for experimental Neurotherapeutics,2010. DOI:10.1016/j.nurt.2009.10.023.
17. Kathleen M. Schoch, Sindhu K. Madathil, Kathryn E. Saatman, "Genetic manipulation of cell death and neuroplasticity pathways in traumatic brain injury" Neurotherapeutics, 2012. DOI: 10.1007/s13311-012-0107-z
18. Michael Galgano, Gentian Toshkezi, Xuecheng Qui, Thomas Russell, Lawrence chin, and Li-Ru Zhao, "Traumatic brain injury: Current treatment strategries and future endeavors," Cell Transplantation 2017.DOI:10.1177/0963689717714102.
19. Erik B. Smith, Jennifer K. Lee, Monica S. Vavilala, Sarah A. lee, "Pediatric traumatic brain injury and associated topics" 2019.DOI:10.1016/j.anclin.2018.10.002.
20. John W.Finnie, Peter C. Blumbergs, "Animal models of pediatric abusive head trauma", 2020.https://doi.org/10.1007/s00381-022-05577-6
21. Ekta J. Shah, Katherine Gurdziel, Douglas M. Ruden, "Mammalian models of traumatic brain injury and a place for dorsophila in TBI research", Frontiers in neuroscience, 2019. Doi:10.3389/fnins.2019.00409.
22. Jun-Xi-Dai, Yan-Bin Ma, Nan-Yang Le, Jun Cao ,Yang Wang, "Large animak models of traumatic brain injury", International journal of neuroscience, 2017.http://dx.doi.org/10.1080/00207454.2017.1380008.
23. Ye Xiong, Asim Mahmood, Michael Chopp, "Animal models of traumatic brain injury", Department of neurosurgery, 2013. DOI:10.1038/nrn3407.
24. Xiaotang Ma, Aswati Aravind, Bryan J. Pfister, Namas Chandra, James Haorah, "Animal models of traumatic brain injury and assessment of injury severity", Molecular Neurobiology, 2018, https://doi.org/10.1007/s12035-018-1454-5
25. Xingyun Quan, Li Song, Xiaomei Zheng, Shenjie Liu, Huaquiang Ding, Sijing Li, Guanghui Xu, Xin Li, Liang Liu, "Reducation of Autophagosome O,verload attenuates neuronal cell death after traumatic brain injury", Neuroscience2021. X.Quanet.al./Neuroscience460(2021)107-119.
26. Chen Chen, Jiaweli Hou, Junfeng Lu, Zeyu Zhu, Yang Yang, Weijia Peng, Rongbiao Pi, "A novel simple traumatic brain injury mouse model", 2020.https://doi.org/10.1186/s41016-022-00273-5.
27. Yihao Zhu, Handong Wang, Jiang Fang, Wei Dai, Jiang Zhou, Xiaoliang Wang, and Mengliang Zhou, "SS-31 provides Neuroprotection by Reversing Mitochondrial Dysfunction after traumatic brain injury," Hindawi, 2018. https://doi.org/10.1155/2018/4783602.
28. Kirsty J. Dixon, "Pathophysiology of traumatic brain injury", 2017.https://dx.org/10.1016/j.pmr.2016.12.001.
29. Brian T. Kalish, Michael J. Whalen, "Weight drop models in traumatic brain injury", Springer, 2016. DOI:10.1007/978-1-4939-3816-1 12.