

Newer insights to pathogenesis of traumatic brain injury

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ABSTRACT

Traumatic brain injury (TBI) is a silent epidemic and a global burden. However, when it comes to advancement in our quest to managing patients with head injuries, we seem to be making circles rather than moving forward. In this review paper, we focus on the current understandings in the pathogenesis of TBI that may aid us in providing newer avenues in management of the same.

Key words: Brain injury, cisterns, lactate, tau, trauma

Introduction

Traumatic brain injury (TBI) is a major public health issue worldwide.^[1] According to the World Health Organization report, TBI is going to surpass many other diseases, such as ischemic heart and cerebrovascular disease, as a major cause of death and disability by 2020 AD.^[2] Research in the management of TBI with therapeutic options for neuroprotection has been rigorously pursued over the last 40 years.^[3] Herein, we try to enlighten on the newer avenues on the pathophysiology of TBI and thereafter highlight on the probable role of opening up the paravascular pathways, which might add to our already existing armamentarium on the management of TBI.

Glutamate Excitotoxicity

There has been a long-standing notion that excitatory amino acid efflux is a major contributor to the development of neuronal damage subsequent to traumatic injury. High extracellular glutamate is thought to initiate and accelerate the process of apoptosis and parthanatos. However, this theory does not withstand scientific scrutiny because the extracellular

glutamate level in TBI is cleared within 5 min, the effect of glutamate receptors antagonists remains effective even after 30 min of insult. Some authors have come up with the theory of spreading depression due to the sodium extrusion, sequelae of calcium influx, and subsequent hyperpolarization to the cause of the phenomenon.^[4]

There has also been evidence that astrocytic glutamate transporters such as GLAST and GLT-1 and splice variant are downregulated shortly following the insult, which then precipitates glutamate-mediated excitotoxic conditions.^[5] These insights should provide novel avenues for therapeutic intervention of following TBI.

Lactate Storm

The injured brain continues to produce lactate within minutes following severe TBI.^[6,7] There is a glial-neuronal uncoupling resulting in a lactate storm in the already failing metabolic environment. Furthermore, it has been shown that extracellular lactate increase is independent of brain hypoxic ischemia in severe TBI.^[8,9] There has been a number of studies highlighting the implication of raised lactate level in the cerebrospinal fluid (CSF) and the magnetic resonance spectroscopy and the subsequent outcome in the patients with TBI.^[10-12]

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Access this article online	
Quick Response Code:	Website: www.asianjns.org
	DOI: 10.4103/1793-5482.180882

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How to cite this article: Munakomi S, Cherian I. Newer insights to pathogenesis of traumatic brain injury. Asian J Neurosurg 2017;12:362-4.

It is thereby a safe option to safely chelate the excess lactate,^[13] buffer the pH effect^[14] or inhibit glial metabolism^[15,16] as opposed to further administering lactate as some of the contemporary research have been suggesting.^[17,18] Lactates, because of its role as a supplementary fuel to the brain, can be a friend only in an aerobic environment.^[19] Lactate substitution is, in fact, a foe in such a lethal and stormy metabolic milieu, and can paradoxically lead to the unsalvageable brain.

Taupathy

There has been a recent upsurge in the link between Glymphatic pathways in the brain and its association with tauopathies following TBI.^[20,21] This pathway facilitates the clearance of interstitial solutes, including amyloid, from the brain. One study has recently verified in mice that extracellular tau is cleared from the brain along these paravascular pathways mediated by Aquaporin-4 channel.^[20] After TBI, glymphatic pathway function was significantly impaired for at least 1 month postinjury, thereby promoting the development of neurofibrillary pathology and neurodegeneration in the posttraumatic brain. These findings have provided newer insights to the fact that chronic impairment of glymphatic pathway function after TBI may be a key factor that renders the posttraumatic brain vulnerable to tau aggregation and the onset of neurodegeneration thereafter.

Immunoexcitotoxicity

TBI can prime microglia.^[22,23] These leads to its activation to either of neurotrophic, neurodestructive, or intermediate states each responding to a different set of membrane signals, which can be time and cytokine dose dependent.^[24] The release of chemokines like monocyte chemoattractant protein-1 also stimulate the recruitment of peripheral monocytes/macrophages to the central nervous system, especially via the circumventricular organs.^[25] At the face of the excitotoxic environment, microglial cells release NO and interleukin-1b thereby contributing to subacute neuronal degeneration.^[26,27]

Normally, the activated microglial cells go into reparative ramified mode wherein they secrete neurotrophins and the anti-inflammatory cytokines helping in the repair process. Repeated trauma leads to priming of these activated microglia cells to become hyper-reactive, releasing much higher concentrations of inflammatory cytokines and excitotoxins than are normally released.^[28]

It has been proposed that with chronic microglial neurodegeneration, this switching process to ramified form does not occur, leading to progressive and prolonged neuronal injury.^[29] Gliosis and the scar associated with the neurodegeneration lead to the impairment of the paravascular clearance pathway of the amyloid and the tau proteins.

Amyloid deposits are known to occur rapidly after TBI and persist in 30% of severe head trauma cases, even in children.^[29]

Hemodynamic Alteration

There are specific hemodynamic alterations following the TBI.^[30] In the first 24 h, there is oligemia attributable to cellular edema, sympathetic adrenergic surge at the face of trauma, and the microvascular thrombi. In the subsequent 3 days, there is a phase of hyperemia because of vasomotor paralysis, luxury perfusion, and the hyperglycolysis. Then from the 4th day to following 2 weeks, the phase of vasospasm sets in because of the degraded blood products such as deoxyhemoglobin and bilirubin. Hence, the concept of correct fluid resuscitation and replacement has a paramount importance while managing patients with TBI. Fluids should be restricted in the hyperemic phase whereas induced hypertension, hemodilution, and hypervolemia should be instituted during the phase of vasospasm.

Future Directives

Role of opening the cisternal webs in the brain

The implications of opening the cisterns in TBI, though demanding, can have ripple effects in the management of TBI.^[31,32] It immediately lax the tight brain due to egress of the CSF. Furthermore, it improves the compliance of the vessels and reduces the risk of subsequent vasospasm clearing the cisternal and subarachnoid blood invariably associated with TBI. Cisternal drain helps in clearing away the lactate and tau proteins thereby reducing the hazardous cellular milieu and also minimizing the risk of subsequent development of neurodegenerative lesions. Hence, it may be the time we pass on the baton to this new therapeutic armamentarium, that targets the paravascular pathways, in our quest to conquer the silent epidemic of TBI.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Corrigan JD, Selassie AW, Orman JA. The epidemiology of traumatic brain injury. *J Head Trauma Rehabil* 2010;25:72-80.
2. Murray CJ, Lopez AD. Evidence-based health policy – Lessons from the Global Burden of Disease Study. *Science* 1996;274:740-3.
3. Vink R, Bullock MR. Traumatic brain injury: Therapeutic challenges and new directions. *Neurotherapeutics* 2010;7:1-2.
4. Obrenovitch TP, Urenjak J. Is high extracellular glutamate the key to excitotoxicity in traumatic brain injury? *J Neurotrauma* 1997;14:677-98.
5. Yi JH, Hazell AS. Excitotoxic mechanisms and the role of astrocytic glutamate transporters in traumatic brain injury. *Neurochem Int* 2006;48:394-403.
6. Kraig RP, Petito CK, Plum F, Pulsinelli WA. Hydrogen ions kill brain

- at concentrations reached in ischemia. *J Cereb Blood Flow Metab* 1987;7:379-86.
7. Timofeev I, Carpenter KL, Nortje J, Al-Rawi PG, O'Connell MT, Czosnyka M, *et al*. Cerebral extracellular chemistry and outcome following traumatic brain injury: A microdialysis study of 223 patients. *Brain* 2011;134(Pt 2):484-94.
 8. Sala N, Suys T, Zerlauth JB, Bouzat P, Messerer M, Bloch J, *et al*. Cerebral extracellular lactate increase is predominantly nonischemic in patients with severe traumatic brain injury. *J Cereb Blood Flow Metab* 2013;33:1815-22.
 9. Vespa P, Bergsneider M, Hattori N, Wu HM, Huang SC, Martin NA, *et al*. Metabolic crisis without brain ischemia is common after traumatic brain injury: A combined microdialysis and positron emission tomography study. *J Cereb Blood Flow Metab* 2005;25:763-74.
 10. Sanchez JJ, Bidot CJ, O'Phelan K, Gajavelli S, Yokobori S, Olvey S, *et al*. Neuromonitoring with microdialysis in severe traumatic brain injury patients. *Acta Neurochir Suppl* 2013;118:223-7.
 11. Kamada K, Houkin K, Hida K, Iwasaki Y, Abe H. Serial changes in metabolism and histology in the cold-injury trauma rat brain model – proton magnetic resonance imaging and spectroscopy study. *Neurol Med Chir (Tokyo)* 1995;35:1-7.
 12. Toczyłowska B, Chalimoniuk M, Wodowska M, Mayzner-Zawadzka E. Changes in concentration of cerebrospinal fluid components in patients with traumatic brain injury. *Brain Res* 2006;1104:183-9.
 13. Kishi K, Wariishi H, Marquez L, Dunford HB, Gold MH. Mechanism of manganese peroxidase compound II reduction. Effect of organic acid chelators and pH. *Biochemistry* 1994;33:8694-701.
 14. Péronnet F, Aguilaniu B. Lactic acid buffering, nonmetabolic CO₂ and exercise hyperventilation: A critical reappraisal. *Respir Physiol Neurobiol* 2006;150:4-18.
 15. Hassel B, Paulsen RE, Johnsen A, Fonnum F. Selective inhibition of glial cell metabolism *in vivo* by fluorocitrate. *Brain Res* 1992;576:120-4.
 16. Hassel B, Bachelard H, Jones P, Fonnum F, Sonnewald U. Trafficking of amino acids between neurons and glia *in vivo*. Effects of inhibition of glial metabolism by fluoroacetate. *J Cereb Blood Flow Metab* 1997;17:1230-8.
 17. Ichai C, Armando G, Orban JC, Berthier F, Rami L, Samat-Long C, *et al*. Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. *Intensive Care Med* 2009;35:471-9.
 18. Alessandri B, Schwandt E, Kamada Y, Nagata M, Heimann A, Kempfski O. The neuroprotective effect of lactate is not due to improved glutamate uptake after controlled cortical impact in rats. *J Neurotrauma* 2012;29:2181-91.
 19. Bouzat P, Oddo M. Lactate and the injured brain: Friend or foe? *Curr Opin Crit Care* 2014;20:133-40.
 20. Iliff JJ, Chen MJ, Plog BA, Zeppenfeld DM, Soltero M, Yang L, *et al*. Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. *J Neurosci* 2014;34:16180-93.
 21. Plog BA, Dashnaw ML, Hitomi E, Peng W, Liao Y, Lou N, *et al*. Biomarkers of traumatic injury are transported from brain to blood via the glymphatic system. *J Neurosci* 2015;35:518-26.
 22. Blaylock RL, Maroon J. Immunoexcitotoxicity as a central mechanism in chronic traumatic encephalopathy – A unifying hypothesis. *Surg Neurol Int* 2011;2:107.
 23. Feuerstein GZ, Wang X, Barone FC. The role of cytokines in the neuropathology of stroke and neurotrauma. *Neuroimmunomodulation* 1998;5:143-59.
 24. Brown GC, Neher JJ. Inflammatory neurodegeneration and mechanisms of microglial killing of neurons. *Mol Neurobiol* 2010;41:242-7.
 25. Langston JW, Forno LS, Tetud J, Reeves AG, Kaplan JA, Karluk D. Evidence of active nerve cell degeneration in the substantia nigra of humans years after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure. *Ann Neurol* 1999;46:598-605.
 26. Love S. Oxidative stress in brain ischemia. *Brain Pathol* 1999;9:119-31.
 27. Takahashi JL, Giuliani F, Power C, Imai Y, Yong VW. Interleukin-1beta promotes oligodendrocyte death through glutamate excitotoxicity. *Ann Neurol* 2003;53:588-95.
 28. Cunningham C, Wilcockson DC, Campion S, Lunnon K, Perry VH. Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. *J Neurosci* 2005;25:9275-84.
 29. Roberts GW, Gentleman SM, Lynch A, Graham DI. Beta A4 amyloid protein deposition in brain after head trauma. *Lancet* 1991;338:1422-3.
 30. Martin NA, Patwardhan RV, Alexander MJ, Africk CZ, Lee JH, Shalmon E, *et al*. Characterization of cerebral hemodynamic phases following severe head trauma: Hypoperfusion, hyperemia, and vasospasm. *J Neurosurg* 1997;87:9-19.
 31. Cherian I, Yi G, Munakomi S. Cisternostomy: Replacing the age old decompressive hemicraniectomy? *Asian J Neurosurg* 2013;8:132-8.
 32. Grasso G. Surgical Treatment for Traumatic Brain Injury: Is It Time for Reappraisal? *World Neurosurg* 2015;84:594.