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ORIGINAL ARTICLE

Nrf2 to Pre-condition the Brain Against Injury Caused by Products of Hemolysis After ICH

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Abstract Brain damage caused by intracerebral hemorrhage is mediated in part by the toxicity of extravascular blood deposited in the brain parenchyma during the hematoma formation. In this paper, we discuss the therapeutic benefits and potential mechanisms associated with the activation of transcription factor Nrf2 regarding its role in defending the brain tissue against toxicity of the blood, a component of secondary injury. We emphasize the pleiotropic capacity of Nrf2 as it recruits multiple pathways aiming at reducing deleterious effects of blood lysis products.

Keywords Intracerebral hemorrhage · Nrf2 · Oxidative stress · Cytoprotection

Introduction

Hemorrhagic stroke (intracerebral hemorrhage (ICH)) is the third leading cause of death in the USA. An estimated 37,000 to 52,400 people in the USA suffer an ICH each year. This rate is expected to double by 2050 as a result of an aging population and changing racial demographics, and to date, there are no specific treatments for human ICH [1–3]. The strongest predictor of the poor clinical outcome after ICH is the volume of hematoma. The deposited blood is damaging initially via mass effect and then via blood (hemolysis products) toxicity and pro-inflammatory responses. These blood products, primarily through oxidative damage, may contribute to delayed neuronal loss, vascular injury, blood–brain barrier opening, edema, and neurological deficit or death [3, 4].

Hemolysis Product Toxicity and Detoxification Mechanisms After ICH

There is an immediate mass effect with physical disruption and increased intracranial pressure. In addition, there is secondary brain injury due to clot-derived factors including hemoglobin (Hb) and Hb degradation products (heme and iron). Hb is the most abundant RBC protein. Normally, it takes approximately 1–4 days for RBCs to undergo massive lysis, resulting in the release of cell-free Hb [5, 6]. The cell-free Hb is a potent oxidant which is toxic to all brain cells, neurons and oligodendrocytes in particular [1, 6–8]. The deposited RBCs are considered to be benign to the brain tissue until the hemolysis begins. In agreement with this notion, intracranial injection of lysed RBCs could within hours reproduce most of the pathological features normally found days after injection of whole (not lysed) blood [9]. Since the onset of Hb-, heme-, or iron-mediated toxicity is significantly delayed apart from the ICH ictus, it is likely that the pre-conditioning therapies started hours after ICH could help the brain to gain extra resistance to these toxic/pathogenic factors.

Normally, to neutralize the toxicity imposed by cell-free Hb, haptoglobin (Hp; assuming its availability) tightly binds to free Hb, forming Hb–Hp complexes that are subsequently cleared by the microglia/macrophages (Mϕ) expressing specialized Hb scavenger receptor, CD163 [10, 11] (Fig. 1). Analogous to Hp, hemopexin (Hx) [12, 13] may bind heme and form chemically stable heme–Hx complexes that are cleared through Mϕ scavenger receptor CD91 [14]. Once internalized by Mϕ, heme is catabolized by heme oxygenases (HOs),

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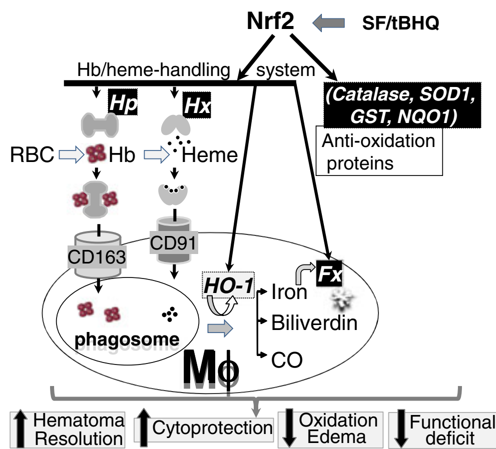

Fig. 1 The endogenous detoxification system for hemolytic products (Hb, heme, and iron). It is proposed that the cell-free Hb and heme are initially neutralized by binding to Hp and Hx, respectively, forming stable Hb–Hp and heme–Hx complexes. The complexes can be endocytosed by Mϕ through the Hb scavenger receptor CD163 [68] and the heme scavenger receptor CD91[14], respectively. Heme in Mϕ is catabolized by HO-1 to biliverdin, CO, and free iron [52]. The latter one is sequestrated within Mϕ by intracellular iron-binding protein, Fx. Activation of Nrf2 with SF or tBHQ may upregulate production of (a) enzymes constituting the antioxidant/cytoprotective defense system (e.g., SOD1, catalase, γGCS, GR, TG, Prxs, GST, and NQO1) [69] and (b) detoxification enzymes (e.g., Hp, Hx, HO-1, and Fx) for preventing the toxic effect of hemolytic products. Thus, approaches aiming at stimulating Nrf2 prior to hematoma hemolysis may ameliorate oxidative stress directly by controlling production of antioxidant enzymes and indirectly by upregulating components capable of blocking the toxic effect of iron-containing hemolytic products

enzymes that mediate breakdown of the porphyrin ring of heme into biliverdin, carbon monoxide (CO), and iron [15]. Iron must be immediately sequestered to prevent additional oxidative stress. Ferritin (Fx) is the most likely candidate for this function [16]. Fx synthesis normally occurs in microglia depending on the local concentration of iron and the presence of iron regulatory proteins [17]. Thus, pre-conditioning approaches (treatment initiated prior to hemolytic process is initiated) allowing for (1) boosting the scavenging/cleanup of hemolytic products (Hb, heme, and iron) by Mϕ, (2) improving production of Hp, Hx, Fx, and heme oxygenase-1 (HO-1), as well as (3) improving overall resistance of brain cells to oxidative stress, could represent uniquely effective strategies allowing the brain to better withstand the ICH-induced secondary injury caused by hemolysis products. Interestingly, all the above-mentioned pre-conditioning components can be achieved via activation of a ubiquitous pleiotropic transcription factor, nuclear factor-erythroid 2 p45-related factor 2 (Nrf2).

Nrf2

Nrf2 is a basic-region leucine zipper (bZIP) protein in the CNC-bZIP subfamily and a master genomic regulator of the cellular antioxidant defense system and detoxification. In response to oxidative stress (and electrophilic compounds), Nrf2 is activated, which will boost the expression of cytoprotective and antioxidative target genes and prepare the cells to be more resistant to oxidative stress [18, 19]. Normally, Nrf2 is sequestered in the cytoplasm by interacting with inhibitory protein Kelch-like ECH-associated protein 1 (Keap1). In most cells, Nrf2 is present at low concentrations due to continuous Nrf2 degradation through the proteasome pathway. Nrf2 degradation is Keap1-dependent via binding to the Cul3 E3 ligase complex to mediate a rapid ubiquitination and proteasome degradation. The t1/2 for Nrf2 is considerably short and proposed to be 10–40 min [19, 20]. Keap1 contains 25 cysteine residues that likely represent a direct target for inducers of Nrf2 activation. Alkylation, oxidation, or reduction of the sulfhydryl group on these cysteine residues of Keap1 may represent an initiating step in Nrf2 activation. Ultimately, Nrf2 forms the heterodimeric complexes with Mif family proteins to transactivate the antioxidant response elements.

The Beneficial Effect of Nrf2 on ICH Pathogenesis

Oxidative Stress

As indicated above, one of the key factors linked to ICH pathogenesis is oxidative stress [3]. Taking this into account, we have recently shown that Nrf2 activation may play an essential role in protecting the brain from oxidative damage imposed by ICH [21]. Nrf2 is known to control the expression of numerous enzymes constituting an antioxidant/cytoprotective defense system, e.g., gamma-glutamylcysteine synthetase (γGCS), superoxide dismutase (SOD; primarily SOD1), catalase, glutathione reductase (GR), thioredoxin reductase, peroxiredoxins (Prxs), or glutathione (GSH) *S*-transferase (GSTs). By using sulforaphane (SF) to activate Nrf2 in rodents subjected to ICH injury, we have demonstrated that both the pre-treatment and, most importantly, post-treatment with SF were uniquely effective in upregulating the expression of many of these Nrf2-regulated antioxidative proteins, causing the reduction in oxidative burden to the brain tissue and ultimately improving neurological functional recovery. We and others also showed that Nrf2-deficient mice suffered from the more pronounced injury in response to ICH, suggesting loss of the self-protective effect via Nrf2 [21, 22]. Furthermore, SF was no longer effective in Nrf2-deficient mice, indicating that the protective effect of SF was indeed through Nrf2. At cellular level, existing studies suggest that Nrf2 activation may benefit neurons [23], astrocytes [24], oligodendrocytes [25], and microglia (our unpublished data) regarding susceptibility to oxidative damage, indicating high relevance of this therapeutic approach to the entire neurovascular unit.

Hemoglobin Detoxification by Haptoglobin

Hp is an acute-phase α2-acid response glycoprotein which is well known to form highly stable Hb–Hp complexes with free Hb [26]. Because iron-rich Hb via Fenton oxidation reaction may cause robust lipid peroxidation, oxidative DNA damage, neuronal death, and consequently inflammation [27–29], the neutralization of Hb by Hp may prevent Hb-mediated toxicity. Following hemolysis, Hp appears to act as a main player in the clearance of Hb from the extracellular environment. Normally, Hp is produced primarily in the liver and secreted into the blood circulation, though tissue-specific expression of Hp exists in the brain, lung, and kidney [30–32]. In the brain, Hp was identified in the neural retina [33] and oligodendrocytes [34]. In response to hemolysis, including after ICH, sequestration of Hb by Hp may cause the level of Hp in the blood or affected tissue to decrease, leading to hypohaptoglobinemia (HHp) [34, 35]. At this stage, until Hp is re-synthesized, the clearance of Hb could be compromised, leading to prolonged and more robust Hb cytotoxicity [36]. In the context of ICH, HHp and Hp deficiency could result in more severe brain damage. In our recent study, we demonstrated that after ICH, the levels of Hp in the blood plasma and in the ICH-affected brain were robustly increased in animals that were treated with the Nrf2 activator, SF [34]. We also identified that the most likely sources of Hp in the brain are oligodendroglia, cells in which the robust synthesis and secretion of Hp take place in response to Nrf2 activation with SF or *tert*-butylhydroquinone (tBHQ).

Hemopexin

Similar to free Hb, extracellular heme is highly cytotoxic. Specifically, heme can intercalate into cell membranes and other lipophilic structures, causing cell damage and pathologic inflammatory conditions through the potent pro-oxidative effects [37–39]. Hx is a 60 kDa protein that binds heme with the highest affinity out of any known protein–protein interactions [12, 40]. The formation of heme–Hx complexes could occlude the strong pro-oxidative features of free heme [41, 42]. Heme–Hx dimer may be readily removed from the extracellular space via microglia/macrophages expressing the CD91 scavenging receptor [10, 14]. Hx, similar to Hp, is primarily produced by the liver [40]; however, its production by the CNS, retina, and peripheral nerves has also been suggested [33, 43]. With regard to ICH, we found that Hx is upregulated in the peri-hematoma area, mainly in neurons and phagocytes (microglia/macrophages). We propose that this increase in Hx production forms the auxiliary line of defense against hemolysate-mediated oxidative damage [44]. The complementary role of Hx and Hp in models of acute hemolysis was demonstrated by showing that mice with both Hp and Hx inactivated are much more sensitive to hemolytic stress than mice with single Hp or Hx deficiency [45]. Interestingly, the strong evidence exists for Hx expression increase in response to Nrf2 activation [46, 47], including our results (Fig. 2), suggesting that activation of this transcription factor can assist in the elimination of not only Hb, but also heme.

Heme Oxygenase-1

In contrast to HO-2 that is expressed constitutively, the HO-1 gene is inducible and transcriptionally regulated via oxidative stress signals and Nrf2 [48–50]. HO is the rate-limiting enzyme participating in the catabolism of Hb/heme to biliverdin, free iron, and carbon monoxide [51, 52]. Whereas inhibition of HO-1 with SnPP may effectively reduce generation of the pro-oxidative iron in the hematoma, SnPP may have an adverse effect on the clearance of RBCs from the hematoma (our unpublished data). HO-1 is protective to many cell types in various models of injury, including excitotoxicity and cerebral ischemia [53–56]. Interestingly, HO-1 in ICH may have distinct roles, as numerous studies suggest that HO inhibitors (ZnPP or SnPP) could benefit the hemorrhagic brain by reducing edema after ICH [57–60].

Ferritin

Fx is a ubiquitous and highly conserved iron storage protein, with the function in maintaining iron homeostasis and preventing free iron toxicity [61]. In phagocytes, iron is stored by Fx-containing hemosiderin which is particularly abundant in phagocytic cells after hemorrhage. Fx synthesis normally occurs in Mϕ depending on the local concentration of iron and the presence of iron regulatory proteins [17]. While Fx expression is primarily regulated at the translational level, the additional transcriptional regulation of Fx expression is also accepted and is an important protective mechanism in some pathological situations such as in ischemia [62]. Nrf2 plays an important role in the transcriptional regulation of Fx expression [63, 64] and Fig. 2. Overall, Fx represents a key component of

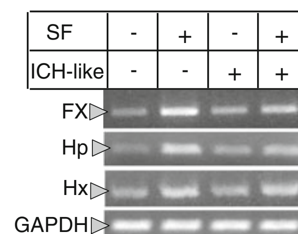

Fig. 2 Photograph of RT-PCR products in rat brain cortical neuron–glial co-cultures. The expression of Fx, Hp, and Hx is upregulated in the SF-treated cells with or without the presence of lysed RBCs. The GAPDH served as the internal control. SF was pre-incubated for 30 min, and the gene products are checked at 6 h after exposure to lysed RBCs. "ICH"—"ICH-like" injury (lysed RBCs)

the detoxification system for Hb/heme downstream from Hp and Hx. Based on the promising studies with deferoxamine (an iron chelator that is evaluated as treatment for ICH), additional strategies aiming at iron chelating would have great potential in preventing hemolytic product-mediated toxicity after ICH [65–67].

In conclusion, in contrast to ischemic stroke, a considerably longer therapeutic window may exist for preventing the secondary injury caused by the toxic hemolytic products after ICH. As such, we postulate that the pre-conditioning by activating Nrf2 within several hours after ICH (prior to hemolytic events are initiated) could prime the ICH-affected brain to better handle the noxious hemolytic products. This Nrf2-mediated priming may include (1) upregulation of antioxidant enzymes in all the affected brain cells to increase their resistance to oxidative stress and (2) upregulation of detoxification proteins to neutralize the toxic hemolysis products around the hematoma.

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Conflict of Interest The authors declare that they have no conflict of interest.

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