Progress in Neurobiology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Proton-sensitive cation channels and ion exchangers in ischemic brain injury: New therapeutic targets for stroke?

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ARTICLE INFO

Article history:
Received 26 August 2013
Received in revised form 28 November 2013
Accepted 24 December 2013
Available online xxx

Keywords:
Acidosis
ASIC
Calcium
NHE1
TRPM7
Zinc

ABSTRACT

Ischemic brain injury results from complicated cellular mechanisms. The present therapy for acute ischemic stroke is limited to thrombolysis with the recombinant tissue plasminogen activator (rtPA) and mechanical recanalization. Therefore, a better understanding of ischemic brain injury is needed for the development of more effective therapies. Disruption of ionic homeostasis plays an important role in cell death following cerebral ischemia. Glutamate receptor-mediated ionic imbalance and neurotoxicity have been well established in cerebral ischemia after stroke. However, non-NMDA receptor-dependent mechanisms, involving acid-sensing ion channel 1a (ASIC1a), transient receptor potential melastatin 7 (TRPM7), and Na^+/H^+ exchanger isoform 1 (NHE1), have recently emerged as important players in the dysregulation of ionic homeostasis in the CNS under ischemic conditions. These H^+-sensitive channels and/or exchangers are expressed in the majority of cell types of the neurovascular unit. Sustained activation of these proteins causes excessive influx of cations, such as Ca^{2+}, Na^+, and Zn^{2+}, and leads to ischemic reperfusion brain injury. In this review, we summarize recent pre-clinical experimental research findings on how these channels/exchangers are regulated in both *in vitro* and *in vivo* models of cerebral ischemia. The blockade or transgenic knockdown of these proteins was shown to be neuroprotective in these ischemia models. Taken together, these non-NMDA receptor-dependent mechanisms may serve as novel therapeutic targets for stroke intervention.

Contents

Abbreviations: AA, arachidonic acid; ADF, actin depolymerizing factor; AIF, apoptosis-inducing factor; ASIC, acid-sensing ion channel; BBB, blood–brain barrier; BK, bradykinin; CAMKII, Ca^{2+}/calmodulin (CaM)-dependent protein kinase II; CHP, calcineurin homologous protein; DEG/ENaC, degenerin/epithelial sodium channel; ERK, extracellular signal-regulated kinase; ERM, ezrin radixin moesin; GFAP, glial fibrillary acidic protein; HI, hypoxia–ischemia; IL, interleukin; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCAO, middle cerebral artery occlusion; MMP, matrix metalloproteinase; NCX, Na^+/Ca^{2+} exchanger; NHE, sodium/hydrogen exchanger; NIK, Nck-interacting kinase; NMDA, N-methyl-D-aspartate; NOX, NADPH oxidase; OGD, oxygen and glucose deprivation; $p90^{RSK}$, p90 ribosomal S kinase; p160ROCK, p160 Rho-associated kinase; pH_i, intracellular pH; PIP2, phosphatidylinositol 45-bisphosphate; REOX, reoxygenation; ROS, reactive oxygen species; rtPA, recombinant tissue plasminogen activator; TRPM, transient receptor potential melastatin.

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0301-0082/$ – see front matter © 2014 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.pneurobio.2013.12.008

1. Introduction

A stroke occurs when blood flow to the brain is disrupted by an obstruction (*i.e.*, ischemic stroke) or hemorrhage (*i.e.*, hemorrhagic stroke). Strokes are the leading cause of death in the United States, affecting approximately 800,000 people each year (Roger et al., 2011). They are also a major cause of long-term disabilities, with 20% of all stroke survivors requiring long-term institutional care and 15–30% of them being permanently disabled, unable to resume work and other daily activities (Goldstein et al., 2011; Roger et al., 2011).

The current treatment for acute ischemic stroke is limited to restoring the blood supply to the affected area. Reperfusion therapy consists of administering the thrombolytic agent recombinant tissue plasminogen activator (rtPA), and endovascular mechanical clot extraction (Nesbit et al., 2004). However, rtPA has a narrow therapeutic timeframe of 3–4.5 h (Hacke et al., 2004; Wardlaw et al., 2012) because of the high risk of intracranial hemorrhage after thrombolysis beyond the window, especially in patients with severe strokes or increased age (van der Worp and van Gijn, 2007). Thus, only approximately 5% of stroke patients can benefit from rtPA treatment. Combination therapies with neuroprotective agents have been extensively investigated to prevent delayed neuronal death in stroke. Unfortunately, almost all neuroprotective agents that showed great promise in pre-clinical experimental studies in the past three decades failed in clinical trials (O'Collins et al., 2006). Some clinical trials demonstrated protection in acute ischemic stroke by blocking N-methyl-D-aspartate (NMDA)-mediated neurotoxicity, however, the required early treatment time (immediately after endovascular repair procedure) limits its clinical application (Hill et al., 2012; Kaste, 2012). Therefore, continued effort is needed to better understand the complex processes of stroke-induced brain injury and to identify novel therapeutic targets for stroke intervention.

During a stroke, the disruption of blood flow to the brain deprives cells of energy and disturbs the ionic homeostasis of the cells (Siesjo, 1992). Inhibition of oxidative phosphorylation and depletion of ATP result in the loss of ATP substrate for Na^+-K^+-ATPase, which leads to the dissipation of transmembrane K^+ and Na^+ gradients and subsequent membrane depolarization (Lipton, 1999). Sustained depolarization causes excessive Ca^{2+} entry through voltage-sensitive Ca^{2+} channels, which initiates an excessive release of the neurotransmitter glutamate (Benveniste et al., 1984; Nicholls and Attwell, 1990) and, subsequently, the excessive stimulation of NMDA receptors. The resulting Ca^{2+} overload (Choi, 1988, 1992; Simon et al., 1984) then triggers secondary signal cascades, activating proteases and phospholipases, and producing free radicals (Puyal et al., 2013). This is the well-known excitotoxicity mechanism that contributes to the cerebral ischemia-induced neuronal injury (Lai et al., 2011).

In addition to NMDA-dependent mechanisms, recent studies have shown that other Ca^{2+} permeable channels, such as the acid-sensing ion channel 1a (ASIC1a), transient receptor potential melastatin 7 (TRPM7), and Na^+/H^+ exchanger isoform 1 (NHE1), contribute to neuronal injury after ischemia and reperfusion. Under ischemic conditions, hypoxia enhances glycolysis, resulting in the buildup of lactic acid and subsequent tissue acidosis. Extracellular pH in the brain typically drops to below 6.5 during ischemia under normoglycemic conditions (Nedergaard et al., 1991). However, with hyperglycemia, the concentration of lactate in the brain could rise to 25 μmol/g, causing the pH of the ischemic brain to drop to approximately 6.0 (Rehncrona, 1985). The notion that acidosis exacerbates ischemic brain injury first rises from the observations that ischemic outcomes are worsened in the case of incomplete ischemia or glucose-infused subjects, where additional glucose is delivered to the tissue during the ischemic insult (Siesjo, 1988). Indeed, excessive lactate accumulation can cause edema, BBB dysfunction, and extensive tissue necrosis in part by inhibition on glutamate uptake (Swanson et al., 1995), impairment of brain energetics (Swanson et al., 1997), and oxidative stress (Ying et al., 1999). However, it is notable that recent research also suggests protective effects of mild intracellular pH reduction against NMDA-mediated neuronal toxicity *via* inhibiting the NADPH oxidase (Lam et al., 2013).

Apart from these, acidosis can activate homomeric ASIC1a, causing a large influx of Na^+ and Ca^{2+}, leading to neuronal injury (Xiong et al., 2004; Yermolaieva et al., 2004). Thus, deleting ASIC1a or inhibiting its activation is potentially neuroprotective. Importantly, the effective therapeutic time window for ASIC1a inhibition is longer than 5 h in animal models of stroke (Pignataro et al.,

Please cite this article in press as: Leng, T., et al., Proton-sensitive cation channels and ion exchangers in ischemic brain injury: New therapeutic targets for stroke? Prog. Neurobiol. (2014), http://dx.doi.org/10.1016/j.pneurobio.2013.12.008