DENEYSEL TRAVMATİK BEYİN HASARI MODELLERİ

BÖLÜM 8

Güven AKÇAY[1]

Giriş

Travmatik beyin hasarı, dünya çapında önde gelen mortalite ve morbidite nedenidir. Travmatik beyin hasarı sonrası kişilerde sıklıkla motor, bilişsel ve sensoriyel fonksiyon kaybı görülür. Travmatik beyin hasarı, ölüm, sakatlık ve ruhsal bozukluklar gibi önemli sağlık sorunlarına yol açar. Travmatik beyin hasarı, tüm dünyada giderek artan sağlık sorunu olmaya devam etmektedir. Her yıl yaklaşık 1,7 milyon insanın kafa travması geçirdiği ve bu bireylerden yaklaşık 50.000 kişinin hayatını kaybettiği tahmin edilmektedir. Travmatik beyin hasarı her yaşta ve popülasyonda görülmesine rağmen, vakanın en yüksek olduğu yaş popülasyonunu çocuklar ve yaşlılar oluşturur. Düşme, sportif faaliyetler ve motorlu araç kazaları travmatik beyin hasarının en büyük risk faktörü olarak karşımıza çıkar. Travmatik beyin hasarına yönelik teşhis ve tedavi yöntemlerinin geliştirilmesi için nöropatolojisinin altında yatan moleküler ve hücresel mekanizmaların bilinmesi gerekir. Bundan dolayı farklı modellerde tanımlanmış hafif, orta ve şiddetli deneysel travmatik beyin hasarı modelleri kullanılır. Travmatik beyin hasarının hayvan modellerini genel olarak fokal, difüz ve karışık hasar olarak sınıflandırılır. Travmatik beyin hasarı deneysel araştırmalarında sıvı perküsyon, kontrollü kortikal etki, ağırlık düşürme ve patlama dalgası en sık tercih edilen modellerdir. Bu bölümde, travmatik beyin hasarı için mevcut kemirgen modellerinin güçlü ve zayıf yönleri açıklanacaktır.

[1] Dr. Öğr. Üyesi, Hitit Üniversitesi Tıp Fakültesi, Biyofizik AD., guvenakcayibu@gmail.com

için bir puan verilir: 13–18, şiddeti hasar; 7–12, orta orta hasar; 1-6, hafif hasar. Deneysel çalışmalarda nörolojik şiddet skoru ve motor fonksiyon testleri gibi davranış değişiklikleri değerlendirilmesinin yanında kilo kaybı ve kafa içi basınç artışı gibi fizyolojik değişiklikler; enfarktüs hacmi ve nöronal kayıp gibi histolojik değişiklikler de kullanılır (8, 79, 80).

Sonuç ve Öneriler

Travmatik beyin hasarı, ölüm ve sakatlığın önde gelen nedenlerinden biridir. TBH beyin dokusunun mekanik olarak bozulmasına neden olan dış gücün ve hasarı şiddetlendiren gecikmiş patojenik olayların sonucudur. Bu patojenik yaralanma süreçleri yeterince anlaşılmamıştır ve bu nedenle şimdiye kadar etkili nöroprotektif tedavi mevcut değildir. Deneysel modeller, TBH'nin fizyolojik ve patofizyolojik mekanizmalarının araştırması, yeni terapötik ajanları test edilmesi, klinik denemelerin güvenli ve başarılı olmasını sağlamak için hayvan modelleri gereklidir. İnsan TBH ile ilişkili farklı yaralanma mekanizmalarını modellemek için çeşitli kemirgen TBH modelleri geliştirilmiştir. Travmatik beyin hasarının kemirgen modelleri arasında en sık kullanılanları sıvı perküsyon, kortikal kontüzyon etki, ağırlık düşürme ve patlama dalgası modelleridir. Travmatik beyin hasarında meydana gelebilecek olayların tamamı tek bir kemirgen modeliyle kapsanamayacağından, belirli bir modelin tasarımı ve seçimi sinirbilimciler için büyük bir zorluk teşkil etmektedir. Bu bölümde, travmatik beyin hasarı için mevcut kemirgen modellerinin güçlü ve zayıf yönleri açıklanmıştır.

Kaynaklar

1. Masel, B.E. and D.S. DeWitt, *Traumatic brain injury: a disease process, not an event.* J Neurotrauma, 2010. 27(8): p. 1529-40.
2. Michael G, et al., *A Review of Traumatic Brain Injury Animal Models: Are We Lacking Adequate Models Replicating Chronic Traumatic Encephalopathy?* Journal of Neurology and Neurobiology, 2015. 2(1).
3. Langlois, J.A., W. Rutland-Brown, and M.M. Wald, *The epidemiology and impact of traumatic brain injury: a brief overview.* J Head Trauma Rehabil, 2006. 21(5): p. 375-8.
4. Maas, A.I., N. Stocchetti, and R. Bullock, *Moderate and severe traumatic brain injury in adults.* Lancet Neurol, 2008. 7(8): p. 728-41.
5. Ma, X., et al., *Animal Models of Traumatic Brain Injury and Assessment of Injury Severity.* Mol Neurobiol, 2019. 56(8): p. 5332-5345.
6. Briones, T.L., *Chapter 3 animal models of traumatic brain injury: is there an optimal model that parallels human brain injury?* Annu Rev Nurs Res, 2015. 33: p. 31-73.
7. Davis, A.E., *Mechanisms of traumatic brain injury: biomechanical, structural and cellular considerations.* Crit Care Nurs Q, 2000. 23(3): p. 1-13.
8. Cernak, I., *Animal models of head trauma.* NeuroRx, 2005. 2(3): p. 410-22.

9. Gaetz, M., *The neurophysiology of brain injury.* Clin Neurophysiol, 2004. 115(1): p. 4-18.
10. Hay, J., et al., *Chronic Traumatic Encephalopathy: The Neuropathological Legacy of Traumatic Brain Injury.* Annu Rev Pathol, 2016. 11: p. 21-45.
11. Xiong, Y., A. Mahmood, and M. Chopp, *Emerging treatments for traumatic brain injury.* Expert Opin Emerg Drugs, 2009. 14(1): p. 67-84.
12. Doppenberg, E.M., S.C. Choi, and R. Bullock, *Clinical trials in traumatic brain injury: lessons for the future.* J Neurosurg Anesthesiol, 2004. 16(1): p. 87-94.
13. Maas, A.I., *Neuroprotective agents in traumatic brain injury.* Expert Opin Investig Drugs, 2001. 10(4): p. 753-67.
14. Faden, A.I., *Neuroprotection and traumatic brain injury: theoretical option or realistic proposition.* Curr Opin Neurol, 2002. 15(6): p. 707-12.
15. Schouten, J.W., *Neuroprotection in traumatic brain injury: a complex struggle against the biology of nature.* Curr Opin Crit Care, 2007. 13(2): p. 134-42.
16. Irvine, K.-A. and J.D. Clark, *Chronic Pain After Traumatic Brain Injury: Pathophysiology and Pain Mechanisms.* Pain Medicine, 2018. 19: p. 1315–1333.
17. Povlishock, J.T. and C.W. Christman, *The pathobiology of traumatically induced axonal injury in animals and humans: a review of current thoughts.* J Neurotrauma, 1995. 12(4): p. 555-64.
18. Xiong, Y., A. Mahmood, and M. Chopp, *Animal models of traumatic brain injury.* Nat Rev Neurosci, 2013. 14(2): p. 128-42.
19. Raghupathi, R., *Cell death mechanisms following traumatic brain injury.* Brain Pathol, 2004. 14(2): p. 215-22.
20. Bramlett, H.M. and W.D. Dietrich, *Progressive damage after brain and spinal cord injury: pathomechanisms and treatment strategies.* Prog Brain Res, 2007. 161: p. 125-41.
21. Raghupathi, R., D.I. Graham, and T.K. McIntosh, *Apoptosis after traumatic brain injury.* J Neurotrauma, 2000. 17(10): p. 927-38.
22. Yakovlev, A.G., et al., *Differential expression of apoptotic protease-activating factor-1 and caspase-3 genes and susceptibility to apoptosis during brain development and after traumatic brain injury.* J Neurosci, 2001. 21(19): p. 7439-46.
23. Margulies, S. and R. Hicks, *Combination therapies for traumatic brain injury: prospective considerations.* J Neurotrauma, 2009. 26(6): p. 925-39.
24. Marklund, N., et al., *Evaluation of pharmacological treatment strategies in traumatic brain injury.* Curr Pharm Des, 2006. 12(13): p. 1645-80.
25. McIntosh, T.K., et al., *Traumatic brain injury in the rat: characterization of a lateral fluid-percussion model.* Neuroscience, 1989. 28(1): p. 233-44.
26. Chen J, Xu XM, and X. ZC, *Animal Models of Acute Neurological Injuries.* 2009, Berlin, Germany.
27. Gennarelli, T.A., *Animate models of human head injury.* J Neurotrauma, 1994. 11(4): p. 357-68.
28. Spain, A., et al., *Mild fluid percussion injury in mice produces evolving selective axonal pathology and cognitive deficits relevant to human brain injury.* J Neurotrauma, 2010. 27(8): p. 1429-38.
29. Su, Y., et al., *Taurine improves functional and histological outcomes and reduces inflammation in traumatic brain injury.* Neuroscience, 2014. 266: p. 56-65.
30. Kabadi, S.V., et al., *CR8, a novel inhibitor of CDK, limits microglial activation, astrocytosis, neuronal loss, and neurologic dysfunction after experimental traumatic brain injury.* J Cereb Blood Flow Metab, 2014. 34(3): p. 502-13.
31. Huang, E.Y., et al., *Amantadine ameliorates dopamine-releasing deficits and behavioral deficits in rats after fluid percussion injury.* PLoS One, 2014. 9(1): p. e86354.
32. Hameed, M.Q., et al., *A rapid lateral fluid percussion injury rodent model of traumatic brain injury and post-traumatic epilepsy.* Neuroreport, 2014. 25(7): p. 532-6.
33. Lifshitz, J., B.J. Kelley, and J.T. Povlishock, *Perisomatic thalamic axotomy after diffuse traumatic brain injury is associated with atrophy rather than cell death.* J Neuropathol Exp Neurol, 2007. 66(3): p. 218-29.

34. Cao, T., et al., *Morphological and genetic activation of microglia after diffuse traumatic brain injury in the rat.* Neuroscience, 2012. 225: p. 65-75.
35. Thompson, H.J., et al., *Lateral fluid percussion brain injury: a 15-year review and evaluation.* J Neurotrauma, 2005. 22(1): p. 42-75.
36. Hicks, R., et al., *Temporal and spatial characterization of neuronal injury following lateral fluid-percussion brain injury in the rat.* Acta Neuropathol, 1996. 91(3): p. 236-46.
37. Liu, Y.R., et al., *Progressive metabolic and structural cerebral perturbations after traumatic brain injury: an in vivo imaging study in the rat.* J Nucl Med, 2010. 51(11): p. 1788-95.
38. Hamm, R.J., *Neurobehavioral assessment of outcome following traumatic brain injury in rats: an evaluation of selected measures.* J Neurotrauma, 2001. 18(11): p. 1207-16.
39. Pierce, J.E., et al., *Enduring cognitive, neurobehavioral and histopathological changes persist for up to one year following severe experimental brain injury in rats.* Neuroscience, 1998. 87(2): p. 359-69.
40. Dixon, C.E., et al., *A controlled cortical impact model of traumatic brain injury in the rat.* J Neurosci Methods, 1991. 39(3): p. 253-62.
41. Chen, Y., et al., *A modified controlled cortical impact technique to model mild traumatic brain injury mechanics in mice.* Front Neurol, 2014. 5: p. 100.
42. Smith, S.L. and E.D. Hall, *Mild pre- and posttraumatic hypothermia attenuates blood-brain barrier damage following controlled cortical impact injury in the rat.* J Neurotrauma, 1996. 13(1): p. 1-9.
43. Osier, N.D. and C.E. Dixon, *The Controlled Cortical Impact Model: Applications, Considerations for Researchers, and Future Directions.* Front Neurol, 2016. 7: p. 134.
44. Washington, P.M., et al., *The effect of injury severity on behavior: a phenotypic study of cognitive and emotional deficits after mild, moderate, and severe controlled cortical impact injury in mice.* J Neurotrauma, 2012. 29(13): p. 2283-96.
45. Fox, G.B., et al., *Sustained sensory/motor and cognitive deficits with neuronal apoptosis following controlled cortical impact brain injury in the mouse.* J Neurotrauma, 1998. 15(8): p. 599-614.
46. Marklund, N. and L. Hillered, *Animal modelling of traumatic brain injury in preclinical drug development: where do we go from here?* Br J Pharmacol, 2011. 164(4): p. 1207-29.
47. Dixon, C.E., et al., *Amantadine improves water maze performance without affecting motor behavior following traumatic brain injury in rats.* Restor Neurol Neurosci, 1999. 14(4): p. 285-294.
48. Dixon, C.E., et al., *One-year study of spatial memory performance, brain morphology, and cholinergic markers after moderate controlled cortical impact in rats.* J Neurotrauma, 1999. 16(2): p. 109-22.
49. Kochanek, P.M., et al., *Cerebral blood flow at one year after controlled cortical impact in rats: assessment by magnetic resonance imaging.* J Neurotrauma, 2002. 19(9): p. 1029-37.
50. Mychasiuk, R., A. Farran, and M.J. Esser, *Assessment of an experimental rodent model of pediatric mild traumatic brain injury.* J Neurotrauma, 2014. 31(8): p. 749-57.
51. Morales, D.M., et al., *Experimental models of traumatic brain injury: do we really need to build a better mousetrap?* Neuroscience, 2005. 136(4): p. 971-89.
52. Viano, D.C., et al., *Evaluation of three animal models for concussion and serious brain injury.* Ann Biomed Eng, 2012. 40(1): p. 213-26.
53. Marmarou, A., et al., *A new model of diffuse brain injury in rats. Part I: Pathophysiology and biomechanics.* J Neurosurg, 1994. 80(2): p. 291-300.
54. Flierl, M.A., et al., *Mouse closed head injury model induced by a weight-drop device.* Nat Protoc, 2009. 4(9): p. 1328-37.
55. Adelson, P.D., et al., *A model of diffuse traumatic brain injury in the immature rat.* J Neurosurg, 1996. 85(5): p. 877-84.
56. Statler, K.D., et al., *Isoflurane exerts neuroprotective actions at or near the time of severe traumatic brain injury.* Brain Res, 2006. 1076(1): p. 216-24.

57. Feeney, D.M., et al., *Responses to cortical injury: I. Methodology and local effects of contusions in the rat.* Brain Res, 1981. 211(1): p. 67-77.
58. Albert-Weissenberger, C. and A.L. Sirén, *Experimental traumatic brain injury.* Exp Transl Stroke Med, 2010. 2(1): p. 16.
59. Nilsson, P., et al., *Continuous measurement of changes in regional cerebral blood flow following cortical compression contusion trauma in the rat.* J Neurotrauma, 1996. 13(4): p. 201-7.
60. Lindh, C., et al., *Differences in cell death between high and low energy brain injury in adult rats.* Acta Neurochir (Wien), 2008. 150(12): p. 1269-75;discussion 1275.
61. Shapira, Y., et al., *Experimental closed head injury in rats: mechanical, pathophysiologic, and neurologic properties.* Crit Care Med, 1988. 16(3): p. 258-65.
62. Chen, Y., et al., *An experimental model of closed head injury in mice: pathophysiology, histopathology, and cognitive deficits.* J Neurotrauma, 1996. 13(10): p. 557-68.
63. Zhu, F., et al., *Biomechanical responses of a pig head under blast loading: a computational simulation.* Int J Numer Method Biomed Eng, 2013. 29(3): p. 392-407.
64. Reneer, D.V., et al., *A multi-mode shock tube for investigation of blast-induced traumatic brain injury.* J Neurotrauma, 2011. 28(1): p. 95-104.
65. Koliatsos, V.E., et al., *A mouse model of blast injury to brain: initial pathological, neuropathological, and behavioral characterization.* J Neuropathol Exp Neurol, 2011. 70(5): p. 399-416.
66. Yi, J., et al., *Chronic traumatic encephalopathy.* Curr Sports Med Rep, 2013. 12(1): p. 28-32.
67. Geddes, J.F., et al., *Neuronal cytoskeletal changes are an early consequence of repetitive head injury.* Acta Neuropathol, 1999. 98(2): p. 171-8.
68. Weber, J.T., *Experimental models of repetitive brain injuries.* Prog Brain Res, 2007. 161: p. 253-61.
69. Uryu, K., et al., *Repetitive mild brain trauma accelerates Abeta deposition, lipid peroxidation, and cognitive impairment in a transgenic mouse model of Alzheimer amyloidosis.* J Neurosci, 2002. 22(2): p. 446-54.
70. DeFord, S.M., et al., *Repeated mild brain injuries result in cognitive impairment in B6C3F1 mice.* J Neurotrauma, 2002. 19(4): p. 427-38.
71. Huang, L., et al., *Tissue vulnerability is increased following repetitive mild traumatic brain injury in the rat.* Brain Res, 2013. 1499: p. 109-20.
72. Luo, J., et al., *Long-term cognitive impairments and pathological alterations in a mouse model of repetitive mild traumatic brain injury.* Front Neurol, 2014. 5: p. 12.
73. Rákos, G., et al., *Evans Blue fluorescence permits the rapid visualization of non-intact cells in the perilesional rim of cold-injured rat brain.* Acta Neurobiol Exp (Wars), 2007. 67(2): p. 149-54.
74. Raslan, F., et al., *Inhibition of bradykinin receptor B1 protects mice from focal brain injury by reducing blood-brain barrier leakage and inflammation.* J Cereb Blood Flow Metab, 2010. 30(8): p. 1477-86.
75. Brotfain, E., et al., *Neuroprotection by Estrogen and Progesterone in Traumatic Brain Injury and Spinal Cord Injury.* Curr Neuropharmacol, 2016. 14(6): p. 641-53.
76. Prins, M.L. and D.A. Hovda, *Developing experimental models to address traumatic brain injury in children.* J Neurotrauma, 2003. 20(2): p. 123-37.
77. Potts, M.B., et al., *Traumatic injury to the immature brain: inflammation, oxidative injury, and iron-mediated damage as potential therapeutic targets.* NeuroRx, 2006. 3(2): p. 143-53.
78. Rabinowitz, A.R. and H.S. Levin, *Cognitive sequelae of traumatic brain injury.* Psychiatr Clin North Am, 2014. 37(1): p. 1-11.
79. Osier, N.D., et al., *Chronic Histopathological and Behavioral Outcomes of Experimental Traumatic Brain Injury in Adult Male Animals.* J Neurotrauma, 2015. 32(23): p. 1861-82.
80. Johnson, V.E., et al., *Animal models of traumatic brain injury.* Handb Clin Neurol, 2015. 127: p. 115-28.