Advances in Clinical Medicine 临床医学进展, 2023, 13(5), 8553-8557
Published Online May 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.1351197

Hans汉斯

创伤性颅脑损伤引起低钙血症的机制

宋文敬[1]，李文辉[2]

[1]青海大学临床医学院，青海 西宁
[2]青海大学附属医院神经外科，青海 西宁

收稿日期：2023年4月28日；录用日期：2023年5月21日；发布日期：2023年5月29日

摘 要

创伤性颅脑损伤(traumatic brain injury, TBI)是发达及发展中国家年轻人死亡的主要原因。TBI是一种十分常见的神经外科疾病，它是由多种原因所造成的，其中常见的原因包括高处跌落、交通事故、斗殴伤以及运动伤。TBI对于颅脑的损伤主要分为直接暴力后引起的脑组织原发性损害，如：局灶性大脑挫裂伤和弥漫性轴索损伤；另一种则是由原发性颅脑损伤后引起的血脑屏障破坏、外周血细胞浸润、脑水肿以及多种血电解质紊乱(K^+、Ca^{2+}、Na^+、Mg^{2+}、Cl^-)，这些继发性损害会引起大脑神经元在创伤后数小时破坏凋亡，从而影响预后生存质量。其中低钙血症可作为创伤性颅脑损伤的独立危险因素，现将创伤性颅脑损伤后引起低钙血症相关机制作一综述。

关键词

创伤性颅脑损伤，低钙血症

Mechanism of Hypocalcemia Caused by Traumatic Brain Injury

Wenjing Song[1], Wenhui Li[2]

[1]Clinical Medical College, Qinghai University, Xining Qinghai
[2]Department of Neurosurgery, Affiliated Hospital of Qinghai University, Xining Qinghai

Received: Apr. 28th, 2023; accepted: May 21st, 2023; published: May 29th, 2023

Abstract

Traumatic brain injury (TBI) is the main cause of death among young people in developed and developing countries. TBI is a very common neurosurgical disease, which is caused by a variety of reasons, including high altitude falls, traffic accidents, combat injuries, and sports injuries. The

文章引用: 宋文敬, 李文辉. 创伤性颅脑损伤引起低钙血症的机制[J]. 临床医学进展, 2023, 13(5): 8553-8557.
DOI: 10.12677/acm.2023.1351197

brain injury caused by TBI is mainly divided into primary brain damage caused by direct violence, such as focal brain contusion and diffuse peripheral injury. The other is the destruction of the blood brain barrier, infiltration of peripheral blood cells, brain edema, and various blood electrolyte disturbances (K^+, Ca^{2+}, Na^+, Mg^{2+}, Cl^-) caused by primary brain injury. These secondary damages can cause brain neurons to destroy and apoptosis within a few hours after trauma, thereby affecting the prognosis and quality of life. Among them, hypocalcemia can be an independent risk factor for traumatic brain injury. This article reviews the mechanisms related to hypocalcemia after traumatic brain injury.

Keywords

Traumatic Brain Injury, Hypocalcemia

1. 引言

创伤性颅脑损伤(TBI)是现代社会致残率和死亡率的主要原因之一，也会引起高昂的治疗费用[1]。虽然近年来因创伤性颅脑损伤住院的患者有减少的趋势，但是创伤性颅脑损伤仍然保持着较高的死亡率[2]。TBI 的病理发病过程主要包括原发性和继发性的颅脑损伤，本文主要探讨的是继发性所引起的颅脑损伤，如：炎症、细胞死亡、细胞凋亡氧化应激反应以及多重血电解质紊乱，也是决定 TBI 患者预后的另一重要因素[3]。其中，作为第二信使的钙离子(Ca^{2+})在调节多种细胞生理功能中起着关节的作用。在 TBI 初期伴随着兴奋性神经递质，如：谷氨酸和天冬氨酸的释放，使得大量的钙离子涌入细胞，血清钙离子含量减少，从而激活一系列降解酶(半胱氨酸蛋白酶、核酸内切酶等)通过启动细胞凋亡酶联反应直接或者间接引起细胞死亡。这种酶联反应会引起炎性反应进一步加重神经元损伤从而引起血脑屏障的破坏和脑水肿的发生[4]。持续高水平的细胞内游离钙不一定是高风险的，但是钙离子在进入特定反应途径后会关联到细胞凋亡途径。同时细胞内的储存钙也会导致细胞损伤，以上一系列的改变最终引起神经元细胞的异常生理改变[5]。本文主要从颅脑受到创伤后引起血钙紊乱的机制入手，加强临床医生对创伤性颅脑损伤后血电解质紊乱的进一步认识。

2. 血脑屏障破坏引起的细胞毒性

头部受到暴力外伤后引起血脑屏障破坏，进一步引起神经细胞去极化，从而导致神经递质不受控制的过度释放，这一系列的反应导致细胞稳态的改变，称为细胞毒性反应。谷氨酸主要是在突触囊泡去极化后释放，也有一部分是通过受损的细胞膜泄露而出。此外，由于星形胶质细胞的破坏导致神经细胞重新摄取谷氨酸减少或消除[6]。细胞外过多的谷氨酸会引起大量的钙离子和钠离子涌入神经细[7]过量的细胞内钙离子会触发多种下游信号分子，如：蛋白激酶 C、蛋白磷酸酶、MAPK [8]进一步引起细胞内储存钙离子的一次释放，使得细胞内钙离子含量进一步增多。由于大量的钠离子、钙离子涌入导致被动水运动增多，引起细胞肿胀。一方面，细胞内高钙破坏氧化磷酸化、促进蛋白酶生成增多，导致神经细胞功能丧失。另一方面，钙依赖性蛋白酶被激活，进而导致蛋白质和酶的破坏，从而导致细胞死亡[9]。同时，一氧化氮由一氧化氮合酶产生，产生过程依赖于钙离子，一氧化氮是一种自由基，它与氧自由基反应后形成过氧化亚硝酸盐，会产生有毒作用，导致脂质过氧化、细胞膜裂解和 DNA 片段断裂[10] [11]

[12]。

3. 钙离子过载引发线粒体功能障碍

线粒体损伤是继发性创伤性颅脑损伤的关键，可导致神经元细胞生理功能的改变，最终引起细胞非正常死亡。当细胞内钙离子不断升高时，为了维持细胞内环境稳态，钙离子会在线粒体内储存[13]，钙离子的过度流入会引起活性氧(ROS)的产生以及线粒体膜的去极化[14]，导致电子传递链和线粒体氧化磷酸化受损，钙的调节及代谢功能障碍[15]，在此种情况下，线粒体通透性过渡孔(mPTP)被激活，线粒体膜去极化，导致线粒体通透性增加[16] [17] [18]，水顺渗透压流入线粒体内引起细胞肿胀，最终丧失功能[19]。以上过程进一步加剧，引起促凋亡蛋白－细胞色素 C 的释放，导致氧化应激反应，损伤脂质和蛋白质[20]。

4. 半胱天冬酶和钙蛋白酶介导细胞坏死和凋亡

半胱天冬酶和钙蛋白酶是引起细胞坏死和凋亡的关键酶[21]，其中半胱天冬酶主要导致细胞凋亡[22]钙蛋白酶主要引起坏死，钙蛋白酶活性是由钙离子介导的，特别是钙蛋白酶-1 和钙蛋白酶-2。有学者认为，钙蛋白酶激活与溶酶体膜破坏有关，导致组织蛋白酶渗透老化，进而对细胞造成严重损害，最终导致细胞死亡[21]。

5. 结论

在上述一系列反应下，创伤性颅脑损伤的脑组织坏死和凋亡是同时发生的。虽然一些研究表明，脑细胞的坏死与能量无关，但是脑细胞凋亡发生的过程是需要能量的消耗下进行，即细胞的凋亡过程需要线粒体功能的完整性[23]。因此在广泛线粒体破坏以及过量消耗能量的创伤性颅脑损伤患者的脑组织中，主要发生的是细胞的坏死。在细胞凋亡(又叫细胞的程序性死亡)过程中，细胞膜不会破坏，也不会引起炎性反应。此外一些学者认为，细胞坏死或凋亡的发生与细胞内钙离子的水平有关。相对较低的细胞内钙离子有利于细胞凋亡，反之相对较高的细胞内钙离子将促进细胞坏死[24]。

6. 未来展望

在过去几十年中，钙离子与创伤性颅脑损伤的关系得到了充分研究。最初，神经细胞内钙离子高水平负载被认为完全负责神经细胞死亡，因此早年的治疗策略主要是抑制钙离子进入细胞。例如：钙离子通道阻滞剂(L 型和 N 型)已经被证明在中和细胞内钙离子水平上有益处，可预防创伤性颅脑损伤所诱导的细胞死亡[25] [26] [27]。尼莫地平是一种 L 型钙离子通道阻滞剂，在早年就已报道[25]它在脑灌注和预防神经元损伤具有重要作用，并且已经被证实尼莫地平可以改善自发性蛛网膜下腔出血患者的预后。然而近年来的许多研究更清楚地表明，改变神经细胞的稳态比维持神经细胞内钙离子水平更加重要，因为这样可引起神经细胞内环境的紊乱、促进细胞死亡。由此可见，我们更应该重视如何将基础生理知识转化为创伤性颅脑损伤的新型治疗策略中去。未来对创伤性颅脑损伤的治疗策略不仅仅是单纯地抑制细胞死亡，更要注重的是在颅脑受到创伤后维持现存神经细胞的生理学稳态。

参考文献

[1] Brooks, J.C., Strauss, D.J., Shavelle, R.M., Paculdo, D.R., Hammond, F.M. and Harrison-Felix, C.L. (2013) Long-Term Disability and Survival in Traumatic Brain Injury: Results from the National Institute on Disability and Rehabilitation Research Model Systems. *Archives of Physical Medicine and Rehabilitation*, **94**, 2203-2209. https://doi.org/10.1016/j.apmr.2013.07.005

[2] 李小勇, 王忠诚. 创伤性颅脑损伤治疗新进展[J]. 中华神经外科杂志, 1999(1): 58-60.

[3] Zhang, L., Wang, H., Zhou, X., Mao, L., Ding, K. and Hu, Z. (2019) Role of Mitochondrial Calcium Unipor-

ter-Mediated Ca^{2+} and Iron Accumulation in Traumatic Brain Injury. *Journal of Cellular and Molecular Medicine*, **23**, 2995-3009. https://doi.org/10.1111/jcmm.14206

[4] Galgano, M., Toshkezi, G., Qiu, X., Russell, T., Chin, L. and Zhao, L.R. (2017) Traumatic Brain Injury: Current Treatment Strategies and Future Endeavors. *Cell Transplantation*, **26**, 1118-1130. https://doi.org/10.1177/0963689717714102

[5] Weber, J.T. (2012) Altered Calcium Signaling Following Traumatic Brain Injury. *Frontiers in Pharmacology*, **3**, Article No. 60. https://doi.org/10.3389/fphar.2012.00060

[6] Thapa, K., Khan, H., Singh, T.G. and Kaur, A. (2021) Traumatic Brain Injury: Mechanistic Insight on Pathophysiology and Potential Therapeutic Targets. *Journal of Molecular Neuroscience*, **71**, 1725-1742. https://doi.org/10.1007/s12031-021-01841-7

[7] Choi, D.W. (1987) Ionic Dependence of Glutamate Neurotoxicity. *Journal of Neuroscience*, **7**, 369-379. https://doi.org/10.1523/JNEUROSCI.07-02-00369.1987

[8] Faden, A.I., Demediuk, P., Panter, S.S. and Vink, R. (1989) The Role of Excitatory Amino Acids and NMDA Receptors in Traumatic Brain Injury. *Science*, **244**, 798-800. https://doi.org/10.1126/science.2567056

[9] Pike, B.R., Zhao, X., Newcomb, J.K., Glenn, C.C. anderson, D.K. and Hayes, R.L. (2000) Stretch Injury Causes Calpain and Caspase-3 Activation and Necrotic and Apoptotic Cell Death in Septo-Hippocampal Cell Cultures. *Journal of Neurotrauma*, **17**, 283-298. https://doi.org/10.1089/neu.2000.17.283

[10] Griffith, O.W. and Stuehr, D.J. (1995) Nitric Oxide Synthases: Properties and Catalytic Mechanism. *Annual Review of Physiology*, **57**, 707-736. https://doi.org/10.1146/annurev.ph.57.030195.003423

[11] Cherian, L., Hlatky, R. and Robertson, C.S. (2004) Nitric Oxide in Traumatic Brain Injury. *Brain Pathology*, **14**, 195-201. https://doi.org/10.1111/j.1750-3639.2004.tb00053.x

[12] Hall, E.D., Detloff, M.R., Johnson, K. and Kupina, N.C. (2004) Peroxynitrite-Mediated Protein Nitration and Lipid Peroxidation in a Mouse Model of Traumatic Brain Injury. *Journal of Neurotrauma*, **21**, 9-20. https://doi.org/10.1089/089771504772695904

[13] Nicholls, D.G. (1985) A Role for the Mitochondrion in the Protection of Cells Against Calcium Overload? *Progress in Brain Research*, **63**, 97-106. https://doi.org/10.1016/S0079-6123(08)61978-0

[14] Susin, S.A., Zamzami, N. and Kroemer, G. (1998) Mitochondria as Regulators of Apoptosis: Doubt No More. *Biochimica et Biophysica Acta*, **1366**, 151-165. https://doi.org/10.1016/S0005-2728(98)00110-8

[15] Naga, K.K., Sullivan, P.G. and Geddes, J.W. (2007) High Cyclophilin D Content of Synaptic Mitochondria Results in Increased Vulnerability to Permeability Transition. *Journal of Neuroscience*, **27**, 7469-7475. https://doi.org/10.1523/JNEUROSCI.0646-07.2007

[16] Bernardi, P. (1992) Modulation of the Mitochondrial Cyclosporin A-Sensitive Permeability Transition Pore by the Proton Electrochemical Gradient. Evidence that the Pore Can Be Opened by Membrane Depolarization. *Journal of Biological Chemistry*, **267**, 8834-8839. https://doi.org/10.1016/S0021-9258(19)50355-6

[17] Scorrano, L., Petronilli, V. and Bernardi, P. (1997) On the Voltage Dependence of the Mitochondrial Permeability Transition Pore. A Critical Appraisal. *Journal of Biological Chemistry*, **272**, 12295-12299. https://doi.org/10.1074/jbc.272.19.12295

[18] Kristal, B.S. and Dubinsky, J.M. (1997) Mitochondrial Permeability Transition in the Central Nervous System: Induction by Calcium Cycling-Dependent and -Independent Pathways. *Journal of Neurochemistry*, **69**, 524-538. https://doi.org/10.1046/j.1471-4159.1997.69020524.x

[19] Lifshitz, J., Friberg, H., Neumar, R.W., Raghupathi, R., Welsh, F.A., Janmey, P., Saatman, K.E., Wieloch, T., Grady, M.S. and McIntosh, T.K. (2003) Structural and Functional Damage Sustained by Mitochondria after Traumatic Brain Injury in the Rat: Evidence for Differentially Sensitive Populations in the Cortex and Hippocampus. *Journal of Cerebral Blood Flow & Metabolism*, **23**, 219-231. https://doi.org/10.1097/01.WCB.0000040581.43808.03

[20] Singh, I.N., Sullivan, P.G., Deng, Y., Mbye, L.H. and Hall, E.D. (2006) Time Course of Post-Traumatic Mitochondrial Oxidative Damage and Dysfunction in a Mouse Model of Focal Traumatic Brain Injury: Implications for Neuroprotective Therapy. *Journal of Cerebral Blood Flow & Metabolism*, **26**, 1407-1418. https://doi.org/10.1038/sj.jcbfm.9600297

[21] Huang, Y. and Wang, K.K. (2001) The Calpain Family and Human Disease. *Trends in Molecular Medicine*, **7**, 355-362. https://doi.org/10.1016/S1471-4914(01)02049-4

[22] Kruman, I.I. and Mattson, M.P. (1999) Pivotal Role of Mitochondrial Calcium Uptake in Neural Cell Apoptosis and Necrosis. *Journal of Neurochemistry*, **72**, 529-540. https://doi.org/10.1046/j.1471-4159.1999.0720529.x

[23] Ankarcrona, M., Dypbukt, J.M., Bonfoco, E., Zhivotovsky, B., Orrenius, S., Lipton, S.A. and Nicotera, P. (1995) Glutamate-Induced Neuronal Death: A Succession of Necrosis or Apoptosis Depending on Mitochondrial Function. *Neuron*, **15**, 961-973. https://doi.org/10.1016/0896-6273(95)90186-8

[24] Zipfel, G.J., Babcock, D.J., Lee, J.M. and Choi, D.W. (2000) Neuronal Apoptosis after CNS Injury: The Roles of Glutamate and Calcium. *Journal of Neurotrauma*, **17**, 857-869. https://doi.org/10.1089/neu.2000.17.857

[25] Kostron, H., Twerdy, K., Stampfl, G., Mohsenipour, I., Fischer, J. and Grunert, V. (1984) Treatment of the Traumatic Cerebral Vasospasm with the Calcium Channel Blocker Nimodipine: A Preliminary Report. *Neurological Research*, **6**, 29-32. https://doi.org/10.1080/01616412.1984.11739660

[26] Langham, J., Goldfrad, C., Teasdale, G., Shaw, D. and Rowan, K. (2003) Calcium Channel Blockers for Acute Traumatic Brain Injury. *Cochrane Database of Systematic Reviews*, No. 4, CD000565. https://doi.org/10.1002/14651858.CD000565

[27] Xiong, Y., Mahmood, A. and Chopp, M. (2009) Emerging Treatments for Traumatic Brain Injury. *Expert Opinion on Emerging Drugs*, **14**, 67-84. https://doi.org/10.1517/14728210902769601