Advances in Neuroprotective Strategies: Potential Therapies for Intracerebral Hemorrhage

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Introduction

Despite ongoing medical and surgical advances, intracerebral hemorrhage (ICH) remains the deadliest and least treatable type of stroke [1]. At present, the treatment options are limited with only supportive care and rehabilitation shown to improve the outcome after ICH [2, 3]. Furthermore, therapies developed for hematoma growth prevention, clot removal or optimization of cerebral perfusion pressure have yet to conclusively demonstrate their clinical benefits in randomized clinical trials [4]. In efforts to identify novel therapeutic targets, recent investigations have focused on the mechanisms of secondary brain injury at the hemorrhage site and in the perihematomal zone (PHZ) after ICH [4]. Mounting evidence has indicated that the secondary effects of ICH involve blood-brain-barrier (BBB) disruption, cerebral edema, inflammation, autophagy, and cellular necrosis and apoptosis [5–9]. Furthermore, they are important contributors to the clinical course and outcome after ICH [5]. This has led to a rapidly growing interest in neuroprotective strategies that aim to improve outcomes by reducing ICH-induced secondary pathologic processes.
Neuroprotection consists of heterogeneous strategies that modulate specific cellular and molecular pathways that are triggered after ICH [6, 10]. Numerous neuroprotective agents have been shown to reduce cell death [11], decrease hemorrhage and edema volumes [12–14], and improve functional outcome [15, 16]. Some are currently being investigated in clinical trials and represent novel and promising avenues of ICH therapy [4]. In this article, we review the current understanding of the pathophysiology of ICH-induced secondary brain injury. In addition, we provide an overview of putative neuroprotectants that target hematoma-derived products, inflammatory cascades or proapoptotic pathways.

**Mechanisms of ICH-Induced Secondary Brain Injury**

The current understanding of ICH-induced brain injury is based on both clinical and experimental studies (Fig. 1). Initial injury immediately after ICH onset is from the direct mechanical force of the expanding hematoma [4, 8]. In the first 4 h, physical disruption and stretching of the surrounding neuronal and glial cells lead to excessive neurotransmitter release, calcium influx and mitochondrial dysfunction [8]. When severe, this results in cytotoxic edema and cellular necrosis [17]. In the ensuing days, the degrading hematoma releases its breakdown products, such as thrombin and ferrous iron, which lead to the activation of oxygen free radicals, matrix metalloproteinases (MMPs), complement proteins and inflam-
matory markers [4, 5, 8, 9, 18–20] (fig. 1). These down-
stream molecules increase the BBB permeability [9], re-
cruit inflammatory cells [21], trigger apoptosis [22], and
ultimately exacerbate cerebral edema and neuronal death
[23].

Cerebral edema is a key component of the ICH patho-
physiology (fig. 1). Its rapid development upon onset con-
tributes significantly to the perihematomal volume and
exacerbates mass effect, ischemia and infarction of adja-
cent structures [5, 24]. Although cerebral edema’s relation
to neurological deficit and outcome after ICH remains
controversial, it has served as a target for numerous can-
didate therapies [8, 25–27]. ICH-associated cerebral ede-
ma is primarily vasogenic and develops in the PHZ [8].
Cerebral edema develops immediately after ICH onset,
peaks in the next 5–6 days and lasts up to 2 weeks [8].
Edema formation occurs in 3 phases. During the acute
phase (within the first few hours of onset), hydrostatic
pressure and clot retraction cause clot-derived serum to
move into the PHZ. Subacute (within 2 days of ICH) ac-
tivation of the coagulation cascade and release of throm-
bin contributes to cerebral edema development. This is
further worsened by the erythrocyte lysis and hemoglo-
bin (Hb) toxicity taking place primarily during the later
stages [28]. The BBB disruption, induced by thrombin,
MMPs, complement proteins and hemolytic byproducts,
manifests 8–12 h after ICH onset and is also implicated
in cerebral edema formation [9, 8, 29].

Cellular damage or death, particularly of neurons, is
another critical endpoint of ICH-induced secondary in-
juries [30] (fig. 1). Several interconnected molecular and
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juries [30] (fig. 1). Several interconnected molecular and
Cellular pathways lead to further neuronal injuries, ne-
crosis or apoptosis following ICH [31]. Thrombin, a major
contributor to edema formation and BBB damage, is in-
volved in early brain injury [31]. Hb and its degradation
products, such as heme, are released after erythrocyte ly-
sis and mediate direct neuronal toxicity and death [30].
Infiltrating inflammatory cells, such as macrophages and
neutrophils, aggravate the ongoing injury partly through
production of cytokines, chemokines and reactive oxy-
gen species [32]. Activated microglia and concurrent as-
troglossis are also implicated in inflammatory cellular
damages [33]. Activation of the complement cascade
further heightens the inflammatory response, induces
erthrocyte lysis to release Hb-related molecules and
causes cellular death through the formation of mem-
bane attack complexes [5]. Though deleterious, the in-
flammatory and complement pathways are also critical
for hematoma absorption, cellular debris clearance and
postictal recovery [34, 35].

Fig. 2. Intracerebral-hematoma-derived products and potential
therapies.

Therapeutic Targets and Strategies

Hematoma-Derived Products

Thrombin Inhibition

Thrombin is a serine protease and critical coagulation
protein that is produced rapidly after ICH onset [36]
(fig. 2). Thrombin is a key mediator in stopping the initial
hemorrhage and preventing hematoma expansion [37].
At low concentrations, thrombin confers neuroprotective
effect possibly through the upregulation of heat shock
proteins and iron-handling proteins [38]. However, at
high concentrations, as is usually the case in ICH, throm-
in causes inflammatory cell infiltration, BBB break-
down, cerebral edema formation and neuronal death.

Hirudin and α-N-(2-naphthalenesulfonyl)-glycyl-(D)-
A-aminophenyl-alanyl-piperidine (NAPAP), as thrombin
inhibitors [39], have been shown to decrease cerebral ede-
ma in rat ICH models. Another thrombin inhibitor, arg-
atroban, has recently been studied due to its ability to
inhibit clot-bound thrombin, which is present in signifi-
cant quantities in the hematoma [40]. Direct injection of
argatroban 3 h after ICH significantly reduced the edema
volume in animal models. Similarly, administration of
high-dose systemic argatroban 6 h after ictus led to a sig-
nificant reduction in cerebral edema. These data suggest
that thrombin inhibitors may provide a potentially useful
neuroprotective strategy.
Deferoxamine, an iron chelator, has also been shown to decrease production of hydroxyl radicals, activate compensatory transcription factors and ameliorate Hb-associated neurotoxicity [7] (fig. 2). Deferoxamine may also attenuate cytotoxic edema formation through modulation of aquaporin-4 channel expression [28]. Systemic administration of deferoxamine in ICH models reduced the severity of oxidative damage and cerebral edema, and also led to improved neurological and functional outcome [55, 56]. Deferoxamine therapy in ICH patients has yielded evidence of decreased systemic oxidative stress [7]. Currently, deferoxamine is being investigated as a potential neuroprotectant for ICH patients in a phase I, multicenter, dose-finding, safety and feasibility study.

Upregulation of NF-Erythroid-2-Related Factor 2
NF-erythroid-2-related factor 2 (Nrf2) is a reduction-oxidation-sensitive transcription factor that is activated by oxidative stress [57]. Nrf2 is thought to attenuate Hb- and free radical species-mediated toxicity by inducing antioxidant genes, including Hp [43, 58]. Neurons from Nrf2-knockout mice are more vulnerable to oxidative stress than those of control animals, and transfection of Nrf2 restores reactive oxygen intermediate (ROI) resistance [59]. Furthermore, the knockout mice exhibit more perihematomal cellular DNA damage, apoptosis and neurological deficits as compared to controls after experimental ICH [60]. When Nrf2 was upregulated through the use of the upstream inducer sulforaphane in rats, there was a reduction in neutrophil migration, increase in ROI-detoxifying enzyme levels, and decrease in inflammation and oxidative damage after ICH [61].

Inflammatory Pathways
Cyclo-Oxygenase Inhibition
Cyclo-oxygenase (COX) is a key enzyme involved in the formation of prostanoids through the arachidonic acid pathway [62, 63]. There are 3 isoforms, with COX-2 being the predominant isoform within the central nervous system, present in astrocytes, neurons and microglia [63]. COX-2 is highly inducible [64] and contributes to neuronal death in inflammatory settings [65]. In the setting of ICH, COX upregulates the production of prostaglandins, prostacyclins and thromboxane, which in turn exacerbate the ongoing inflammation at the site of hematoma and the PHZ [66]. Studies have shown that celecoxib, a selective COX-2 inhibitor, reduces inflammation and brain edema in a dose-dependent manner in rats subjected to ICH [67]. Furthermore, celecoxib in conjunction with memantine, a noncompetitive NMDA re-
ceptor antagonist, worked synergistically to improve functional recovery in a rat ICH model (fig. 3) [16].

Targeting Matrix Metalloproteinases
MMPs are a family of zinc-dependent endopeptidases that play a critical role in the degradation and remodeling of extracellular matrix components [68]. These tightly regulated enzymes are implicated in an array of cellular functions and are involved in the inflammatory processes in various disease states [68, 69]. Marked upregulation of MMPs is seen after ICH as a result of their activation by hematoma-derived products, such as plasma, thrombin and ROIs [68]. Thrombin and MMP-9, in particular, exacerbate neurotoxicity and death in human fetal neurons and mice by causing detachment of cellular integrin from the extracellular matrix [70]. GM-6001-mediated inhibition of MMP-9 led to reduction in neutrophil infiltration, oxidative stress, neurodegeneration and brain edema in a murine ICH model [20]. Furthermore, the free radical scavenger edaravone was able to reduce ROI-induced MMP upregulation, and the anti-inflammatory heat shock protein 70 inducer eranylgeranylacetone significantly lowered the MMP-9 expression levels and brain edema in rodent ICH models [71]. Furthermore, the tetracycline antibiotic minocycline also decreases the MMP-2 and -9 levels, reduces MMP-induced microvascular permeability shifts, BBB breakdown, inflammatory cell infiltration and iron-mediated neurotoxicity in cell cultures [72].

Inhibition of Inflammatory Cell Activation
Endogenous microglia become activated after ischemic conditions such as ICH and produce molecules such as interleukin-1β and tumor necrosis factor (TNF)-α that further inflammation in the hematoma site and the PHZ [73]. Tuftsin, a microglial inhibitor, reduces inflammatory cytokine release and attenuates brain edema [74]. Minocycline can also inhibit the microglia and modulate their activity in the setting of ICH [21].

Neutrophils are also involved in ICH-induced inflammatory injuries to the brain [75]. Inflammatory adhesion molecules become upregulated after ICH and lead to increased neutrophil infiltration into the site of hemorrhage and the PHZ [30]. CD18 on neutrophils allows interaction with the endothelium for extravasation, and its deletion results in reduction in cerebral edema after experimental ICH [76]. Selective adenosine A2A receptor agonist, CGS 21680, which activates neutrophilic A2A receptors and blocks leukocytic adherence to the endothelium, also reduces neutrophil degranulation and ROI release [77, 78].

TNF-α Modulation
TNF-α is a proinflammatory cytokine that is strongly implicated in the pathophysiology of ICH-induced brain injury. TNF-α may cause secondary cerebral injuries through interference with astrocyte removal of extracellular glutamate, exacerbation of excitotoxicity, activation of microglia and induction of NFκB-driven production of inflammatory cytokines and ROIs [79]. Studies have
also shown that the TNF-α levels directly correlate with the extent of brain damage following ICH [80].

Adenosine receptor agonists are potent inhibitors of TNF-α production, and adenosine A2A receptor agonist CGS 21680 decreases TNF-α production and neutrophil infiltration after experimental ICH [78]. Due to its short half-life and quick desensitization, other upstream targets are currently being explored [78]. One example is estrogen, which significantly increases A2A receptor expression [81]. Another agent, ORF4-PE, is a TNF-α-specific antisense oligodeoxynucleotide, and its intracerebral administration after ICH led to decrease in cell death and neurobehavioral deficits [82].

AT1 Receptor Blockade

Angiotensin II, a potent vasoconstrictor hormone, has been implicated in inflammatory responses in neurologic conditions [83]. Angiotensin II also is involved in regulating nitric oxide synthase (NOS), and particularly endothelial NOS (eNOS), whose vasodilatory effect is important for preserving the cerebral blood flow and protecting against neuronal oxidative stress and excitotoxicity after ICH [84–86].

Potent angiotensin II receptor subtype AT1 blocker, telmisartan, has been shown to decrease inflammatory cell infiltration and edema volume after ICH induced in rats [87]. Additionally, it decreases the levels of inflammatory and proapoptotic molecules, including TNF-α, Fas and FasL, upregulates eNOS expression, and decreases hemorrhage volume, edema, neutrophil infiltration and cellular apoptosis [87]. Telmisartan is also thought to function as a partial agonist of peroxisome proliferator-activated receptor γ, which is critical for neutralizing free radical species and inhibiting the inflammatory cascade through decreased expression of the transcription factor, NFκB [88, 89]. Due to their ability to target multiple pathways, telmisartan and other angiotensin II receptor subtype AT1 blockers may become particularly useful ICH neuroprotectants.

Proapoptotic Pathways

Valproic Acid

The anticonvulsant drug valproic acid (VPA) has recently become a focus of investigation as a neuroprotectant in ICH. VPA is thought to induce the extracellular signal-regulated kinase/cAMP response element-binding protein pathway to increase the expression of the antiapoptotic gene, bcl-2, after ICH [91]. VPA also increases the expression of heat shock protein 70 [92], which, as aforementioned, downregulates MMP-9, FasL and other proinflammatory cytokines and confers antiapoptotic effects through the inhibition of caspase-3 activation [93]. Studies have demonstrated that VPA protects rat cortical neurons from glutamate-induced excitotoxicity [94] and increases the longevity of cultured cortical neurons. Furthermore, VPA has been shown to significantly limit hematoma expansion, reduce post-ICH upregulation in MMP-9 levels, and increase bcl-2 expression after experimental ICH (fig. 4) [95].

Inhibition of c-Jun N-Terminal Kinase

c-Jun N-terminal kinase (JNK) is a potent stress-activated kinase that mediates apoptosis in the setting of neurological insult [96, 97]. It is thought that JNK is activated in neurons and microglia after ICH through the induction of stress receptors, such as apoptosis signaling kinase 1 and FasL receptors. Intravenous administration of XG-102, a selective inhibitor of JNK, into mice 3 h after ICH induction was associated with significant decrease in both edema and hematoma volume. In addition, XG-102-treated animals had an improved neurological outcome 24 h after ictus [97]. XG-102 is also a mediator of inflammation and has been implicated in microglial activation and TNF-α upregulation [98]. Therefore, XG-102 and
other JNK inhibitors may be useful neuroprotectants able to ameliorate both apoptosis and inflammation following ICH.

N-Methyl D-Aspartate/α-Amino-3-Hydroxy-5-Methyl-4-Isoxazole-Propionate Antagonism

The amino acid glutamate is the most predominant excitatory neurotransmitter in the central nervous system, but causes cellular dysfunction and apoptosis when pathologically released in large quantities [99]. Following ICH, glutamate accumulates at the site of injury and binds to the N-methyl D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate receptors, leading to massive elevation of intracellular calcium and decrease in intracellular adenosine-5’-triphosphate levels [100]. Glucose hypermetabolism also occurs, ultimately leading to the production of oxidative byproducts [101]. Toxicity is thought to be initiated by the thrombin-mediated protease activated receptor-induced phosphorylation of the Src protein [102]. Src proteins enhance glutamate release from synaptic vesicles and potentiate NMDA receptors, thereby enhancing the neurotoxic calcium influx and free radical generation [103]. Targeting this pathway through molecular blockade has been shown to attenuate many of the aforementioned apoptotic and inflammatory effects. For instance, the Src kinase inhibitor, PP1, decreases pathologic glucose hypermetabolism and cell death after ICH [11]. The NMDA antagonist memantine also reduces hematoma expansion, and administration of its functional analog, MK801, has demonstrated a reduction in neurotoxicity, calcium overload and cerebral edema in porcine ICH models [104–106].

Surfactant Poloxamer 188

Surfactant poloxamer 188 is a novel neuroprotective approach in ICH. The compound is thought to facilitate membrane repair of damaged neurons, thereby leading to restoration of intracellular compartmentalization and preservation and recovery of cellular functions [107, 108]. Poloxamer 188 protects cells against excitotoxic injury, possibly by intercalating into neuronal membranes and decreasing the rates of electrophysiological change after insult [107]. It also acts as an anti-inflammatory agent [109], decreasing macrophage infiltration and lipid peroxidation, as well as hematoma volume [13].

Erythropoietin

Erythropoietin (EPO) is a glycoprotein hormone that normally induces the differentiation of hematopoietic stem cells into erythrocytes via the BBB through abundant specific capillary receptors [110]. Evidence suggests that EPO is also an important modulator of various molecular cascades critical to cell functioning, survival and vascular responses, such as the STAT-3 and eNOS pathways, and it may prevent glutamate excitotoxicity, apoptosis and inflammation [110–113]. Recent work has suggested that EPO and its long-lasting analog, darbepoetin α, bind the EPO receptor to exert neuroprotective and antiapoptotic effects through JAK-2- and Akt-dependent mechanisms [114].

Discussion

Neuroprotection constitutes a novel category of ICH therapy with sound biological rationale and significant potential for improving outcomes. Ongoing investigation continues to identify more effective therapeutic targets as well as optimal timing and methods for intervention. Nevertheless, ICH neuroprotection is an emerging field and there remain a number of challenges as it progresses towards becoming an effective treatment option in clinical settings.

Firstly, the development of neuroprotective strategies has been limited by incomplete understanding of ICH pathophysiology and mechanisms of secondary cerebral injuries. Although studies have implicated alterations in various molecular pathways and genetic expression patterns, the exact mechanisms of ICH-induced injuries and their association with outcome are incompletely understood [31, 115]. For instance, the clinical significance of cerebral edema remains controversial. Rodent studies have suggested an association between reduced edema volume and improved functional outcome [55, 116, 117]. However, significant functional recovery can be achieved in the absence of edema reduction, suggesting that absolute edema volume does not independently predict outcome [118]. Furthermore, relative edema volume (edema volume/hematoma volume) has been shown to independently predict improved functional recovery following hyperacute spontaneous ICH (within 3 h after onset) without intraventricular extension; this suggests that hyperacute (within 24 h after onset) and delayed edemas are distinct entities associated with different pathophysiology and outcome [17]. The current controversy underscores the need to better understand the mechanisms of edema formation as a dynamic process that is significantly affected by many factors, such as the etiology of ICH and time since onset [17, 119, 120]. Efforts should be
made to elucidate the relationship between hyperacute and delayed edemas and the timing of edema volume measurement should be carefully noted when interpreting experimental results. In addition, it should be recognized that edema volume may be insufficient as a sole outcome measure to demonstrate potential clinical efficacy and it is becoming increasingly critical for neuroprotectants to show evidence for enhanced functional/neurological outcome in addition to other outcome measures. Deferoxamine, celecoxib/memantine, ORF4-PE and XG-102 are such agents that are promising candidates for further investigation and initial efforts towards clinical translation.

Other aspects of ICH pathophysiology that require further investigation include the contribution of ischemia to edema formation and interactions among cerebral edema, perihematomal hypometabolic-hypoperfusion and cell death [38]. The mechanisms behind neuronal injuries leading to worse neurological outcome also need to be further defined. Timing of key molecular events and temporal alterations in their expression are still being worked out as well. Continued advances in the understanding of ICH will improve the therapeutic efficacies of neuroprotectants through more specific targeting and modulation of pathways of interest, coupled with optimal timing and degree of intervention.

Secondly, ICH-induced brain injuries result from complex interconnected molecular pathways, which further the need for neuroprotective strategies capable of attenuating multiple targets. This approach will better account for the heterogeneity of ICH pathophysiology and maximize the therapeutic benefits. Neuroprotectants such as XG-102 and sulforaphane are examples of agents that are capable of affecting different molecular pathologic pathways. Combination of neuroprotective agents may also allow synergistic effects on outcome, as demonstrated by the dual administration of celecoxib and memantine. Agents that confer protection on multiple cell types would also be useful as mounting evidence indicates that neuronal recovery and survival after ICH are strongly dependent on the status of surrounding non-neuronal cells [33]. Of note, many pathologic molecular pathways triggered after ICH may have beneficial roles at different time points during the clinical course. Examples include the hemostatic and neuroprotective properties of thrombin [37, 121] and the involvement of complement in hematoma absorption, cellular debris clearance and postictal neurogenesis [5, 35]. Therefore, multitargeting agents and combination therapies should allow careful modulation of individual targets.

Thirdly, a majority of ICH neuroprotectants currently under investigation remain experimental and have yet to be tested in a clinical setting [4, 6]. Furthermore, few clinical trials have been attempted to date, and none have been appropriately powered to detect significant clinical benefit. The bench-to-bedside translation of ICH neuroprotective strategies has been challenging largely due to the inherent differences between experimental and clinical ICHs [122]. Although animal models are highly useful for characterizing ICH-associated injuries and underlying mechanisms, they are ultimately insufficient and/or inaccurate representations of human ICH [4]. The rodent intrastriatal autologous blood injection model [123] is widely used but has been limited by its inability to reproduce spontaneous or ongoing bleeding [122]. The bacterial collagenase injection model [124], which is another commonly used method, has been associated with heightened collagenase-induced inflammatory response and neurotoxicity [122]. The 2 models may also differ with regard to their reproducibility, location and degree of structural injury, characteristics of neurological impairment and recovery, and optimal neurological assessment method [122]. Moreover, both methods involve anesthesia and invasive anatomical access, which may alter the molecular environment and treatment response in an uncontrolled manner [4, 8]. In the absence of a model that perfectly mimics human ICH, rigorous, comprehensive and long-term assessment of outcome should proceed with the best available ICH models. Furthermore, cautious interpretation of the existing data, thorough understanding of each model’s strengths and limitations, and insight into the precise differences between experimental and human ICHs will be critical to successful clinical trials.

A number of well-designed trials have recently begun, including the Dose Finding and Safety Study of Deferoxamine in Patients with Brain Hemorrhage, Administration of Celecoxib for Treatment of Intracerebral Hemorrhage, Safety of Pioglitazone for Hematoma Resolution in Intracerebral Hemorrhage and Intravenous Tauroursodeoxycholic Acid trials. Many of these trials have incorporated lessons learned from the previous neuroprotection trials in ischemic stroke and represent an important progress in ICH neuroprotection research. Ongoing efforts towards meticulous consideration of trial design, outcome measures, optimal timing of intervention and heterogeneity among study subjects will significantly expedite the much-anticipated clinical translation of ICH neuroprotection.
Conclusion

As neuroprotective strategies move from bench to bedside, they hold the potential to become an important treatment option for ICH. Increasing insight into the pathophysiology of ICH-induced cerebral injuries will continue to aid the development and refinement of neuroprotective strategies. Furthermore, improved understanding and application of experimental models will enhance the clinical translation of results and contribute to successful randomized clinical trials. In the future, neuroprotection will likely contribute to multimodality managements, along with intensive care and surgical treatments, to optimize the extent of clot removal, increase neuronal survival and improve clinical outcomes after ICH.

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