Mechanism and Therapy of Brain Edema after Intracerebral Hemorrhage

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Key Words

Brain edema · Hematoma · Intracerebral hemorrhage · Inflammation

Abstract

Background: Intracerebral hemorrhage (ICH) is a subtype of stroke with a severe high mortality and disability rate and accounts for about 10–15% of all strokes. The oppression and destruction by hematoma to brain tissue cause the primary brain injury. The inflammation and coagulation response after ICH would accelerate the formation of brain edema around hematoma, resulting in a more severe and durable injury. Currently, treatments for ICH are focusing on the primary injury including reducing intracranial hypertension, blood pressure control, and rehabilitation. There is a short-of-effective medical treatment for secondary inflammation and reducing brain edema in ICH patients. So, it is very important to study on the relationship between brain edema and ICH. **Summary:** Many molecular and cellular mechanisms contribute to the formation and progress of brain edema after ICH; inhibition of brain edema provides favorable outcome of ICH. **Key Messages:** This review mainly discusses the pathology and mechanism of brain edema, the effects of brain edema on ICH, and the methods of treating brain edema after ICH.

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Introduction

Intracerebral hemorrhage (ICH) accounts for about 10–15% of all strokes with high mortality [1], 1-month mortality of ICH is approximate 40% and it increases with age [2]. In the last 2 decades, the high mortality and morbidity of ICH does not decrease over time. In the first few hours after ICH onset, primary brain injury by ICH is mainly caused by the oppression and destruction to the near tissue by hematoma formation. And hematoma could also increase the intracranial pressure; it can even induce brain herniation. The inflammation, thrombin activation, and erythrocyte lysis caused by primary injury could promote the formation of brain edema, which is associated with poor outcome, and could cause more severe and durable injury [3]. Brain edema is a pathological phenomenon that water and brain tissue volume increase. Brain edema after ICH can be divided into perihematomal edema (PHE) and intrahematomal edema. Most patients could survive the initial injury of smaller hemorrhage, but the secondary injury may result in severe neurological deficits and even death [4]. The mechanism of brain edema is complicated; vasogenic factors, thrombin formation, erythrocyte lysis and hemoglobin (Hb) toxicity [5] have been proved to be related to brain edema growth [6]. Currently, therapy for ICH focuses on the primary injury and preventing bleeding again, including de-

hydration and hemostasis. But, all these treatments fail to provide a promising functional outcome or decrease mortality. In recent years, many studies focus on the mechanism of secondary inflammation that can cause brain edema and this may provide new therapy targets for ICH [7]. Animal experiments demonstrated that fingolimod could reduce edema, cell apoptosis and cerebra atrophy and show neuroprotective function in ICH rats [8]. A similar result was observed in a clinical study [9]. Likewise, dexamethasone can reduce cerebral cell apoptosis and inhibit inflammation [10], and deferoxamine (DFX) provides new therapy target [11]. But before these immunomodulators or other anti-inflammatory agents are used clinically, more experiments are needed.

Mechanism of Edema

Brain edema increases in the first 24 h progressively and increases rapidly 3 days after onset, reaches its initial peak at the 4th or the 5th day and remains elevated slowly until 9–14 days and then decreases [12]. PHE develops in response to clot retraction and hydrostatic pressure change [13], mass effect, thrombin formation, erythrocyte lysis, Hb toxicity, complement activation, plasma proteins leakage and blood-brain barrier (BBB) disruption [5]. All of inflammation, thrombin activation and red blood cell (RBC) lysis production contribute to BBB disruption resulting in edema formation, and it can be diversified into 3 phases: (1) clot retraction could force the serum into the perihematomal space to form vasogenic edema (1 h after ICH; fig. 1), (2) inflammation (fig. 2) and thrombin activation (fig. 3)–related cytotoxic brain edema through clotting cascade (peaking at 1–2 days), and (3) erythrocyte lysis and Hb toxicity-related injury (delayed edema formation at about day 3; fig. 4) [14]. Both elevated oncotic pressure of perihematoma space due to the infiltration of blood components from hematoma and BBB disruption caused by inflammation, thrombin cascade and erythrocyte lysis products can aggravate vasogenic edema. However, oxidative stress induced by vasogenic edema, and release of cytotoxic substance could induce cytotoxic edema. So, vasogenic edema and cytotoxic edema interact with each other and lead to a vicious circle. Intrahematomal edema is mainly caused by tension hematoma. Tension hematoma is related to the formation of capsule-like granulation tissue during the absorption of a hematoma. The capsule-like granulation can limit the absorption of liquified hematoma and cytotoxic substance. Subsequently, the oncotic pressure in-

Fig. 1. Mechanism of vasogenic edema.

side the hematoma increases and the infiltration of perihematoma water and plasma increases the tension inside the capsule progressively. Additionally, blood may leak repeatedly from the abundant capillaries contained in the granulation tissue resulting in hematoma enlarging [15].

Vasogenic Factors

Numerous studies show that during the early stage of ICH, vasogenic factors can cause edema. Vasogenic factors mainly include clot formation and contraction [16], decrease in hydrostatic pressure around hematoma space [17] and extravasation of plasma proteins [13]. MRI done 2 h after onset of ICH shows edema in the area surrounding the hematoma [18].

Through MRI perfusion, weighted imaging and diffusion-weighted imaging, some experts found that water diffusion in the perihematoma edema increases significantly and is related to brain water volume independently, and they think that most of the brain water comes from plasma [19]. Injecting autologous blood (control group) or heparinized autologous blood (heparinized group) into brain parenchyma of pigs showed that edema increases significantly 1 h after ICH and lasts longer in the control group, while the heparinized group showed no obvious edema. Meanwhile, they also experimented on rats by injecting thrombin or heparinized thrombin into cerebral parenchyma; the results of these experiments

Fig. 2. Mechanism of inflammation induces edema.

demonstrated that the heparinized group showed significantly less edema. So, they concluded that the formation and existence of clot was important for the formation and progress of brain edema [16]. Compared with spontaneous ICHs (SICHs), thrombolysis-related ICHs have both lower absolute and relative edema observed in clinical test, indicating that intrahematoma blood clotting is a reasonable factor for the formation of hyperacute PHE [20]. Animal experiment showed that plasma proteins can be detected in the tissue around hematoma after 1 h of ICH when BBB is not destructed, and so the leakage of plasma proteins and related edema is not associated with BBB destruction in the hyperacute stage of ICH [13]. Clot contraction can decrease the perihematoma hydrostatic pressure; then it forces the plasma components into perihematoma space, which leads to an increase in perihematoma oncotic pressure close to the plasma level and water infiltration into the perihematoma space from blood followed [16, 21]. Furthermore, destruction by hematoma can induce a low metabolism of the perihematoma tissue, cell death and brain atrophy, which results in the enlargement of perihematoma space and decrease in

hydrostatic pressure. Plasma can also induce oxidative stress and release of inflammatory mediators, which will promote the secondary brain injury besides vasogenic edema [22].

Inflammation

To clarify the cause of edema, Gong et al. [23] conducted an immunocytochemistry experiment on rats. It demonstrated that inflammatory response took place in and around the hematoma after ICH with the infiltration of neutrophils and macrophages and activation of microglia. Inflammation can cause cell swelling and BBB disruption, and then causes brain edema. Activated microglia and infiltrating leukocytes release cytotoxic mediators contributing to secondary injury. Clinical studies have proved that RBCs infiltrate into cerebral immediately, along with leukocyte from peripheral blood, macrophages and plasma proteins [24], and animal experiments had shown that CD4⁺ T lymphocytes were the main cause of brain leukocyte infiltration [25]. But within 12 h after onset of ICH, inflammatory macrophages and dendritic cells comprise a majority of infiltrating leu-

Fig. 3. Mechanism of thrombin induces edema.

kocytes [26]. Neutrophils or polymorphonuclear leukocytes (PMNs) are the first leukocytes to infiltrate the nervous system within 4–5 h after ICH, and reach a peak value at 3 days [27]. PMNs may cause direct neurotoxicity to ICH brain by release matrix metalloproteinases (MMPs), reactive oxygen species (ROS), and tumor necrosis factor- α (TNF- α) or other cytokines. Animal experiments demonstrated that PMNs can induce inflammation, but resting neutrophils could reduce the permeability of BBB and activated neutrophils showed a neutral effect [28]. So, neutrophils-induced inflammation depends on MMPs, ROS and cytokines instead of reducing permeability of BBB. Leukocytes exist only for about 2 days after infiltrating into hemorrhagic brain, but it can cause further damages by stimulating microglia and macrophages [14]. Microglia activation can also be mediated by CD36 in erythrocyte [29], thrombin [30], and by heme via toll-like receptor 4 (TLR4) signaling pathways [31]. Activated microglia/macrophages appear in and around the injury tissue as early as 1 h after ICH [32]. The primary role for resident microglia cell activation is to clear the hematoma, but excessive microglial activation

can express and release diverse toxic factors, which contribute to secondary injury, such as cytokines (interleukin (IL)-1 β and others), chemokines, proteases, ROS, prostaglandins, cyclooxygenase-II and heme oxygenase (HO) [30, 33]. TLRs are molecules that play a critical role in the induction of innate and adaptive immunity, and TLR4 is expressed in microglia and some neurons 6 h through 7 days after ICH [34]. Activated TLR4 can mediate microglial autophagy and activation [35], and induce the dissociation of kappa-B (κ B) with nuclear factor- κ B (NF- κ B); then NF- κ B activates and regulates the transcription of genes related to inflammation after it translates into the nucleus. Animal experiments showed that neutrophil, monocyte, inflammatory monocyte and microglia increased significantly in the perihematomal brain compared to TLR4-deficient mice, and the leukocytes infiltrated from the peripheral blood [36]. Microglia reaches a peak at 72 h, begin to decrease by a week and return to basal levels by 21 days after ICH. Astrocytes can also express MMPs together with activated microglia, and controlling microglia–astrocyte interactions may be a potential way to minimize ICH-induced injury [7]. So, the ear-

Fig. 4. Mechanism of RBC lysis production induces edema.

ly stage of the inflammatory response and brain edema after ICH is caused by microglia activation, infiltration of inflammatory cells including leukocytes and macrophages, and accumulation of proinflammatory mediators released from these cells.

Thrombin

The coagulation cascade is activated as soon as blood flows into the brain tissue, and thrombin is an essential component of the coagulation cascade [4, 5]. Thrombin induces disruption of BBB function and parenchymal cell death, and both of BBB disruption and cell toxicity by thrombin can trigger the formation of brain edema after ICH [37]. Thrombin induces endothelial cell contraction and the opening of intercellular tight junctions by activating protease-activated receptors (PARs), which are thrombin receptors [38]. MMPs protein is a zinc-containing extracellular-matrix degrading protease and they can degrade the entire extracellular matrix after being activated. MMP-9 can be an important biomarker of complications and for selecting patients for trials investigating hemicraniectomy in ICH [39]. MMP-2 protein can

degrade substrates including collagens IV, V, VII, and X, gelatin, laminin, and fibronectin, most of which are components of capillary basal membranes. So MMP-2 activation leads to basal membrane degradation that is a vital part of BBB. And thrombin can trigger MMP-2 expression and membrane degradation by activating PARs [38]. Thrombin also activates the phosphorylation of Src kinase (a proto-oncogene protein family with tyrosine protein kinase activity), which leads to the injury of brain microvascular endothelial cell (BMVEC) and peri-vascular astrocyte, resulting in the disruption of BBB and formation of edema through its PARs [40, 41]. However, Src kinase proto-oncogene members can stimulate the proliferation of newborn BMVECs and peri-vascular astrocytes after 2–6 days; it then promotes the resolution of edema and the recovery of BBB permeability. Thrombin also releases nitric oxide, TNF- α , IL-12, and IL-6, and thrombin-induced brain injury is partly mediated by complement [42]. Activation of microglia and mitogen-activated protein (MAP) kinases also play an important role in causing thrombin-induced neurological injury after ICH [43].

RBC Lysis Production

RBCs lysis occurs within 24 h of ICH and induces the release of Hb and heme, which are taken up by microglia and neurons [14]; heme can be degraded by HO into biliverdin, carbon monoxide and iron. All of Hb, heme and iron causes significant brain edema after the first 24 h, which is related to a threefold increase of BBB permeability [44]. Animal experiments showed that intracerebral injection of packed RBCs does not produce significant edema on the first day but does at 3 days; so RBCs can cause delayed brain edema, which results from cellular lysis and BBB disruption by RBCs [44, 45]. Brain iron is an erythrocyte degradation product; iron deposition is found in the perihematoma brain tissue during the 1st day after ICH, peaking after 7 days and remaining at a high level for at least 2 weeks, and perihematoma water content increases progressively over course of time [46]. Aquaporin-4 (AQP4) is involved in brain volume homeostasis and water balance; AQP4 is localized in perihematoma region at 6 h post-ICH and AQP4 mRNA and AQP4 protein are increased post-ICH [47]. So, edema post-ICH is closely connected with AQP4. Upregulation of AQP4 around hematoma brain is observed and reached a peak at 3–7 days, and animal experiments showed that the changes of brain water content are accompanied by an alteration of AQP4, and this expression is affected by iron concentration [46]. Clinical study demonstrates that iron overload is associated with the progress of PHE indicating a poor outcome and high in-hospital mortality [6]. And heme can promote microglial activation through TLR4; this in turn will induce NF- κ B activation through the myeloid differentiation primary response gene 88 (MyD88) or toll/IR-1 domain-containing adaptor protein-inducing interferon-beta (TRIF) signaling pathway, and finally increase cytokine expression and inflammatory injury in ICH [31]. Hb can trigger inflammation after ICH through the assembly of TLR2/TLR4 heterodimers, and MyD88 is required for ICH-induced TLR2/TLR4 heterodimerization [48].

In addition to all the discussion mentioned earlier, arginine vasopressin (AVP) receptors, glutamate and endothelin-1 (ET-1) may also be involved in the formation of brain edema. Experiments showed that AVP can induce the formation of brain edema by effects on astrocytes after ischemic stroke and the induction can be decreased by AVP receptors antagonist [49, 50]. And, animal tests have found that AVP receptors antagonist SR49059 significantly decreases cerebral edema at 24 and 72 h post-ICH injury and improved neurobehavioral deficits at 72 h [51]. So, AVP receptors may play an important role in the

formation of edema after ICH through reduced BBB permeability or AQP4 levels, but the details of the mechanism are still unknown [52]. An in vivo microdialysis study shows that glutamate, taurine and asparagines accumulate transiently in extracellular fluids in the perihematoma region during the early period of ICH. These amino acids may play an important role in the pathology of ICH, but the intricacies of the mechanism are not very clear [53]. A recent study shows that blood glutamate grabbing cannot reduce the hematoma nor improve the neurologic deficit in ICH but is a safe excitotoxic treatment modality [54]. Animal experiments demonstrated that ET-1 expression increased significantly at 6, 12, 18, and 24 h after ICH, and they observed a positive correlation between the number of ET-1-positive endothelial cells and BBB permeability [55]. New findings show that ET-1 can lead to an increase in gene expression, including genes associated with the inflammatory response, oxidative stress, heme metabolism and iron homeostasis [56]. So, ET-1 may be related with BBB disruption and it plays an important role in causing the secondary injury after ICH.

Effects of Edema

Studies have shown that brain edema is significantly associated with hematoma enlargement and increased midline shift, which lead to poorer functional outcome of ICH [4]. Mass effect can contribute to the formation of PHE [5]; it can also be a result of PHE [57]. Clinical observation shows that mass effect progresses within 2 days after ICH due to hematoma enlargement, and progresses again during the second and third weeks because of increased brain edema [57]. So, we can see that the interaction between mass effect and edema may lead to an unfavorable outcome. PHE may be a risk factor of acute progressing hemorrhagic stroke, and delayed PHE may contribute to subacute progression of hemorrhagic stroke, both these 2 types of stroke have worse clinical outcome than the nonprogressing types of hemorrhagic stroke [15]. Multivariable logistic regression analysis shows that absolute edema volume is not related to function outcome nor mortality, but relative edema volume (absolute edema volume/hematoma volume) during the first 24 h after ICH is an independent predictor of favorable 12-week functional outcome in hyperacute SICH without intraventricular extension [58]. Similarly, in a prospective cohort study, the relative edema is proved to be associated with an improved outcome at 12 weeks but

Fig. 5. Treatments of brain edema after ICH.

is not related to mortality in supratentorial SICH without intraventricular extension [59]. And results demonstrate that hematoma volume is the strongest independent predictor of a poorer prognosis of supratentorial SICH. It seems that absolute edema volume is not related to the outcome significantly, but it can contribute to hematoma expansion, which in turn independently predicts mortality. They excluded infratentorial SICH and those with intraventricular extension, as these 2 factors have been found to be associated with poor prognosis [58, 59].

Treatments of Brain Edema after ICH

Currently, treatments for ICH mainly focus on the primary injury and on preventing bleeding again; focus is also directed toward primary supportive treatment, including dehydration, hemostasis, blood pressure and intracranial pressure monitoring, and so on. All these therapies fail to provide a promising favorable outcome or

decrease mortality of ICH. Recently, some experiments reviewed secondary inflammation, which contributes to brain edema and the results of these experiments may provide new ways of treatment for ICH [7]. Medical treatments of treatment on brain edema post-ICH include inhibition of inflammation, thrombin activation and Hb degradation products-mediated toxicity [60], traditional dehydration and so on (fig. 5). A clinical study shows that blood pressure reduction (systolic blood reduction goals are 170–199, 140–169 and 110–139 mm Hg, respectively) can reduce hematoma expansion and brain edema ratio after ICH with no significance between every group [61]. However, some large clinical studies show that intensive and continuous blood pressure reduction in the acute phase of ICH can improve functional outcomes by decreasing the hematoma expansion rate, and blood pressure should be controlled to be under 140/90 mm Hg in the first hour after onset or within 24 h [62–64]. And these new therapeutic strategies focusing on multiple inflammatory pathways seem to be more effective than those focusing on single pathways [65]. Besides these new

therapies, another effective way is surgical treatment to remove hematoma, which will reduce mass effect and hematoma-induced injury [60].

Traditional Dehydration Therapy

Dehydration is often used to decrease intracranial pressure during the acute phase of ICH, and hypertonic dehydration of somotherapy is the most common treatment. Usual osmotherapy medicines are mannitol, glycerin fructose and albumin, other dehydrants include furosemide, glucocorticoid, acetazolamide and so on, and mannitol is the most widely used dehydrant. We should choose and use dehydrants on the basis of the brain edema type and evaluation of BBB integrity, as brain edema mechanism differs from each other.

Animal experiments found that after an injection of mannitol through the internal carotid artery, BBB disruption was observed and BBB permeability increased by 4–5 times at 5 min and then reversed within minutes, the mechanism may be that mannitol can induce the shrinkage of cerebrovascular endothelial cells and vasodilatation [66, 67]. Hence, the use of mannitol may lead to the opening of BBB and aggravate brain edema before BBB is disrupted (within 6 h after ICH generally). Pharmacokinetics study on mannitol for treatment of vasogenic edema shows that about 84% of the infused mannitol is excreted through urine. But mannitol accumulation is detected in the cerebral tissue after multiple injections, even exceeding the mannitol concentration in the plasma; this experiment observed a reversal of the osmotic concentration gradient between plasma and edematous brain, which can aggravate vasogenic brain edema. This study demonstrates that a single dose of mannitol is unable to reduce brain water content in edematous brain tissue or edema progression after 4 h of injection, but multiple doses can increase brain water content in edematous tissue [68]. Mannitol accumulates in the injured brain tissue, which would increase osmotic pressure; then water in perihematoma flows into the hematoma; this results in hematoma expansion even midline shift. Mannitol should be used while being closely monitored for plasma osmotic pressure; mannitol is not suitable to use when plasma osmotic pressure is >320 mOsm because high plasma osmotic pressure leads to dehydration, but mannitol can increase osmotic pressure of hematoma and reverse the osmotic pressure gradient [69]. Meantime, the early use of mannitol can shrink the normal brain and increase the pressure gradient between hematoma and normal brain. So, for those ICH patients who are still bleeding, early use of mannitol may lead to ICH progress [69]. A random-

ized controlled study on 128 supratentorial ICH patients shows that mannitol (20%, 100 ml every 4 h for 5 days, tapered in the next 2 days) failed to improve the outcome at the end of 1 month and decrease mortality significantly [70]. Systematic reviews show similar results that there is not enough evidence to support the routine use of mannitol in acute ICH patients without increased intracranial pressure, but intracranial pressure should be monitored closely [71]. When there exist clinical features or image examination changes of intracranial hypertension, especially brain herniation, mannitol should be used immediately to decrease intracranial pressure. Hypertonic saline (3 or 23.4%) can also be used as a dehydrant, which has a more lasting effect than mannitol without BBB disruption [72]. But hypertonic saline use has limitations, as it can cause disorders in water and salt metabolism. Animal experiments have demonstrated that mannitol produces a dose-dependent increase in plasma osmolality and reduction of brain water content, and furosemide alone shows no effect on plasma osmotic pressure nor brain water content [73]. Combination of mannitol and furosemide has a greater effect on plasma osmolality and reduction of water content than mannitol alone in the rat ICH model [73]. Combination of furosemide and hypertonic saline has a better effect on reducing brain water content compared with hypertonic saline alone, and the combination causes no more increase of osmolality and sodium concentration than that induced by hypertonic saline alone [74]. For subacute progressing, ICH excluding rebleeding after CT, dehydrant and intracranial pressure monitoring should be applied [75].

In conclusion, dehydration is not recommended for ICH patients without intracranial hypertension. When BBB is not disrupted (within 6 h after ICH generally) or plasma osmotic pressure is >320 mOsm, mannitol especially frequent mannitol using is not suitable, hypertonic saline alone or with furosemide can be alternative options. However, if there is intracranial hypertension especially brain herniation or progressing ICH excluding rebleeding, dehydration should be used. In case the anticipated dehydration target after multiple use of mannitol is not achieved, combination with furosemide or hypertonic saline can be a substitute for adding mannitol dose, as multiple doses of mannitol can increase brain water content in edematous tissue.

Inhibition of Inflammation

Inflammation plays an important role in brain edema after ICH and it can induce cytotoxic edema through multiple ways. So, inhibition of inflammation may be

beneficial to ICH. In the early stages of ICH, inflammation is mainly caused by PMNs infiltration and microglia activation.

Inhibition of PMNs Infiltration and Microglia Activation

Neutrophil depletion by using anti-PMN can reduce BBB permeation, MMP-9 expression, perihematomal axonal injury and the astrocytic and microglia/macrophage responses and provide a better outcome of ICH [76, 77]. Similarly, MMP inhibitor (GM6001), ROS scavengers or TNF- α R neutralizing antibody can decrease the neurotoxicity caused by PMNs, and then protect neurons from injury [27].

Activation of microglia can lead to the release of diverse toxic factors (such as cytokines, proteases, ROS and so on), which contribute to secondary injury after ICH. So, inhibition of microglia activation may be beneficial to ICH. It has been proved that Minocycline, an inhibitor of microglia activation, can reduce PHE, ICH-induced brain tissue loss and improve functional outcome in ICH rats [78]. And minocycline can also ameliorate the damage after ICH by protecting BBB, decreasing TNF- α and MMPs expression, and reducing microvessel loss and extravasation of plasma proteins and the numbers of TNF- α -positive cells and neutrophils [79]. In another rat experiment, it was found that coinjection of iron and minocycline significantly reduced brain edema, BBB leakage and brain cell death caused by iron, compared with an injection of iron alone [80]. Tuftsin, another inhibitor of microglia activation, can reduce brain edema after ICH as well [81]. Tuftsin fragment 1–3, a macrophage/microglial inhibitory factor, is a neuroprotective agent for ICH treatment, as it can reduce stroke volume, edema, degenerating neurons, and neurobehavioral deficits [81]. TLR4 can mediate the autophagy of microglia; treatment of autophagy inhibitor (3-methyladenine) decreases microglial activation and inflammatory injury [35].

Immunomodulator

Edema is significantly associated with hematoma enlargement and increased midline shift, resulting in poorer functional outcome of ICH. Agents that can reduce PHE process provide protective effects for ICH. Fingolimod (FTY720), a sphingosine 1-phosphate receptors analog, is an immune-modulating drug that can prevent the migration of lymphocytes from primary and secondary lymphoid organs and may ameliorate cerebral inflammation, it can improve neurobehavior and cognitive outcomes in experiment ICH mice [82]. Fin-

golimod can also reduce brain edema, apoptosis and brain atrophy [8]. Further study shows that fingolimod decreases not only the number of perihematomal T-lymphocytes in brain but also the expressions of cytokines (interferon- γ , and IL-17) [83]. And in this animal experiment, fingolimod had functions of reducing brain edema, improving short-term sensorimotor function and long-term motor and coordination and cognitive function in rats after experimental ICH [83]. Fu et al. [9] conducted a 2-arm proof-of-concept study including 23 patients with primary supratentorial ICH with hematomal volume of 5–30 ml. These 23 patients received standard treatment alone (control group) or combined with fingolimod (0.5 mg, orally for 3 consecutive days). Results revealed that the fingolimod group has a significantly better outcome compared with that of the control group. Patients treated with fingolimod have a higher Glasgow Coma Scale score, lower National Institutes of Health Stroke Scale score, improved neurologic function and fewer ICH-related lung infections without differences in the occurrence of adverse events when compared with the control group. Dexamethasone can promote the recovery of ICH injury by inhibiting the inflammatory response and reduce brain edema because of its capacity to decrease apoptotic cell death and inhibiting the intercellular adhesion molecule-1 and MMP-9 expression [10, 84].

Inhibition of Thrombin

Thrombin inhibitor, Hirudin, can prevent the BBB disruption caused by thrombin, but it can also affect the clotting hemostatic function; it may not be an assured form of treatment [40]. Acute administration of the Src inhibitor PP2 blocks the thrombin pathway, decreases glucose hypermetabolism and cell death around ICH, and reduces brain edema that occurs after ICH without affecting coagulation [40, 41]. But delayed and chronic administration of PP2 prevents edema resolution and BBB repair because chronic Src kinase activation can promote the BBB repair after ICH. N-acetylheparin is an inhibitor of complement activation; it can attenuate the brain injury induced by thrombin, and it may be a neuroprotective agent for ICH [85]. Both argatroban or cycloheximide can prevent thrombin cytotoxicity and exhibit an obviously neuroprotective function against ICH-induced injury; MAP kinase inhibitor (PD98059) and a c-Jun N-terminal kinase inhibitor (SP600125) can also prevent ICH-induced neuron loss [43]. However, these drugs have no effect on hematoma volume or brain edema after ICH.

Inhibition of RBCs Lysis and Hb Toxicity

RBC lysis releases Hb and heme; brain iron is a heme degradation product; excess iron released is found to induce secondary brain injury [46]. DFX, an iron chelator, has been proved to be neuroprotective in nature in many ICH animal experiments. By injection of autologous blood into the pigs cerebral, Gu et al. [86] found that DFX can reduce perihematoma volume, through chelating iron directly and may be also by inhibiting oxidative stress-induced cell death. In another experiment, results showed that DFX can reduce white matter edema after ICH in piglets, decrease levels of TNF- α and receptor-interacting protein kinase 1 [87]. A rats experiment showed that DFX can penetrate BBB rapidly and reduce ICH-induced ventricle enlargement, brain edema and brain atrophy without severe side effects [88]. DFX can reduce free iron in cerebrospinal fluid as well as ICH-induced neurological deficits and acute neuronal death in rat experiment. It can also inhibit the endogenous response to ICH and the upregulation of ferritin and AQP4, which are related to a poor outcome of ICH [46, 89, 90]. Pro-oxidant heme, which is released from Hb catabolism of heme, plays an important role in the resolution of hematoma. HO controls the degradation of pro-oxidant heme and HO-2 may provide protection for ICH-induced brain injury [91]. Heme activates microglial via TLR4 signaling pathway, and TLR2 and TLR4 play an important role in the secondary injury [31, 48]. So, inhibition of TLR2 and TLR4 may be beneficial for ICH and some experiments have proved this hypothesis. An ICH mouse model demonstrates that TAK-242 (ethyl (6R)-6-(N-(2-chloro-4-fluorophenyl)sulfamoyl)cyclohex-1-ene-1-carboxylate, Takeda), which is a TLR4 antagonist, can reduce brain water content, neurological deficit scores, and levels of inflammatory factors. TAK-242 also decreases the levels of deoxyribonucleic acid (DNA) damage, neuronal degeneration and the expression of TLR4 downstream signaling molecules [92]. Specific TLR4 antibody (Mts510) and TLR4-knockout have a similar function of reducing brain edema and neurological deficits [31].

An increasing number of proinflammatory mediators and cytotoxins are released by blood components after ICH. Lysis of extravasated erythrocytes in the hematoma releases cytotoxic Hb, heme and iron, resulting in secondary injury. Phagocytic cells, brain's microglia and hematogenous macrophages can phagocytose and process extravasated erythrocytes and subsequent toxicity occurs before lysis after ICH. CD36 and catalase are proteins that can mediate phagocytosis of damaged, apoptotic, or se-

nescent cells, including RBCs. Rosiglitazone is a peroxisome proliferator-activated receptor γ (PPAR γ) agonist. It can increase PPAR γ -regulated gene (catalase and CD36) expression, but reduce proinflammatory gene (TNF- α , IL-1 β , MMP-9, and so on) expression and neuronal damage [29]. So, PPAR γ agonist can promote the resolution of hematoma and is a potential treatment of ICH.

Other Medicines

In addition to all that has been discussed earlier, there exist many other potential therapy targets for ICH. The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors or statins have pleiotropic effects, and continued statins use after ICH is associated to lower mortality within 6 months and early neurological improvement because of its anti-inflammation and neuroprotective function [93]. Depletion of GR-1-positive (GR-1(+)) cells by the administration of anti-GR-1 can reduce circulating GR-1(+) cells and astrocyte immunoreactivity and decrease brain neutrophils after ICH; it may be a neuroprotective agent [94]. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key transcriptional factor for antioxidant response element-regulated genes and it can induce and upregulate cytoprotective and antioxidant genes that attenuate tissue injury. Nrf2 is neuroprotective by reducing leukocyte infiltration, excessive free radical oxidative injury, DNA damage, and cytochrome c release during the early phase of ICH [95]. Pyrroloquinoline quinone (PQQ) has roles of antioxidant properties, cofactor of dehydrogenase, and amine oxidase is a neuroprotective agent in experimental stroke and spinal cord injury models. Animal test demonstrates that PQQ can improve the locomotor functions, reduce the hematoma volumes and alleviate the expansion of brain edema after ICH. Also, pre-treated rats with PQQ significantly reduce the production of ROS after ICH, probably due to its antioxidant effects [96]. SR49059, an AVP V(1a) receptor competitive antagonist is proved to have a function of reducing brain edema and neurobehavioral deficits after ICH by decreasing the BBB disruption and AQP4 levels [51, 52]. Animal experiments demonstrated that granulocyte-colony stimulating factor can protect ICH by reducing BBB permeation, cell apoptosis and brain edema [97]. Erythropoietin can protect BBB and decrease BBB disruption and brain edema post-ICH [98].

Surgical Treatment

Due to lack of optimal treatment of ICH, clinicians have devoted to the hematoma clearance especially for patients with hematoma volume that is >30 ml or more,

by surgical intervention or thrombolytic evacuation. The operation forms include craniotomy, decompressive craniectomy, stereotactic or transcatheter aspiration, laparoscopic aspiration and so on.

Early Clot Removal

A clinical study demonstrated that hematoma removal by surgery can significantly reduce the volume of the mass including brain edema and hematoma in putaminal hemorrhage patients as compared to the conservative group [99]. Another set of clinical data showed that surgical treatment of hypertensive putaminal hematoma with 30 ml or more decreases mortality and provides better outcome compared with the non-operation group [100]. Burr hole craniectomy of hypertensive basal ganglia hemorrhage can decrease brain edema grades and reduce secondary injury by coagulation end products-activated inflammatory cascade [101]. And the experiment showed that gross-total removal of hematoma group has a better outcome than the sub-total removal of the hematoma group; this indicates that residue hematoma can still promote secondary injury and may result in a comparatively worse result [101]. However, a parallel-group trial about surgical trial in ICH (STICH) found that early surgery (within 24 h after onset) has no overall benefit compared with initial conservative treatment for spontaneous supratentorial ICH patients [102]. Meta-analysis showed that early surgery before the patients deteriorate would improve ICH outcome for spontaneous supratentorial ICH patients without intraventricular hemorrhage meeting the conditions: undertaken within 8 h of ictus, the volume of the hematoma was 20–50 ml, the Glasgow Coma Score was between 9 and 12, or the patient was aged between 50 and 69 [103]. And large clinical randomised trial (STICH II) also showed that early surgery (within 12 h after onset) for spontaneous superficial ICH patients without intraventricular hemorrhage would improve clinical functional outcome, and no increasing death or disability rate was observed at 6 months [104]. Another meta-analysis about minimal invasive surgery (MIS) demonstrated that MIS can reduce primary and secondary brain injury for supratentorial ICH patients meeting the following conditions: age of 30–80 with superficial hematoma, Glasgow Coma Scale score of ≥ 9 , hematoma volume between 25 and 40 ml, and within 72 h after onset of symptoms [105]. For cerebellar hemorrhage, urgent clot removal should be undertaken before deterioration if there exists totally the 4th ventricular obliterated [106]. When cerebellar hemorrhage occurs with blood collections exceeding 3 cm in diameter

or brainstem compression resulting in aggravating consciousness disturbance (Glasgow Coma Scale score ≤ 13), clot clearance should be applied before the condition of the patient deteriorates to relieve oppression and save life. If cerebellar hematoma exceeds 3 cm in diameter but the 4th ventricle is not totally obliterated, surgical clot removal may not be required and conservative treatment or ventricular drainage can be a feasible treatment [106–108].

In recent years, some trials have shown that MIS or minimal-invasive hematoma evacuation in combination with thrombolytics have encouraging outcome [109, 110]. Animal experiments found that MIS can reduce the glutamate content [111], neurological deficit scores, perihematomal ET-1 levels, BBB permeability and brain water content compared to the model control group, especially performing MIS at 6–12 h after ICH [112]. In a cohort study, MIS combined with recombinant tissue-type plasminogen activator significantly reduced the 30-day mortality and without effects on early or delayed PHE formation [113]. MIS with local fibrinolysis decreased lethality from 35 to 21% among patients with parenchymal ICH and from 98 to 48% among patients with ventricular hemotamponade compared to treatment without use of fibrinolytics, and the local use of fibrinolytics had no systematic effect on the blood coagulation system [114]. Meta-analysis demonstrates that neuroendoscopic approach with external ventricular drainage may be a better management for intraventricular hemorrhage secondary to spontaneous supratentorial hemorrhage than neuroendoscopic with intraventricular fibrinolysis [115].

Early clot removal seems to have great benefit for ICH patients, but the effect of surgery is still controversial and depends on many factors, such as body condition, hematoma location, volume and so on. Clinicians should assess patients' condition comprehensively before surgical treatments.

Surgical Treatment for Intrahematoma Edema

Intrahematoma edema is mainly caused by tension hematoma. Tension hematoma is related to the formation of capsule-like granulation, and conservative treatment has no favorable effect. So, surgical treatment should be applied if tension hematoma is diagnosed after imaging examination. A clinical test from China found that for patients with tension hematoma, dehydration therapy fails to ameliorate symptoms, and surgery can improve clinical conditions and decrease intracranial pressure. And intracranial hematoma puncture drainage may be superior to craniotomy [116].

Conclusions

ICH is a subtype of stroke with severe outcome and is short of efficient treatment. The secondary injury induced by ICH is involved with numerous cellular and molecular mechanisms. Edema after ICH plays an important role in ICH-induced injury and is associated with poor outcome of ICH. Vasogenic factors, inflammation, thrombin activation, RBC lysis and Hb toxicity contribute to the formation of brain edema after ICH. Dehydration therapy and new targets that block the inflammation cascade inhibit the thrombin activation, prevent or alleviate the lysis of RBC, and surgical treatment may be effective treatments.

Immunomodulator such as fingolimod or dexamethasone are neuroprotective agents. However, to apply new treatments of ICH in clinic needs much more randomized controlled trials, animal and clinical experiments.

Disclosure Statement

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