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Pathophysiology of brain edema formation

Guohua Xi, MD, Richard F. Keep, PhD, Julian T. Hoff, MD*

Department of Neurosurgery, University of Michigan, MC, TC 2128, 1500 East Medical Center Drive, Ann Arbor, MI 48109–0338, USA

Intracerebral hemorrhage (ICH) is a common and often fatal subtype of stroke that produces severe neurologic deficits in survivors. Although death may occur acutely after an ICH, delayed neurologic decline often occurs in patients with a large hematoma (Fig. 1). Deterioration may be related to brain edema formation. Perihematomal edema is commonly observed during the acute and subacute stages, and it plays an important role in secondary brain injury after ICH [1]. It appears as hypodensity around a hematoma on CT scan (Fig. 2) and as hyperintensity on T2-weighted or flair MRI [2]. The mechanisms of perihematomal brain edema formation and the pathways of edema resolution are reviewed here.

Classification of brain edema

Brain edema is an increase in the water content of brain tissue. Such edema can cause an increase in brain volume and an increase of intracranial pressure. It occurs in a variety of neurologic diseases. Brain edema is not vasodilation in the brain or an increase of ventricular volume. During the last century, many classifications of brain edema were reported. The most popular classification was offered by Klatzo [3] in 1967. He divided brain edema into two basic types, vasogenic and cytotoxic. Vasogenic edema follows an increase in permeability of the blood–brain barrier (BBB). It is characterized by an open BBB and an accumulation of plasma protein–rich fluid within the extracellular space. It is usually most obvious in white matter. Cytotoxic edema, also called cellular edema, is caused by parenchymal cell dysfunction. There is swelling of parenchymal cells without BBB disruption, and it is most apparent in gray matter. Cytotoxic edema is associated with a decrease of extracellular fluid volume. This classification is still widely used. In 1975, Fishman [4] recommended the term *interstitial edema* to characterize water accumulation seen in hydrocephalus, where it is most obvious in periventricular white matter. Two other types of edema, osmotic and hydrostatic edema, were later named by Go [5]. Osmotic edema is diffuse throughout the brain and occurs from water intoxication and plasma hypo-osmolality, and hydrostatic edema occurs in severe hypertension, where it is associated with increased intravascular pressure and hypertensive encephalopathy [5].

Betz et al [6] recently suggested using a classification based on BBB integrity. They defined edema as either "intact-barrier" or "open-barrier" edema. Intact-barrier edema results from a disturbance in cellular ion homeostasis and is characterized by cell swelling and a reduction of extracellular space. Open-barrier edema occurs when BBB permeability is increased. Hydrostatic pressure and oncotic forces also contribute to open-barrier edema formation. Edema of this variety is mainly located in the extracellular space.

It should be noted that multiple forms of edema may be present in many types of brain injury depending on the severity and progression of the injury. For example, several types of edema develop after ICH. The primary type of edema is vasogenic, although the cellular form is also present. Interstitial edema caused by early clot retraction is also found soon after ICH and osmotic edema, resulting from liquefaction of the

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* Corresponding author.
E-mail address: jhoff@umich.edu (J.T. Hoff).

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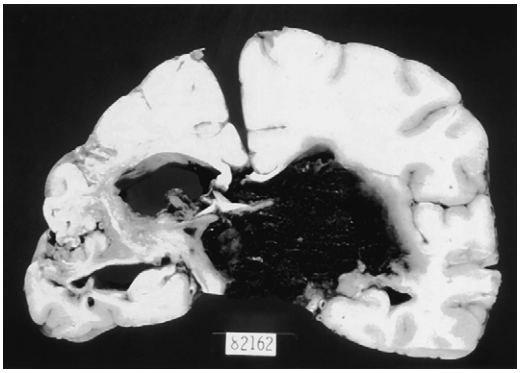

Fig. 1. Postmortem specimen showing large right putaminal capsular hemorrhage with extension into the lateral ventricle. Note the old infarct on the opposite side. (*From* Advanced imaging and image-guided therapy of the nervous system. Philadelphia (PA): Mosby; with permission.)

hematoma occurring several days after the hemorrhage [6,7].

Time line of perihematomal edema development

Brain edema develops immediately after an ICH, peaking several days later [7,8]. In animal models, perihematomal edema increases in several hours, peaks around the third or fourth day after the hemorrhage, and then declines gradually [9–12]. For example, perihematomal edema remains in the rat for more than a week and is then resolved within 2 weeks (unpublished data). The most severe edema is detected around the clot [10]. The volume of brain edema may be larger than that of the hematoma itself [13]. Edema formation after ICH is variable in human beings depending on clot size and localization. Serial MRI or CT scans usually document edema in adjacent brain around the clot [2]. CT scans show that perihematomal edema develops within 3 hours of symptom onset in most patients and reaches its maximum between 10 and 20 days after the ictus [14,15].

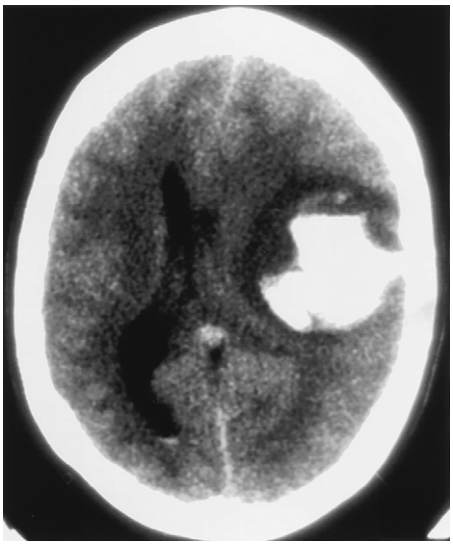

Fig. 2. CT scan with clot retraction and serous "halo" consisting of edema and serum 3 days after ictus.

Mechanisms of brain edema formation after intracerebral hemorrhage

Mechanisms of edema formation after ICH have been identified during the past decade. We now know that several processes are responsible for edema formation around the clot. These include hydrostatic pressure during the clot formation, clot retraction [7,16–18], coagulation cascade activation with thrombin production [19–23], red blood cell (RBC) lysis with hemoglobin-induced toxicity [11], complement cascade activation in the brain parenchyma [24], mass effect [25,26], secondary ischemic/reperfusion injury [25–28], and BBB disruption [12,22,29].

Hydrostatic pressure and clot retraction

In the first several hours after ICH, brain edema around the clot results from hydrostatic pressure and clot retraction. Hydrostatic forces may contribute to edema during clot formation. After the clot is formed, hydrostatic pressure gradients between the hematoma and surrounding brain tissue may still contribute to early perihematomal edema [6].

After a clot forms, it undergoes a period of retraction, which results in expulsion of serum from the clot. Clot retraction in the test tube is shown in Figure 3. This in vitro phenomenon also occurs in the brain. Serum around the clot contributes to hyperacute edema and may cause a low cerebral blood flow (CBF) zone to form around the clot in the first several hours after ICH. Early CT scans also indicate that the hypodensity rim around the clot is caused by clot retraction [16,18]. In addition, brain edema is present within minutes after the intracerebral injection of autologous blood in dogs, implying that edema is formed by plasma components from the hematoma itself [8]. Furthermore, Brott et al [17] found

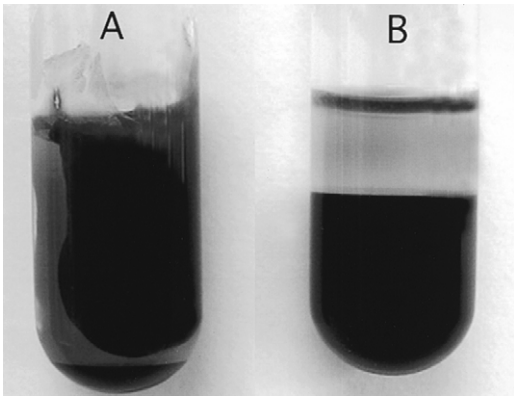

Fig. 3. Clot retraction at 6 hours in test tubes. (A) Normal rat whole blood. Note the serum surrounding the clot. (B) Heparinized rat whole blood.

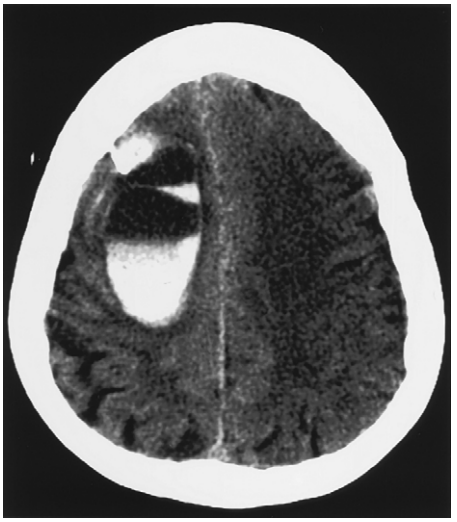

Fig. 4. CT scan in a heparinized patient with an intracerebral hematoma. There are two blood-fluid levels in the clot minimally surrounding brain edema (hypodensity ring around the clot). A ventriculostomy was placed at the site of the intracerebral hemorrhage before coiling of a basilar apex aneurysm. (*From* Advanced imaging and image-guided therapy of the nervous system; with permission.)

that edema around the clot can be detected by CT scan within 3 hours in human patients and suggested that perihematomal edema is caused by clot retraction. The phenomenon of clot retraction was confirmed in a porcine model of ICH by Wagner et al [7]. They showed that white matter edema formed within 1 hour after ICH when the BBB was still intact. The same phenomenon was also found in the rat in our laboratories [12]. These findings have been supported by other studies as well [9,30–32].

Coagulation cascade activation and thrombin formation

Activation of the coagulation cascade plays a key role in early edema formation after ICH [20,23,33]. In an experimental model, we found that nonclotting, heparinized, autologous whole blood fails to produce perihematomal edema within 24 hours in pigs [23]. The same phenomenon happens in human beings. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial, investigators found that brain edema around the clot is diminished in thrombolysis-related ICH compared with spontaneous ICH in patients with normal clotting [33,34]. In patients with significant anticoagulation, the hematoma appears multilayered on CT scans because of a separation of plasma and erythrocytes. ICH in anticoagulated patients is associated with little perihematomal edema (Fig. 4). Reasons for less brain edema around an unclotted hematoma include no clot retraction as shown in the test tubes (see Fig. 3) and less thrombin production stemming from interrupted coagulation.

Thrombin is a serine protease derived from prothrombin and an essential component in the clotting cascade. It is responsible for early brain edema development after ICH (Fig. 5) [19–21,23]. Hirudin, a specific thrombin inhibitor found in leeches, inhibits edema formation in a rat ICH model [21]. In addition, perihematomal edema is attenuated by another thrombin inhibitor, *N*-α-(2-naphthalenesulfonylglycyl)-4-amidino-DL-phenylalaninepiperidide [20]. Thrombin-induced brain edema is partly caused by breakdown of the BBB [22].

Thrombin is produced immediately as blood clots after ICH. It is known that 1 mL of whole blood produces about 260 to 360 U of thrombin, and intracerebral infusion of 5 U of thrombin causes marked edema in the rat. Thrombin is probably produced in the clot constantly until prothrombin is depleted [21]. In addition, prothrombin from plasma may pass through the BBB into the brain parenchyma, where it is converted into thrombin after the BBB breaks down. One study found that perihematomal brain edema in human beings is less after systemic treatment with argatroban, a thrombin inhibitor, even 24 hours

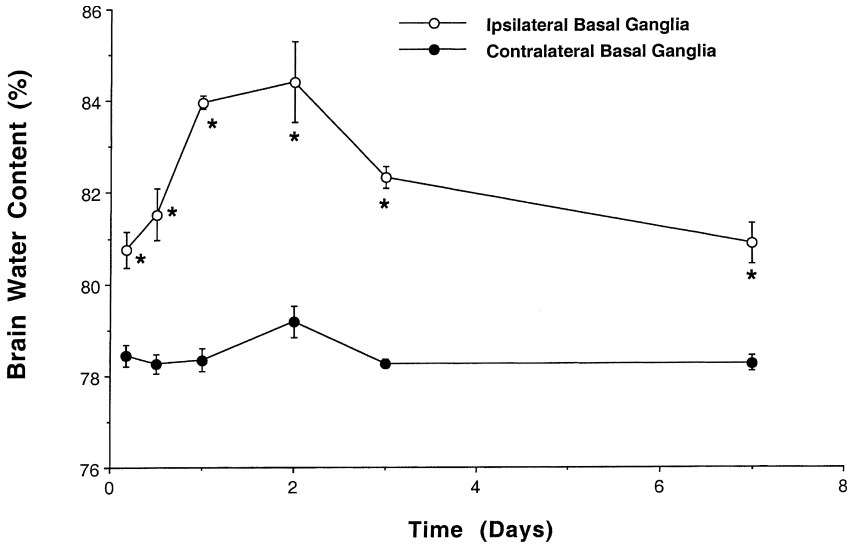

Fig. 5. Time courses of brain edema in the basal ganglia after intracerebral thrombin (5 U) infusion. Values are expressed as the mean ± SEM in five or six rats. *$P < 0.01$ versus contralateral side (*Data from* Xi G, Keep RF, Hoff JT. Erythrocytes and delayed brain edema formation following intracerebral hemorrhage in rats. J Neurosurg 1998;89:995.)

after onset [35]. It should be noted that some of the thrombin produced during coagulation may remain within the hematoma, where it is associated with fibrin [36], and it may be released slowly into the surrounding brain.

The brain itself is a site of thrombin production. In vitro studies have shown that prothrombin mRNA is expressed in cells of the nervous system [37]. Prothrombin mRNA is upregulated after spinal cord injury [38]. These results suggest that thrombin may be formed in the brain after ICH even if the BBB is intact.

In addition to its effect on brain edema, direct intracerebral infusion of minute amounts of thrombin causes inflammation, seizure, scar formation, and reactive gliosis in the brain [39,40]. Thrombin kills cultured cells in vitro [22,41] and may also contribute to cytotoxic edema.

Red blood cell lysis and hemoglobin toxicity

Edema around a hematoma reaches its peak between day 3 and day 7 [9,10,42]. The edema peak occurs on the third or fourth day after experimental whole-blood infusion in rats (Fig. 6) [11,12]. Hydrostatic pressure and clot retraction only cause very early edema (several hours), however, and thrombin-induced brain edema peaks within 48 hours (see Fig. 5) [11]. These differences in the time course of edema formation produced by either ICH, clot retraction, or thrombin infusion suggest there may be delayed edema formation triggered by RBC lysis and hemoglobin release. Infusion of packed erythrocytes causes edema after approximately 3 days, suggesting that RBCs are associated with delayed edema formation. A clinical study of edema and ICH indicates that delayed brain edema is related to significant midline shift after ICH in human beings [43]. This delayed brain edema (in the second or third week after onset) is probably caused by hemoglobin and its degradation products.

Infusion of lysed RBCs but not packed RBCs into the basal ganglia of rats results in marked brain edema formation within 24 hours (Fig. 7). Although infusion of packed RBCs did not produce dramatic brain edema during the first 2 days, it did induce a marked increase in brain water content 3 days postinfusion (Fig. 8). Erythrocyte-induced edema formation seems to be mediated by hemoglobin, because methemoglobin at concentrations found in RBCs mimic the effects of RBCs on edema formation [11].

Oxyhemoglobin is a spasmogen that causes cerebral vasospasm in subarachnoid hemorrhage [44]. Its effects seem to be different in ICH, however. An intracerebral infusion of RBC hemolysate (oxyhemoglobin) induces marked edema, but CBF in the vicinity remains close to normal. It seems that the edema formation is related to

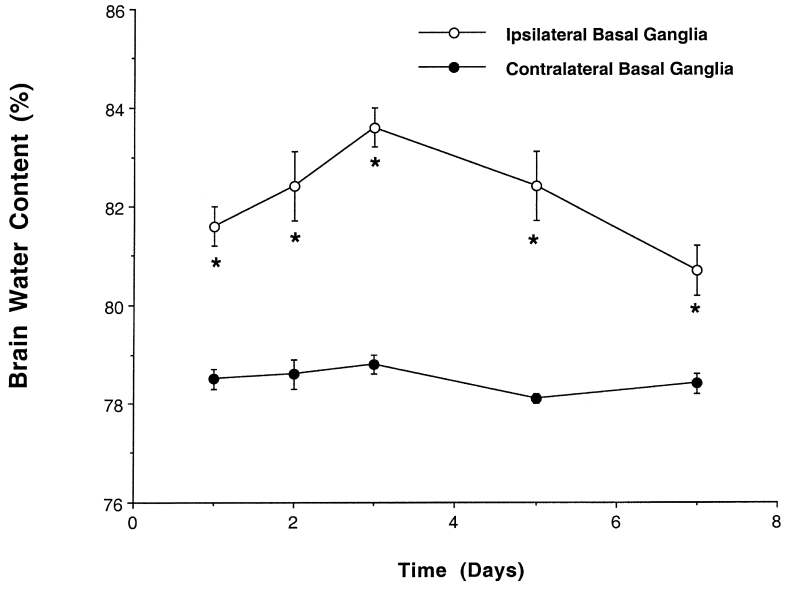

Fig. 6. Graph showing brain water content at 1, 2, 3, 5, and 7 days after infusion of 100 μL of autologous whole blood into the right basal ganglia in a rat intracerebral hemorrhage model. Values are expressed as the mean ± SEM in five or six rats. $*P < 0.01$. (*Data from* Xi G, Keep RF, Hoff JT. Erythrocytes and delayed brain edema formation following intracerebral hemorrhage in rats. J Neurosurg 1998;89:993.)

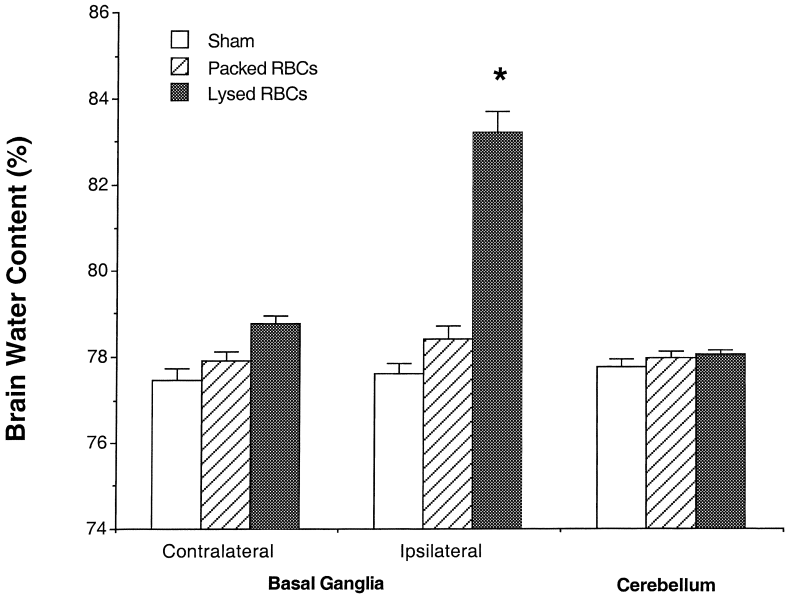

Fig. 7. Bar graph showing brain water content 24 hours after sham operation or infusion of 30 μL of either packed or lysed red blood cells (RBCs). Values are expressed as the mean ± SEM in five rats. $*P < 0.01$ compared with the sham-operated and packed RBC groups. (*Data from* Xi G, Keep RF, Hoff JT. Erythrocytes and delayed brain edema formation following intracerebral hemorrhage in rats. J Neurosurg 1998;89:993.)

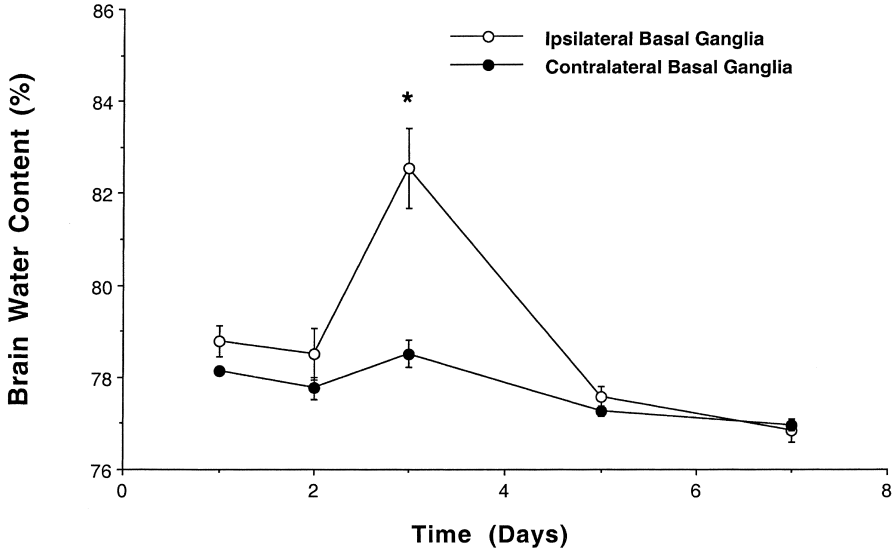

Fig. 8. Time course of brain water content in the basal ganglia after infusion of 50 μL of packed red blood cells into the right basal ganglia in a rat intracerebral hemorrhage model. Values are expressed as the mean ± SEM in five or six rats. $*P < 0.01$. (*Data from* Xi G, Keep RF, Hoff JT. Erythrocytes and delayed brain edema formation following intracerebral hemorrhage in rats. J Neurosurg 1998;89:993.)

marked BBB disruption from the toxic effect of lysed RBCs rather than from ischemia. Such disruption occurs in response to artificially lysed RBCs or natural lysis after the infusion of packed RBCs [29]. In addition, intracortical infusion of lysed blood but not unlysed blood induces strong expressions of heat shock protein 70, a neuronal injury marker, in both the ipsilateral and contralateral neocortex and hippocampus [45]. Exposure of cultured rat spinal cord cells to hemoglobin produces concentration-dependent cell toxicity that can be measured by lactate dehydrogenase release [46].

Hemoglobin degradation products

Heme from hemoglobin is degraded by heme oxygenase (HO) in the brain into iron, carbon monoxide, and biliverdin. Biliverdin is then converted to bilirubin by biliverdin reductase [47]. Our recent studies demonstrate that an intracerebral infusion of hemoglobin and its degradation products (hemin, iron, and bilirubin) causes the formation of brain edema within 24 hours. Hemoglobin itself induces heme oxygenase-1 (HO-1) upregulation in the brain, and HO inhibition by tin-protoporphyrin reduces hemoglobin-induced brain edema. In addition, an intraperitoneal injection of a large dose of deferoxamine (an iron chelator) attenuates brain edema induced by hemoglobin. These results indicate that hemoglobin causes brain injury by itself and through its degradation products (Fig. 9) [48].

A cortical injection of iron causes focal epileptiform paroxysmal discharges [49,50]. Iron and lipid peroxidation also have an important role in hemoglobin-induced brain injury. For example, a subpial injection of $FeCl_2$ induces brain edema and lipid peroxidation in the brain [51]. Iron can also stimulate the formation of free radicals, leading to neuronal damage. It is known that ferrous (Fe^{2+}) and ferric (Fe^{3+}) iron react with lipid hydroperoxides to produce free radicals [52].

Bilirubin is toxic to the brain. Fifty years ago, Jackson [53] injected bilirubin into the cisterna magna of dogs, causing severe inflammatory reactions. Amit and Brenner [54] found that bilirubin is toxic to neurons and astrocytes in vitro. Conversely, interruption of HO activity, which reduces bilirubin and free iron production, has provided a protective effect against hemorrhagic [55], ischemic [56], and traumatic [57] brain injury. It should be noted that micromolar concentrations of bilirubin may also act as an antioxidant [58,59].

HO consists of three enzymes, HO-1, HO-2, and HO-3 [60,61]. Upregulation of HO-1 in a heme-rich environment with a high level of HO-2, which can be detected in the perihematomal zone,

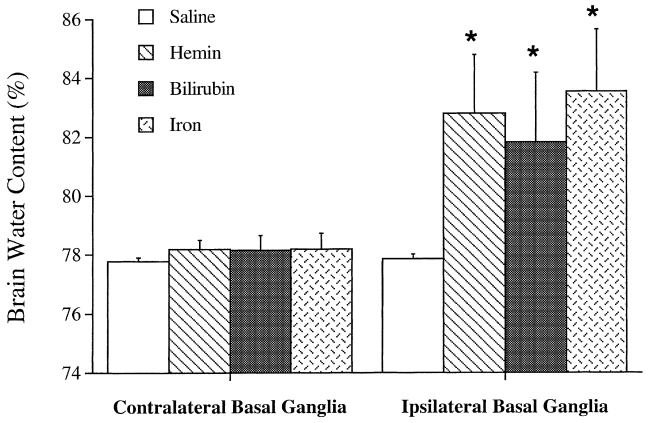

Fig. 9. Bar graph showing brain water content 24 hours after infusion of 30 μL of either saline, hemin, bilirubin, or $FeCl_2$. *$P < 0.01$ versus saline group.

might cause excess free iron and bilirubin accumulation, resulting in brain injury. This finding is supported by Suttner and Dennery [62], who found that HO-1 overexpression and reactive iron accumulation are associated with oxygen cytotoxicity. In addition, Lamb et al [63] found that hemoglobin stimulates lipid peroxidation in microsomal and cellular systems and that peroxidation is reduced by HO inhibitors and iron chelators.

Carbon monoxide is another heme degradation product. Carbon monoxide is a free radical that causes brain injury analogous to nitric oxide–mediated damage [64–66].

Complement cascade activation in brain parenchyma

The complement system is involved in various immune reactions, including cell lysis and the inflammatory response. Complement is normally excluded from the brain parenchyma by the BBB, but entry can occur after ICH as part of the extravasated blood or, later, as the result of BBB disruption. There is evidence that the complement cascade is activated in the brain parenchyma after ICH. For example, *N*-acetylheparin, a heparin congener without anticoagulant properties, inhibits the complement cascade and attenuates perihematomal brain edema [24].

Complement-related brain injury may be caused by membrane attack complex (MAC) formation and the classic inflammatory response. MAC consists of C5b-9 complement forms and is assembled after complement activation [67]. MAC formation can cause the formation of a pore in the cell membrane, which leads to cell lysis. Thus, MAC formation may be involved in the lysis of RBCs within the clot. MAC insertion may occur in neurons, glia, and endothelial cells as well, causing neuronal death and BBB leakage. Our studies have also shown that MAC is assembled after ICH and that clusterin, an inhibitor of MAC formation, is upregulated in the brain parenchyma [24]. Recent studies have demonstrated that MAC not only causes cell lysis but also modulates cellular functions, such as the release of cytokines, oxygen radicals, and matrix proteins [68].

Anaphylatoxin complement C5a is generated after complement activation. C5a is also a potent chemoattractant for polymorphonuclear leukocytes and contributes to inflammatory cell injury [69]. Complement C5a can be detected around the clot [70]. Systemic complement depletion by cobra venom factor, a nontoxic protein in cobra venom, reduces perihematomal edema in the rat ICH model [70].

Mass effect

Whether brain edema and injury caused by ICH result from mass effect of the clot alone or from other factors was first investigated by Suzuki and Ebina [8]. They injected either autologous whole blood or an oil-wax mixture into the lateral portion of the internal capsule in dogs. Brain edema around the clot was more severe in the blood injection group than in the "control" group, suggesting that the edema results primarily from a "toxic" effect of blood rather than from simple mass effect. Others have also tested mass

effect. Sinar et al [26] demonstrated that inflation of a microballoon in the basal ganglia of the rat reduced CBF to less than 20 mL per 100 g per minute transiently but that brain edema did not follow after 24 hours.

Although erythrocytes are responsible for most of the mass effect created by the hematoma, packed RBCs alone fail to produce marked brain edema at 24 hours [11,21]. An intracerebral infusion of plasma causes rapid edema formation, however [71]. Further, nonclotting blood produces minimal edema in both rat and porcine models [23]. In human patients on anticoagulants, perihematomal edema is slight despite a fairly large mass, especially in ICH, where demarcation between plasma and RBCs in the hematoma can be seen on CT scans [33,34,72]. Although hematoma mass causes brain injury by mechanical force and increased intracranial pressure, especially if the hematoma is large, brain edema that follows ICH in patients who survive the ictus is not simply caused by mass effect produced by the clot.

Secondary ischemic/reperfusion brain injury

Whether secondary ischemia contributes to edema formation around the hematoma is still controversial. Experiments have shown that CBF adjacent to a hematoma decreases [73] but that the reduction is temporary and modest [28]. Previous work in our laboratory shows similar results [12]. These results indicate that critical levels and durations of hypoperfusion do not occur after experimental ICH and that perihematomal brain edema is not principally produced by cerebral ischemia provided that the hematoma is not massive.

There is additional evidence that ischemia is not an important mechanistic component in early perihematomal brain edema formation. Wagner et al [74] measured ATP and phosphocreatine levels in the perihematomal edema zone at 1, 3, 5, and 8 hours after ICH. Although severe brain edema was present around the hematoma at all time points, ATP levels stayed normal, and brain phosphocreatine contents increased with time during the first 8 hours. Although intracranial pressure was increased remarkably in an experimental ICH study, an ischemic zone was not present in the first 5 hours after ICH [75]. It should also be noted that thrombin contributes to edema formation after ICH but that an intracerebral injection of thrombin does not result in significant reduction of CBF in the vicinity of the clot [22].

The site of the hematoma is a major factor affecting CBF. Patel et al [76] injected equal volumes of autologous whole blood into either the subdural space or the caudate nucleus of the rat. Although the subdural hematoma induced significant reductions in CBF, ICH induced only modest reductions. Brain infarction was observed in the cerebral cortex after subdural hemorrhage, but minimal infarction was detected near the ICH.

CBF has been measured by single photon emission computerized tomography in patients with ICH. A zone of low CBF found around the clot soon after the ictus resolved within 48 hours. Because this low CBF zone correlates with the perihematomal edema rim, the investigators suggested that reperfusion injury might contribute to edema formation [27]. CBF reduction after ICH was also reported by Tanaka et al [77]. In a positron emission tomography study, however, Diringer et al [78] could not find secondary ischemic injury after ICH. Using diffusion-weighted MRI and proton MRI spectroscopy, widespread ischemia was not found around an intracerebral clot [79]. Recently, Zazulia et al [80] measured perihematomal CBF, cerebral metabolic rate of oxygen, and oxygen extraction fraction in 19 ICH patients with positron emission tomography. They found that both cerebral metabolic rate of oxygen and CBF were reduced in the perihematomal zone, resulting in reduced oxygen extraction fraction. Thus, the reduction in CBF may result from reduced metabolism around the clot.

Some differences in CBF data between patients and animal models may be caused by the volume of the hematoma. First, hematoma size in human beings averages approximately 30 to 40 mL, whereas the hematoma volume is proportionately smaller in animal models. For example, a 50-μL clot in rats or a 2-mL clot in pigs corresponds to a 30-mL clot in human beings. Second, clinical measurements of hematoma size are derived from CT scans. Because the hematocrit in the clot can be as high as 90% as a result of clot retraction, hemorrhage volume in human beings may be greater than the hematoma size measured by CT. Moreover, early clot retraction, which separates the hematoma into an erythrocyte mass with a high hematocrit and a surrounding serum zone (see Fig. 3), may create a low CBF zone around the hematoma.

If ischemia is not a major mediator of ICH-induced edema formation, whether the mechanisms involved in ischemic brain injury also play a role in ICH-induced injury remains a question.

Some mechanisms probably overlap, such as free radical–induced injury, although the underlying causes of free radical injury may differ between ischemia and ICH. Conversely, some mechanisms may not overlap. Excitotoxicity caused by glutamate release is an important mechanism in brain injury after cerebral ischemia in animal models [81]. For example, MK-801, the *N*-methyl-D-aspartate antagonist, reduces brain injury in many studies of focal cerebral ischemia in the rat. MK-801 fails to reduce brain injury from ICH in the same species, however [82]. Whether MK-801 is protective in a microballoon model of ICH is uncertain [25,83].

Blood–brain barrier disruption

BBB dysfunction occurs after ICH and contributes to brain edema formation. After ICH, the BBB remains intact to large molecules, such as albumin, for several hours [7]. Eight to 12 hours later, however, BBB permeability in the perihematomal region increases markedly and continues to rise for 48 hours [12]. Early BBB disruption after ICH is related to thrombin formation, because thrombin in the amounts produced by the hematoma causes a significant increase in BBB leakage [22]. After RBC lysis, hemoglobin further aggravates BBB disruption [29].

BBB dysfunction may contribute to edema formation in other ways. Movement of fluid across systemic capillaries is determined by a balance between hydrostatic and oncotic pressure gradients. In the normal BBB, the hydraulic conductivity of the capillaries is low, because tight junctions link the endothelial cells. It is thought that fluid movement across these capillaries occurs by diffusion and active secretion [6]. In diseases where the BBB is disrupted, however, hydraulic conductivity rises and the rate of fluid movement driven by hydrostatic and oncotic pressure gradients is enhanced. With ICH, the presence of plasma proteins in the brain dissipates the oncotic pressure gradient that normally acts to retain water in the circulating blood. Hydrostatic pressure may then become the principal driving force determining fluid movement. Arterial pressure influences hydraulic conductivity and plays an important role in edema formation after BBB disruption [84].

Resolution of brain edema

Various pathways are involved in edema resolution after ICH. Cerebrospinal fluid (CSF) is the primary pathway for edema clearance [85–87]. If the hydrostatic pressure gradient between edematous brain tissue and CSF is elevated, the drainage of edema fluid into the ventricular system increases [86]. Edema fluid is cleared into CSF not only within the ventricular system but also through the subarachnoid spaces [87]. Ohata and Marmarou [85] found that edema clearance to the subarachnoid spaces is mainly through extracellular space. Edema resorption occurred chiefly within the subarachnoid space rather than within the ventricular system in a rabbit ICH model. Increased intracranial pressure inhibits edema resorption [88].

Uptake of edema fluid proteins by neurons and glia also contributes to edema resolution. Extravasated serum proteins accumulate in neurons, astrocytes, and oligodendrocytes [89–91]. In addition, brain edema may resolve through the vascular system [92].

Summary

A number of mechanisms seem to be involved in edema formation after an ICH. At least three phases of edema are involved in ICH. These include a very early phase (first several hours) involving hydrostatic pressure and clot retraction, a second phase (first 2 days) involving the activation of the coagulation cascade and thrombin production, and a third phase (after 3 days) involving RBC lysis and hemoglobin-induced neuronal toxicity. Activation of the complement system in brain parenchyma also plays an important role in the second and third phases.

There are potential therapeutic strategies to address each of these mechanisms. Because the adverse effect of an ICH seems to result from a toxic effect of blood components on brain tissue, early clot removal may be the best strategy, because it results in the removal of all the toxic components [93].

Hematoma aspiration after tissue plasminogen activator (tPA) infusion has also been shown to be relatively safe and effective in animal models. Kaufman et al [94] reported that tPA lysed the hematoma in minutes and did not cause inflammation or bleeding in rabbits. Because clots lysed with tPA can be aspirated through a needle or catheter, mechanical brain injury by this method is minimized. In a rat model, aspiration of clot with tPA reduced clot volume and brain injury [95,96]. Recently, Wagner et al [97] infused tPA into hematomas in a porcine model at 3 hours after

induction and aspirated the liquified clots 1 hour later. Clot removal after tPA treatment resulted in a 72% reduction in hematoma volume compared with untreated controls. Clot removal also reduced brain edema volume and BBB disruption and improved cerebral tissue pressure [93].

Six randomized trials have been accomplished, but surgical evacuation of the clot remains controversial [98–103]. Recently, thrombolysis and aspiration under CT guidance reduced the hematoma volume effectively [104]. Infusion of tPA directly into the hematoma before clot aspiration has also been used in human beings. Up to 90% of the original hematoma volume can be removed [105, 106]. Schaller et al [107] injected tPA directly into a hematoma 72 hours after the ictus in patients. The hematomas were lysed, and the liquified clots were drained in 14 patients. Two patients died, but none had recurrent hemorrhage.

In conclusion, much has been learned about the basic mechanisms involved in edema formation after ICH. Animal models indicate that a number of components of blood are capable of inducing brain injury and brain edema. Now, it is time to translate that basic information into clinical trials.

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