Mini Review

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2021.39.006293

Therapeutic Strategies of Ischemic Stroke Based on Proton-Activated Chloride Channel

Fanglin Peng[1,2], Yi Wu[2,3]* and Peng Huang[2,4]*

[1]*School of Medical Instrument and Food Engineering USST, University of Shanghai for Science and Technology, Shanghai 200093, China*

[2]*Collaborative Innovation Center for Biomedicine, Shanghai University of Medicine & Health Sciences, Shanghai 201318, China*

[3]*School of Pharmacy, Shanghai University of Medicine & Health Sciences, Shanghai 201318, China*

[4]*School of Clinical Medicine, Shanghai University of Medicine and Health Sciences, Shanghai 201318, China*

***Corresponding author:** Yi Wu, Assistant professor, PhD, Shanghai University of Medicine & Health Sciences, Shanghai and Peng Huang, Associate professor, PhD, Shanghai University of Medicine & Health Sciences, Shanghai, China

ARTICLE INFO

Received: October 02, 2021

Published: October 12, 2021

Citation: Fanglin Peng, Yi Wu, Peng Huang. Therapeutic Strategies of Ischemic Stroke Based on Proton-Activated Chloride Channel. Biomed J Sci & Tech Res 39(3)-2021. BJSTR. MS.ID.006293.

ABSTRACT

Ischemic stroke is a leading cause of death and disability worldwide with limited therapeutic options. The newly identified proton-activated chloride channel (PAC) has received increasing attentions in recent years and has been reported to provide partial neuroprotection in tissue acidosis resulting from ischemic stroke. This review discusses two therapeutic strategies with high potential based on PAC properties, in order to indicate a new direction for the treatment of ischemic stroke.

Keywords: Ischemic Stroke; PAC; Hypothermia; Nano-Systems; Acidosis

Introduction

Ischemic stroke is a multifactorial disease with high rate of morbidity, mortality and disability rate worldwide [1]. When acute ischemia occurs, it leads to excessive oxidative stress, causing irreversible damage to nervous tissue [2,3]. However, current treatment strategies of ischemic stroke are relatively limited, actually, a large number of neuroprotective agents that have proved ineffective in clinical trials [4]. PAC, also known as ASOR (acid-sensitive outwardly rectifying anion channel) [5] or PAORAC (proton-activated outwardly rectifying anion channel) [6], which was first observed in rat Sertoli cells in 2003[7], has shown encouraging results in providing partial neuroprotection against tissue acidosis caused by ischemic stroke.

Pac Channel and its Therapeutic Potential

Under normal physiological condition, the pH of extracellular fluid, including the blood plasma, is normally tightly regulated between 7.32 and 7.42 by the chemical buffers, the respiratory system, and the renal system [8]. However, in cerebral acidosis caused by ischemic stroke, the pH of the ischemic core may be as low as 6.0 [9]. Ischemic tissue acidosis is a sensitive metabolic indicator for the progression of cerebral ischemic injury. PAC was reported to be activated by extracellular acidity as well as its sensitivity to temperature and pH [5]. The threshold pH for PAC activation is relatively low, around pH 5.5 at room temperature and around pH 6.0 at 37°C [10]. As a highly conserved channel ubiquitously expressed in mammals, the core protein of PAC (TMEM206) has the highest molecular expression in the cerebral cortex of human [11]. By cooperating with other ion transporters and channels such as V-ATPase, acid-sensing ion channel 1a (ASIC1a), and Na+/H+ exchanger (NHE), PAC is activated by extracellular acidity and mediates Cl- influx into the cell, cytotoxic edema and cell necrosis ensue [12-14]. The simultaneous increase in intracellular Ca2+

promotes cell death cascade associated with intracellular Ca^{2+} accumulation [15].

Several studies have reported that inhibition of PAC provides partial neuroprotection against tissue acidosis after ischemic stroke:

1. Neurons undergoing massive necrosis 1h after exposure to acidic solution were not only protected by PAC channel blockers but also by cooling down to 25 °C [10],
2. Knocking down the core component of PAC (TMEM206) almost abolished proton activated Cl- current in rat neurons and reduced neuronal cell death caused by acid treatment [16],
3. Application of the chloride channel blocker 4,4′-Diisothiocyano-2,2′-stilbenedisulfonic acid (DIDS) *in vivo* attenuated cell injury induced by ischemia-reperfusion in hippocampal CA1 neurons [17],
4. Knockout of mouse PAC abolished proton-activated Cl- current in neurons and attenuated brain damage after ischemic stroke [11]. Based on above lines of evidence, PAC is a promising therapeutic target to protect neurons in cerebral ischemia.

Therapeutic Strategies of Ischemic Stroke Targeting PAC Channels

Metabolic acidosis occurring in ischemic stroke is a sensitive metabolic indicator capable of targeting drugs to the salvageable ischemic penumbra with high specificity. Targeting ischemic brain tissue using pH sensitive marker polymers or nanoparticles has enabled medical imaging to accurately distinguish ischemic tissues from normal ones [18,19]. The development of bio-responsive materials that undergo conformational or solubility changes under acidic environments offers great promise for the development of smart targeted drug delivery nano-systems [20], such as the hydrophobically modified chitosan nanoparticles (Chit NPs) with C6-side chains were released the Ca2+ channel blocker nimodipine (NIMO) drug at the pH of ischemic tissue (=6.0), while at normal pH (=7.4) the drug molecules was remained closed in polymer shell [21]. pH directing effect and bio-responsive nanomaterials have been applied in solid tumor therapy and inspired the application of nanotechnology in the treatment of ischemic stroke [22,23]. Selective delivery of PAC specific blockers to the ischemic penumbra via a pH responsive smart nanosystem holds promise for the treatment of injury sites without adverse nontargeted side effects. However, currently there are only several universal drugs available to target chloride channels, such as DIDS, niflumic acid (NFA), and 5-nitro-2-(3-phenylpropylamino) benzoic acid (NPPB), specific PAC blocker has not yet been reported [11,12].

Therapeutic hypothermia has been regarded as one of the most effective neuroprotective strategies since 1987 [24,25]. Over the past few decades, the neuroprotective effects of hypothermia in cardiac arrest [26] and resuscitation from neonatal hypoxic-ischemic encephalopathy [27] have been confirmed by multiple clinical trials. Numerous preclinical studies based on vascular recanalization models have shown that hypothermia exerts neuroprotective effects mainly by reducing the cerebral metabolic rate [28], but also involves cell death, inflammation and white matter integrity [29], and the temperature sensitivity of PAC also provides potential mechanisms [16]. Intra-arterial selective cooling infusion (IA-SCI), as a novel therapeutic method of hypothermia, utilizes the characteristics of high blood flow to the brain to directly perfuse hypothermic fluid into the cerebral arteries for rapid and selective cooling [30]. IA-SCI can precisely achieve regional cooling of brain tissue with a much faster cooling compared with traditional superficial cooling and systemic transvenous cooling and can be combined with mechanical thrombectomy to avoid the side effects brought by systemic cooling [31,32], which has been clinically validated in rodent models [33], large animal models [34] and ischemic stroke patients [35]. Precise cooling of the acidotic brain tissue in ischemic stroke by IA-SCI can elevate opening threshold of PAC, thereby shutting the channel, thereby reducing the influx of Cl-, improving cytotoxic edema, and achieving neuroprotection [10,12].

Conclusion

Targeted delivery of PAC blockers by smart nano-systems is highly specific and efficient and enables the gradual release of drugs to extend the time of drug exposure, reducing the risk of adverse side effects or off target toxicity. Compared with the simultaneous closure / blockade of multiple cationic channels associated with cellular edema (such as ASICs and NHEs, etc.), the blockade of a single and unique anion channel (PAC) by hypothermia has higher applicability and feasibility experimentally or clinically. Although there is currently a lack of sufficient experiments to validate the above two therapeutic strategies, smart drug targeting nano-systems and hypothermia therapy that inhibit PAC also pose an promising opportunity for translational trials to protect brain tissue.

References

1. Collaborators G B D L R O S, Feigin V L, Nguyen G, Kelly Cercy, Catherine O Johnson, et al. (2018) Global, Regional, and Country-Specific Lifetime Risks of Stroke, 1990 and 2016. N Engl J Med 379(25): 2429-37.
2. Xia D, Zhang Z, Zhao Y (2018) Acteoside Attenuates Oxidative Stress and Neuronal Apoptosis in Rats with Focal Cerebral Ischemia-Reperfusion Injury [J] Biol Pharm Bull 41(11): 1645-51.
3. Dai Y, Zhang H, Zhang J, Mingguang Yan (2018) Isoquercetin attenuates oxidative stress and neuronal apoptosis after ischemia/reperfusion injury via Nrf2-mediated inhibition of the NOX4/ROS/NF-kappaB pathway. Chem Biol Interact 284: 32-40.
4. O'collins V E, Macleod M R, Donnan G A, Laura L Horky, Bart H vander Worp, et al. (2006) 1,026 experimental treatments in acute stroke. Ann Neurol 59(3): 467-77.

5. Wang H Y, Shimizu T, Numata T, Yasunobu Okada (2007) Role of acid-sensitive outwardly rectifying anion channels in acidosis-induced cell death in human epithelial cells. Pflugers Arch 454(2): 223-33.
6. Lambert S, Oberwinkler J (2005) Characterization of a proton-activated, outwardly rectifying anion channel. J Physiol 567(Pt 1): 191-213.
7. Auzanneau C, Thoreau V, Kitzis A, Frederic Becq (2003) A Novel voltage-dependent chloride current activated by extracellular acidic pH in cultured rat Sertoli cells. J Biol Chem 278(21): 19230-6.
8. Hamm L L, Nakhoul N, Hering-Smith K S (2015) Acid-Base Homeostasis. Clin J Am Soc Nephrol 10(12): 2232-42.
9. Back T, Hoehn M, Mies G, E Busch, B Schmitz, et al. (2000) Penumbral tissue alkalosis in focal cerebral ischemia: Relationship to energy metabolism, blood flow, and steady potential. Annals of Neurology 47(4): 485-92.
10. Sato-Numata K, Numata T, Okada Y (2014) Temperature sensitivity of acid-sensitive outwardly rectifying (ASOR) anion channels in cortical neurons is involved in hypothermic neuroprotection against acidotoxic necrosis. Channels 8(3): 278-283.
11. Yang J H, Chen J N, Vitery M D, James Osei-Owusu, Jiachen Chu, et al. (2019) PAC, an evolutionarily conserved membrane protein, is a proton-activated chloride channel. Science 364(6438): 395-399.
12. Okada Y, Sato-Numata K, Sabirov R Z, Tomohiro Numata (2021) Cell Death Induction and Protection by Activation of Ubiquitously Expressed Anion/Cation Channels. Part 2: Functional and Molecular Properties of ASOR/PAC Channels and Their Roles in Cell Volume Dysregulation and Acidotoxic Cell Death. Front Cell Dev Biol 9.
13. O M T, Menyhart A, Frank R, Dóra Hantosi, Eszter Farkas, et al. (2020) Tissue Acidosis Associated with Ischemic Stroke to Guide Neuroprotective Drug Delivery. Biology Basel 9(12): 460.
14. Rungta R L, Choi H B, Tyson J R, Aqsa Malik, Lasse Dissing-Olesen, et al. (2015) The cellular mechanisms of neuronal swelling underlying cytotoxic edema. Cell 161(3): 610-21.
15. Xiong Z G, Zhu X M, Chu X P, Manabu Minami, Jessica Hey, et al. (2004) Neuroprotection in ischemia: blocking calcium-permeable acid-sensing ion channels. Cell 118(6): 687-98.
16. Osei-Owusu J, Yang J, Del Carmen Vitery M, Mengnan Tian, Zhaozhu Qiu (2020) PAC proton-activated chloride channel contributes to acid-induced cell death in primary rat cortical neurons. Channels Austin 14(1): 53-8.
17. Inoue H, Okada Y (2007) Roles of volume-sensitive chloride channel in excitotoxic neuronal injury [J]. J Neurosci 27(6): 1445-55.
18. Yu L, Chen Y, Chen M, Xiaojie Luo, Shanshan Jiang, et al. (2019) Amide Proton Transfer MRI Signal as a Surrogate Biomarker of Ischemic Stroke Recovery in Patients with Supportive Treatment. Front Neurol 10: 104.
19. Huang G, Zhao T, Wang C, Kien Nham, Yahong Xiong, et al. (2020) PET imaging of occult tumours by temporal integration of tumour-acidosis signals from pH-sensitive (64) Cu-labelled polymers. Nat Biomed Eng 4(3): 314-24.
20. Liu J, Huang Y, Kumar A, Aaron Tan, Shubin Jin, et al. (2014) pH-sensitive nano-systems for drug delivery in cancer therapy. Biotechnol Adv 32(4): 693-710.
21. Janovak L, Turcsanyi A, Bozo E, Ágota Deák, László Mérai, et al. (2018) Preparation of novel tissue acidosis-responsive chitosan drug nanoparticles: Characterization and *in vitro* release properties of Ca(2+) channel blocker nimodipine drug molecules. Eur J Pharm Sci 123: 79-88.
22. Shenoy d, Little s, Langer r, Mansoor Amiji (2005) Poly(ethylene oxide)-modified poly(beta-amino ester) nanoparticles as a pH-sensitive system for tumor-targeted delivery of hydrophobic drugs: part 2. *In vivo* distribution and tumor localization studies. Pharm Res 22(12): 2107-14.
23. Poon Z, Chang D, Zhao X, Paula T Hammond (2011) Layer-by-layer nanoparticles with a pH-sheddable layer for *in vivo* targeting of tumor hypoxia. ACS Nano 5(6): 4284-92.
24. Busto R, Dietrich W D, Globus M Y, I Valdés, P Scheinberg, et al. (1987) Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury [J]. J Cereb Blood Flow Metab 7(6): 729-38.
25. Kuczynski A M, Demchuk A M, Almekhlafi M A (2019) Therapeutic hypothermia: Applications in adults with acute ischemic stroke. Brain Circ 5(2): 43-54.
26. Hypothermia After Cardiac Arrest Study G (2002) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346(8): 549-56.
27. Jacobs S E, Morley C J, Inder T E, et al. (2011) Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. Arch Pediatr Adolesc Med 165(8): 692-700.
28. Kurisu K, Yenari M A (2018) Therapeutic hypothermia for ischemic stroke; pathophysiology and future promise. Neuropharmacology 134(Pt B): 302-9.
29. Yenari m a, Han H S (2012) Neuroprotective mechanisms of hypothermia in brain ischaemia. Nat Rev Neurosci 13(4): 267-78.
30. Esposito E, Ebner M, Ziemann U, Sven Poli (2014) In cold blood: intraarteral cold infusions for selective brain cooling in stroke. J Cereb Blood Flow Metab 34(5): 743-52.
31. Slotboom J, Kiefer C, Brekenfeld C, L Remonda, K Nedeltchevet, et al. (2004) Locally induced hypothermia for treatment of acute ischaemic stroke: a physical feasibility study. Neuroradiology 46(11): 923-34.
32. Wu L, Wu D, Yang T, Jin Xu, Jian Chen, et al. (2020) Hypothermic neuroprotection against acute ischemic stroke: The 2019 update. J Cereb Blood Flow Metab 40(3): 461-81.
33. Song W, Wu Y M, Ji Z, Ya-Bin Ji, Sheng Nan Wang, et al. (2013) Intra-carotid cold magnesium sulfate infusion induces selective cerebral hypothermia and neuroprotection in rats with transient middle cerebral artery occlusion. Neurol Sci 34(4): 479-86.
34. Caroff J, King R M, Mitchell J E, Miklos Marosfoi, Joseph R Licwinko, et al. (2020) Focal cooling of brain parenchyma in a transient large vessel occlusion model: proof-of-concept. J Neurointerv Surg 12(2): 209-13.
35. Chen J, Liu L, Zhang H, Xiaokun Geng, Liqun Jiao, et al. (2016) Endovascular Hypothermia in Acute Ischemic Stroke: Pilot Study of Selective Intra-Arterial Cold Saline Infusion. Stroke 47(7): 1933-5.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2021.39.006293

Yi Wu, Peng Huang. Biomed J Sci & Tech Res