Review Article

Disrupted Ionic Homeostasis in Ischemic Stroke and New Therapeutic Targets

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Background: Stroke is a leading cause of long-term disability. All neuroprotectants targeting excitotoxicity have failed to become stroke medications. In order to explore and identify new therapeutic targets for stroke, we here reviewed present studies of ionic transporters and channels that are involved in ischemic brain damage. *Method:* We surveyed recent literature from animal experiments and clinical reports in the databases of PubMed and Elsevier ScienceDirect to analyze ionic mechanisms underlying ischemic cell damage and suggest promising ideas for stroke therapy. *Results:* Dysfunction of ionic transporters and disrupted ionic homeostasis are most early changes that underlie ischemic brain injury, thus receiving sustained attention in translational stroke research. The Na^+/K^+-ATPase, Na^+/Ca^{2+} Exchanger, ionotropic glutamate receptor, acid-sensing ion channels (ASICs), sulfonylurea receptor isoform 1 (SUR1)–regulated $NC_{Ca\text{-}ATP}$ channels, and transient receptor potential (TRP) channels are critically involved in ischemia-induced cellular degenerating processes such as cytotoxic edema, excitotoxicity, necrosis, apoptosis, and autophagic cell death. Some ionic transporters/channels also act as signalosomes to regulate cell death signaling. For acute stroke treatment, glutamate-mediated excitotoxicity must be interfered within 2 hours after stroke. The SUR1-regulated $NC_{Ca\text{-}ATP}$ channels, Na^+/K^+-ATPase, ASICs, and TRP channels have a much longer therapeutic window, providing new therapeutic targets for developing feasible pharmacological treatments toward acute ischemic stroke. *Conclusion:* The next generation of stroke therapy can apply a polypharmacology strategy for which drugs are designed to target multiple ion transporters/channels or their interaction with neurotoxic signaling pathways. But a successful translation of neuroprotectants relies on in-depth analyses of cell death mechanisms and suitable animal models resembling human stroke. **Key Words:** Ischemic stroke—cell death—ionic transporters—ionic channels—sodium ions (Na^+)—Calcium ions (Ca^{2+}).

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Introduction

The adult brain is only ~2.5% of the total body weight, but it consumes ~25% of oxygen and energy in the blood flow to maintain its normal function. The brain is the center of our life that contains approximately 100 billion neurons that control our bodily functions of sight, smell, hearing, sensor and motor, and learning and memory. Stroke is a kind of brain attack resulting from cerebral bleeding (hemorrhagic stroke) or an occlusion of a cerebral artery (ischemic stroke), characterized by a rapid cell death in the implicated area and corresponding disability. Ischemic stroke is the most common type of stoke throughout the world.[1,2] In China, hemorrhagic stroke constitutes one third of all stroke subtypes; this proportion is higher than that in Western countries.[3] In the United States, stroke is the fifth leading cause of human death, but it still remains a leading cause of long-term disability.[4] Stroke causes huge economic and social burdens across the world.

Ischemic stroke occurs when the cerebral blood flow is suddenly blocked by artery occlusion resulting from thrombosis or embolism. If blood supply to the entire or the majority of the brain is stopped, this will lead to the global ischemia category. Stroke epidemiology indicates that focal ischemic stroke is the most common category because cerebral blood flow is most prevalently reduced in a specific brain region.[5] During a stroke attack, interruption of circulation causes detrimental changes such as anoxia, oxygen and glucose deprivation (OGD), loss of adenosine triphosphate (ATP), acidosis due to anaerobic generation of lactate, disrupted cell ionic homeostasis, excitotoxicity, reactive oxygen species (ROS), and other subsequent events. These conditions initially trigger cell death in the territory where cerebral blood flow is arrested, eventually leading to a central ischemic core; meanwhile, the remaining tissue within the peri-infarct region (or penumbra) is hypoperfused (25~50% of normal) and partially injured. Without therapeutic intervention and reperfusion, the peri-infarct area will face the encroachment of infarction over the ensuing days to weeks and will ultimately be recruited into the ischemic core. Therefore, efficacious treatment for ischemic stroke lies in early restoration of ceased blood flow and neuroprotective therapies interfering with the ischemic events that underlie cell death in the penumbra. Currently, the clot-dissolving agent, the tissue plasminogen activator (tPA), is the only approved drug for clinical use in the thrombolytic treatment of acute ischemic stroke. In clinical practice, however, only 3%-4% of all stroke patients can receive an administration of the tPA because of the narrow therapeutic window of 4.5 hours and the increased risk of intracranial hemorrhage.[6] Most stroke patients must rely on, although not yet validated, the strategy of neuroprotection and salvage of the degenerating cerebral parenchyma.

Over the past three decades, a large amount of efforts have been invested on neuroprotection research, and more than 100 neuroprotectants were found effective in preventing neuronal death in animal stroke models.[7,8] However, all of these drugs failed to demonstrate beneficial outcomes in stroke patients.[7,9] The reasons behind the failure of the translation are complex. One important reason is unrevealed cell death mechanisms that are involved in brain tissue injury and crucial for developing more effective neuroprotective agents. The active cell death mechanisms crossing the ischemic core and penumbra are characterized by a spectrum of time-dependent pathological changes that have been described as necrosis, apoptosis, and much less studied autophagy. The detailed introduction of ischemic cell death, along with stroke risk factors and plasticity for rehabilitation, can be learned from other reviews.[10-12] This review concentrated on the dysfunction of plasma membrane transporters, ion channels, and disrupted ionic homeostasis that underlie cellular toxicity during the acute stage of ischemia and attempts to suggest promising ideas for translational stroke research.

Necrosis, Apoptosis, and Autophagy in Ischemic Stroke

Clinically, stroke patients are diagnosed and imaged with a brain computed tomography, magnetic resonance imaging, or positron emission tomography scans.[13] The mechanisms and morphological features of ischemic cell death in the brain parenchyma were mostly collected from a rodent stroke model and examined by histological methods. The experimentally derived data describe the main processes through which injured glial cells and neurons are killed as coagulation necrosis, apoptosis, and recently highlighted autophagy. In coagulation necrosis, the glial cell undergoes swelling, then shrinkage and pyknosis. For example, in a cerebral ischemia rat model, astrocytes and oligodendrocytes swell in the ischemic core 30 minutes after middle cerebral artery (MCA) occlusion.[14] On the contrary, neurons initially shrink then swell. The shrinking neurons can be identified in ischemic brain parenchyma at 30 minutes, while swelling and necrotic neurons (plasma membrane damage, pyknosis, and karyolysis) are visible in small numbers at 1 hour and increase significantly at 6-12 hours after MCA occlusion.[15] In the ischemic core, necrosis is the predominant cell death mechanism at the early stage of stroke and often causes irreversible tissue damage, especially because most patients cannot reach hospitals within 3 hours.[16,17] Fortunately, the delayed cell death via apoptosis in the penumbra develops hours or days after stroke and possesses the potential to be salvaged; therefore, this became the focus of translational research for stroke. Different from necrosis, apoptosis is an orderly process in which cells are programmed to die through certain routes