The kallikrein-kinin system as mediator in vasogenic brain edema

Part 3: Inhibition of the kallikrein-kinin system in traumatic brain swelling

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Evidence has previously been provided that administration of kinins to the cerebrum causes edema and opening of the blood-brain barrier. It has further been shown that these highly active compounds are formed in the brain under pathophysiological conditions. Their formation was enhanced when cerebral blood flow became compromised by an increase in intracranial pressure. Final evidence, however, was not available as to whether specific inhibition of the kallikrein-kinin (KK) system has a therapeutic function in acute head injury. The authors have demonstrated in rabbits that inhibition of the activating enzyme kallikrein by aprotinin or by aprotinin plus soybean trypsin inhibitor (SBTI), which interfere with plasma and tissue kallikrein, is associated with a decrease in formation of posttraumatic swelling after a standardized cold lesion to the brain. Saline-treated control animals with cerebral cold-induced injury had an increase in hemispheric weight 24 hours later of 13.0% ± 0.8% (standard error of the mean) in the damaged hemisphere compared to the contralateral nondamaged hemisphere. Administration of aprotinin or aprotinin plus SBTI led to a significant reduction of hemispheric swelling of 10.1% ± 0.7% or 10.4% ± 0.7%, respectively. In animals receiving SBTI only, hemispheric swelling evolving from cold injury was not significantly reduced. Therapeutic reduction of brain edema by aprotinin cannot be attributed to a nonspecific effect on the blood pressure, which in the experimental groups remained almost normal as compared to the control animals. Failure of SBTI to influence posttraumatic brain swelling may have resulted from disturbances in intravascular coagulation. Measurements of aprotinin in plasma and tissue demonstrate that the inhibitor doses employed are within an effective therapeutic range. Attenuation of brain edema by specific inhibition of the KK system provides evidence for a mediator role of kinins in vasogenic edema. Clinical trials with inhibitors of the KK system in acute forms of traumatic lesions associated with vasogenic edema appear worthwhile.

KEY WORDS • kallikrein-kinin system • aprotinin • soybean trypsin inhibitor • vasogenic brain edema • rabbit
brain after a primary lesion. Mediator compounds are formed in necrobiotic tissue, contused areas, and areas of ischemic infarction, or enter the brain from the intravascular compartment.\(^4\) Experimental evidence has been provided for a role of the kallikrein-kinin (KK) system as a mediator in vasogenic brain edema.\(^26\) Cerebral administration of kinins or plasma as a carrier of kininogens induces edema.\(^32,42\) Moreover, activation of the KK system occurs after focal injury of the brain in and around the lesion.\(^5,26\) However, it has not been demonstrated yet whether specific inhibition of kinin formation in injured brain prevents or attenuates vasogenic edema. Investigation of these questions is mandatory, not only to obtain evidence of a mediator function of the KK system in brain edema, but also to explore new forms of treatment that influence this process more specifically than the currently used methods.

The authors have studied aprotinin and soybean trypsin inhibitor (SBTI) as inhibitors of the KK system for the treatment of brain swelling due to perifocal cold injury edema. Aprotinin is a polyvalent protease inhibitor with an inhibitory capacity predominantly affecting tissue kallikrein, whereas SBTI preferentially antagonizes plasma kallikrein.\(^4,46\) Reduction of vasogenic edema was quantitatively assessed from the decrease in weight of the traumatized hemisphere.

**Materials and Methods**

**Experimental Procedure**

Experiments were performed on 63 rabbits of either sex weighing an average of 3.3 ± 0.6 kg. The animals were intravenously anesthetized with ketamine (7 mg/kg) and xylazine (2 mg/kg). Intra-arterial and intravenous catheters were inserted into the ear vessels for administration of drugs, measurement of blood pressure, or to obtain blood samples. After exposure of the skull in a stereotaxic frame, a circular craniotomy was made over the left hemisphere. Injury to the dura was carefully avoided, and hemorrhages resulting from craniotomy were stopped. The animals were injected intravenously before trauma with 2% Evans blue dye (1 ml/kg) for visualization of vasogenic edema.

A cold injury, 10 mm in diameter, was created in the exposed brain by application for 60 seconds of a copper cylinder which was cooled by a mixture of dry ice and acetone to −68°C. The scalp was subsequently sutured. Intravenous administration of either saline solution or acetone to −68°C was performed. Two animals received saline only, and four animals (nine rabbits) received SBTI (6 mg/kg/hr); Group 2 animals (14 rabbits) received aprotinin (Inhibin, 6 mg/kg/hr, equivalent to 42,000 kallikrein inactivator units (KIU)/ml); and Group 3 animals (10 rabbits) received SBTI plus aprotinin (3 mg/kg/hr of each drug). The SBTI and aprotinin were dissolved in 0.9% NaCl.

The cerebral water content of both hemispheres was gravimetrically analyzed after drying at 110°C for 48 hours. The infusion rate was 2 ml/kg/hr, or 48 ml/kg in 24 hours.

The animals were placed in cages without access to food or water until sacrifice. Arterial blood pressure was recorded with a Statham transducer* in five animals per group until 2 hours after injury. Arterial blood was drawn for determination of pH, \(pO_2\), and \(pCO_2\). Partial thromboplastin time (PTT) and aprotinin concentrations were measured in arterial blood 30 minutes before and after trauma, as well as 3, 6, and 24 hours after trauma. Twenty-four hours after induction of the cold lesion, the animals were anesthetized and rapidly exsanguinated by cardiac puncture. The brain was removed and the injured and uninjured control hemispheres were meticulously separated in the median plane. The experimental protocol is given in Fig. 1. Cerebral uptake of aprotinin into normal and injured cerebral tissue was determined as the difference between the fresh weight of the traumatized (\(fw_t\)) and the nontraumatized contralateral (\(fw_c\)) hemispheres, according to the following equation:

\[
\text{swelling}(\%) = \frac{fw_t - fw_c}{fw_c} \times 100.
\]

The cerebral water content of both hemispheres was gravimetrically analyzed after drying at 110°C for 48 hours.

**Analytical Procedure**

Swelling of the traumatized hemisphere was determined as the difference between the fresh weight of the traumatized (\(fw_t\)) and the nontraumatized contralateral (\(fw_c\)) hemispheres, according to the following equation:

\[
\text{swelling}(\%) = \frac{fw_t - fw_c}{fw_c} \times 100.
\]

* Statham transducer manufactured by Statham Instruments, 2230 Statham Boulevard, Oxnard, California.
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Fig. 2. Increase in weight of the traumatized hemispheres expressed in grams (left) and percent of control hemisphere (right) (mean ± standard error of the mean) of animals with and without treatment. In animals receiving aprotinin or aprotinin plus soybean trypsin inhibitor (SBTI), the hemispheric weight increase was significantly reduced. Treatment with SBTI alone had no significant effect. Significance determined by t-tests.

Results

Cold injury to the cerebral cortex resulted in a standardized area of hemorrhagic necrosis 4 to 5 mm in depth and 10 to 11 mm in diameter. The primary lesion was surrounded by a perifocal edematous halo of variable size involving gray and white matter. Animals receiving aprotinin appeared to have a smaller necrotic lesion and limited staining of perifocal tissue by Evans blue dye. The mean increase in weight of the injured hemisphere compared to the uninjured contralateral hemisphere was 0.47 ± 0.10 gm (mean ± standard error of the mean) in control animals, 0.43 ± 0.05 gm in Group 1 after SBTI only, 0.39 ± 0.08 gm in Group 3 after aprotinin plus SBTI, and 0.37 ± 0.09 gm (t-test: p < 0.05 versus control animals) in Group 2 after treatment with aprotinin only (Fig. 2 left). The differences in weight were also given as a percentage of the uninjured hemisphere to compute the amount of tissue swelling. Cold injury led to a weight increase of 13.0% ± 2.6% in untreated control animals, 11.7% ± 1.6% in Group 1 animals receiving SBTI only, 10.4% ± 2.1% (t-test: p < 0.02 versus control animals; Bonferroni/ Holm: p < 0.05) in Group 3 animals receiving SBTI plus aprotinin, and 10.1% ± 2.5% (t-test: p < 0.01 versus untreated control animals; Bonferroni/Holm: p < 0.05) in Group 2 animals receiving aprotinin only (Fig. 2 right).

Analysis of variance of the data revealed that: 1) aprotinin reduced traumatic brain swelling at a confidence level of 99%, 2) SBTI given alone was a therapeutic failure, and 3) there was no additional effect of SBTI when that drug was given together with aprotinin. A reduction in hemispheric swelling after cold injury from 13.0% to 10.1% by aprotinin is equivalent to an attenuation of brain swelling of 22%. The cerebral water and electrolyte content of the traumatized and contralateral hemispheres is given in Table 1. Traumatized cerebral hemispheres had a statistically significant increase in water content (p < 0.001). This was most pronounced in animals receiving saline and least pronounced in animals receiving aprotinin. Water content of the contralateral uninjured hemisphere was 79.5 ml/100 gm fresh weight. The hemispheric water content of animals without cold injury was 79.8 ml/100 gm fresh weight. The hemispheric water content of animals without cold injury was 79.5 ml/100 gm fresh weight. The hemispheric water content of animals without cold injury was 79.8 ml/100 gm fresh weight. The hemispheric water content of animals without cold injury was 79.8 ml/100 gm fresh weight. The hemispheric water content of animals without cold injury was 79.8 ml/100 gm fresh weight.
of Na⁺ and a decrease of K⁺. The differences between various groups did not attain statistical significance, however.

The arterial blood pressure was recorded in experimental subgroups to evaluate any potential influence of treatment. Measurement of this parameter is important because formation of vasogenic edema may be attenuated by arterial hypotension.³⁰,³⁴ Systemic blood pressure was not affected by cold injury or by treatment with aprotinin (Fig. 3). The mean arterial blood pressure was 85 mm Hg in control animals during cold injury and 73 mm Hg in animals receiving aprotinin. Two hours later, mean arterial blood pressure rose to 100 mm Hg in control rabbits and to 92 mm Hg in animals subjected to treatment (a nonsignificant increase). The normal PTT in control animals without saline treatment was 16 to 24 seconds. Fifteen minutes after the start of infusion with SBTI, the mean PTT increased to 42 seconds and eventually rose to 72 seconds at termination of the experiment 24 hours later. Animals receiving aprotinin also had an increase of PTT (Fig. 4), albeit delayed. Aprotinin concentrations in plasma are shown in Fig. 5. Forty-five minutes after the start of infusion, mean plasma levels were 120 KIU/ml and rose to 450 KIU/ml at 24 hours. Measurable concentrations of aprotinin were found only in focal and perifocal areas of injured cerebral tissue, and amounted to 494 ± 173 KIU/gm fresh weight (mean ± standard error of the mean) in necrotic tissue or 171 ± 59 KIU/gm fresh weight in perifocal edematous brain. These levels were sufficient for inhibition of the KK system. Normal cerebral tissue in the contralateral hemisphere had no measurable aprotinin concentrations.

**Discussion**

Although impressive, the current evidence is incomplete with regard to an involvement of chemical media-

tor compounds in the secondary process such as brain edema that follows head injury. According to the requirements for identification of a mediator,¹⁴,²⁶,⁴² the specificity of inhibition is questionable. Our current findings that posttraumatic swelling and edema may be restricted by an inhibitor of the KK system increases evidence that kinins are mediator compounds.

Since the first discovery by Kraut, et al.,²¹ of compounds with inhibitory potential, many substances have been found that interfere more or less specifically with the activating enzyme kallikrein. Soybean trypsin inhibitor, detected by Kunitz,²² is a peptide of 181 amino acids with a molecular weight of 20,100.⁴⁶ It is predominantly an inhibitor of serum kallikrein, but also inhibits trypsin and other proteases.⁴⁶ Aprotinin was isolated from bovine pancreas by Kraut, et al.,²¹ and by Kunitz and Northrop.²³ It has a wide inhibitory spectrum including trypsin and other proteases.⁴⁶ Inhibition of plasmin with aprotinin is used clinically for the treatment of hyperfibrinolysis. Aprotinin and SBTI interfere with contact activation of the intrinsic coagulatory system and block platelet aggregation (see Fig. 6).¹,¹⁴,²⁹ The half-life of aprotinin in blood is 7 hours under steady-state conditions.³⁴ In studies in our laboratory using a chromogenic substrate,¹¹,³⁸ it was con-

![Fig. 3. Mean arterial blood pressure (MABP, ± standard error of the mean) during the first 2 hours after trauma in control animals receiving 0.9% NaCl and in animals infused with aprotinin (150 mg/kg/24 hrs) followed by successful attenuation of hemispheric swelling. No significant differences in MABP were found between the groups.](image1)

![Fig. 4. Mean partial thromboplastin time (PTT, ± standard error of the mean) in control animals and in animals subjected to treatment. The PTT of control animals was 20 ± 4 seconds (s) and remained constant throughout the experiment. Infusion of soybean trypsin inhibitor (SBTI) caused a substantial delay of PTT, beginning 30 minutes after the start of infusion, and a further increase at the termination of the experiment at 24 hours. After infusion of aprotinin or aprotinin plus SBTI, the PTT rose only marginally (p < 0.02 versus pretreatment values).](image2)
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![Graph](image)

**Fig. 5.** Mean aprotinin concentrations in plasma (± standard error of the mean) in six animals infused with a total inhibitor dose of 150 mg/kg/24 hrs. Continuous infusion of aprotinin (6 mg/kg/hr; equivalent to 42,000 kallikrein inactivator units (KIU)/ml) led to a steady increase of the plasma concentration. The steep rise between 6 and 24 hours is the result of an interruption of the time scale. The aprotinin concentrations in plasma can be considered sufficient to inhibit formation of kinins. For data on aprotinin concentrations in focal and perifocal brain tissue see text.

It has been observed that aprotinin and SBTI inhibited plasma kallikrein of rabbits. Although aprotinin has been studied in various disorders, including life-threatening conditions (for example, disseminated intravascular coagulation, septicemia, pancreatitis, and hemorrhagic shock), its therapeutic significance is still open to debate.3,14,18,27,41 Limited experience is available on inhibition of the KK system in acute lesions of the central nervous system. Czernicki10 observed that aprotinin influenced cerebral edema secondary to surgical trauma, cold injury, or sudden decompression of the intracranial compartment. However, involvement of nonspecific side effects, such as a decrease of blood pressure, cannot be ruled out since they used cats in their experiments (according to our observations, cats develop hypotension during infusion with aprotinin). In addition, the aprotinin dose administered by Czernicki within 6 hours was only 40,000 KIU/kg, a dose considerably less than that found necessary for the current investigations. Due to a lower affinity of aprotinin to serum kallikrein of rabbits,55 we chose a dose of 150 mg/kg/24 hours (corresponding to 500,000 KIU/kg) in our experiments. Clinical studies in head-injured patients given aprotinin were reported by Auer, but the results were inconclusive. No clinical studies have yet been conducted with SBTI.

Cold injury as described by Klatzo20 has been used as a model for induction of edema, since standardized lesions can be produced. Freezing of exposed cerebral tissue is certainly an artificial injury not representative of the enormous complexity of head injuries. Nevertheless, it has been employed fruitfully in many studies to improve our understanding of a most intriguing pathophysiological problem.8,16,19,20,34,36 Cold injury is considered to be equivalent to cerebral contusion in causing a hemorrhagic lesion and perifocal edema. Other experimental models of severe head injury, such as fluid percussion, the captive-bolt humane stunner, gunshot wounds, and rapid translational or rotational acceleration/deceleration of the brain, have their own merits with respect to the underlying problem.8,15,28,33,39,40 Yet, none of these comprehensively model the wide spectrum of mechanisms involved in head injury.

The effectiveness of treatment with inhibitors of the KK system was evaluated in the current studies by comparing the increase in weight of traumatized hemispheres of animals receiving treatment with the increase in weight of the traumatized hemispheres of untreated control animals. The hemispheric weight increase is considered to reflect most faithfully the amount of uptake of edema fluid by the traumatized hemisphere as compared to other methods. Cerebral water content or tissue swelling calculated from the water content12 are only relative measures. Nevertheless, agreement is usually excellent between tissue swelling directly determined as an increase in weight, and indirectly determined according to the equation of Elliot and Jasper3,14,27 as follows:

### TABLE 1

<table>
<thead>
<tr>
<th>Feature Tested &amp; Group</th>
<th>Injured Hemisphere</th>
<th>Uninjured Hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>water content (ml/100 gm fw)</td>
<td>value</td>
<td>no.</td>
</tr>
<tr>
<td>uninjured untreated</td>
<td>79.43 ± 0.37</td>
<td>10</td>
</tr>
<tr>
<td>saline</td>
<td>80.71 ± 0.41</td>
<td>12</td>
</tr>
<tr>
<td>SBTI</td>
<td>80.62 ± 0.60</td>
<td>9</td>
</tr>
<tr>
<td>SBTI + aprotinin</td>
<td>80.51 ± 0.39</td>
<td>10</td>
</tr>
<tr>
<td>aprotinin</td>
<td>80.51 ± 0.64</td>
<td>14</td>
</tr>
<tr>
<td>Na⁺ content (mM/kg dw)</td>
<td>value</td>
<td>no.</td>
</tr>
<tr>
<td>uninjured untreated</td>
<td>285.37 ± 16.06</td>
<td>10</td>
</tr>
<tr>
<td>saline</td>
<td>351.75 ± 25.36</td>
<td>12</td>
</tr>
<tr>
<td>SBTI</td>
<td>388.38 ± 31.00</td>
<td>9</td>
</tr>
<tr>
<td>SBTI + aprotinin</td>
<td>412.98 ± 30.13</td>
<td>10</td>
</tr>
<tr>
<td>aprotinin</td>
<td>379.04 ± 34.91</td>
<td>14</td>
</tr>
<tr>
<td>K⁺ content (mM/kg dw)</td>
<td>value</td>
<td>no.</td>
</tr>
<tr>
<td>uninjured untreated</td>
<td>431.21 ± 29.48</td>
<td>9</td>
</tr>
<tr>
<td>saline</td>
<td>387.65 ± 13.41</td>
<td>12</td>
</tr>
<tr>
<td>SBTI</td>
<td>391.05 ± 24.81</td>
<td>9</td>
</tr>
<tr>
<td>SBTI + aprotinin</td>
<td>389.53 ± 19.80</td>
<td>10</td>
</tr>
<tr>
<td>aprotinin</td>
<td>391.44 ± 23.28</td>
<td>10</td>
</tr>
</tbody>
</table>

*Values are means ± standard deviations. SBTI = soybean trypsin inhibitor; fw = fresh weight; dw = dry weight. The increase of water and Na⁺ content as well as the decrease of K⁺ content in the injured hemisphere is significantly (p < 0.001) different from that of the corresponding contralateral hemisphere in all groups with cold injury. No. = number of rabbits in each group.
where $P$ is percent dry weight of normal tissue, $P_1$ is percent dry weight of the edematous tissue, and $p$ is percent dry weight of the edema fluid. In the group of animals with aprotinin treatment, for example, tissue swelling as directly determined by weight increase was 10.1%, whereas swelling was 9.5% according to the equation of Elliot and Jasper, assuming a percent dry weight of the vasogenic edema fluid of 8%. Still, tissue water content as determined by the dry/wet weight method is an indirect parameter because it gives a ratio of the water content to the fresh weight of the tissue. Obviously, the relationship of water to fresh weight is not as sensitive as is the absolute mass for determination of weight increase in the quantitative assessment of fluid uptake, since the composition of solids is also affected, albeit less markedly. Thus, reduction of swelling by treatment is more obvious when analyzing the differences in weight of traumatized hemispheres with and without treatment as compared to the corresponding tissue water content.

Accurate gravimetric determination of hemispheric swelling requires that, under normal conditions, both hemispheres have identical masses and that separation yields truly symmetrical hemispheres. In control experiments, weight differences between uninjured hemispheres of normal brain were less than 0.5%. Spillover of edema into the contralateral hemisphere through the corpus callosum could be a source of error of direct weight determination of hemispheric swelling. The extent of this error can be quantified, however, by direct comparison of the weights of the contralateral hemispheres of uninjured control animals and of animals with a freezing lesion, or of the hemispheric water content in both groups. In this study, comparison of the hemispheric weights yielded a considerable variance. Determination of the contralateral hemispheric water content (dry/wet weight ratio) revealed a slight increase of weight in experimental animals over control animals without lesions. However, the differences were not statistically significant. Nevertheless, the question is whether and how such an error would influence the experimental result of the study; that is, the finding that treatment by protease inhibition reduces the swelling of cold-injured hemispheres. An increase in weight of the contralateral hemisphere by spillover of edema fluid would reduce the difference in weight between the experimental and control hemispheres, the quantitative measure of hemispheric swelling used in this study. As a consequence, the degree of tissue swelling would be underestimated. Accordingly, effectiveness of a given treatment would be underestimated. This may imply that attenuation of formation of vasogenic edema after cold injury by aprotinin or by aprotinin plus SBTI was in fact even more effective than was detectable by the method used.

The specificity of inhibition of the KK system in brain edema by aprotinin or by aprotinin plus SBTI is another point that merits discussion. Although aprotinin inhibits trypsin and other proteases, no evidence has been provided yet as to whether trypsin, plasmin, or other enzymes influenced by the inhibitors are involved in posttraumatic swelling and vasogenic brain edema. As shown in Fig. 3, inhibition of swelling by aprotinin is unlikely to have resulted from decreased arterial blood pressure. Blood pressure was barely affected by the inhibitor. The current experiments do not directly assess inhibition of formation of kinins by aprotinin in damaged brain. Nevertheless, specific therapeutic effectiveness may be concluded from the high amounts of inhibitor found in plasma and in samples from focal and perifocal areas of injured brain tissue. Aprotinin concentrations in plasma of 125 KIU/ml or

$$P - P_1 \times 100,$$

FIG. 6. Flow chart showing the sequence of activation of the kallikrein-kinin (KK) system due to a primary cerebral injury. A primary insult triggers contact activation as the initial step of the intrinsic coagulation cascade resulting from exposure to negative surface charges, free collagen, etc. Factor XIIa (activated Hageman factor) is a prekallikreinase leading to activation of kallikrein as the final step necessary for the formation of kinins. The sites of inhibition of the cascade by aprotinin or by soybean trypsin inhibitor (SBTI) are the kinin-forming enzyme kallikrein and contact activation. Integration of the KK system with the network of coagulation and fibrinolysis, complement, and the arachidonic acid system is indicated. Thus, pathophysiological mechanisms elicited by kinins in the brain (for instance, vasodilation, opening of the blood-brain barrier (BBB), and brain edema) may be enhanced by additional factors associated with activation of the KK system.
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higher are considered to antagonize serum kallikrein completely. Such concentrations were present 1 hour after cold injury. The failure of SBTI to reduce edema may be attributed either to a deficient inhibition of kallikrein in cerebral tissue (SBTI is a predominant inhibitor of plasma kallikrein) or to disturbances of coagulation, for instance, as is reflected by a marked increase of PTT (Fig. 4). It has been shown that platelet inhibition enhances development of brain edema.

Figure 6 summarizes schematically the sequence of reactions triggered by the primary traumatic insult to the brain. Contact activation resulting from trauma stimulates formation of Factor XIIa from Hageman factor, which, as a prekallikreinase, catalyzes formation of kallikrein from prekallikrein, finally leading to the release of the highly active kinins. The sites of inhibition of this sequence by aprotinin or by SBTI are shown together with diverse interactions with the coagulatory and complement system and an activation of lipolysis. Formation of kinins in damaged brain as an ultimate step in the cascade induces a variety of secondary pathophysiological mechanisms such as cerebral vasodilation, enhancement of blood-brain barrier opening, and, finally, formation of brain edema. These same effects have been elicited in the brain by direct administration of kinins. An interaction with coagulation and fibrinolysis, complement, and formation of arachidonic acid and its metabolites integrates the KK system into a complex but highly active organization of blood and tissue mediators.

Conclusions

Specific inhibition of the KK system associated with a significant reduction of posttraumatic brain swelling can be viewed as the piece of evidence that has been missing for identification of kinins as mediators of secondary brain damage. There are only a few mediator candidates for which the evidence is as comprehensive as that of the KK system. Nevertheless, it is certainly unwarranted to believe the KK system is the only mediator in a process as complex as cerebral edema. It has been shown that arachidonic acid and its metabolites, glutamic acid, and others have the potential to cause damage, and that they are formed in nervous tissue under pathological circumstances. Yet, it is not known whether specific inhibition of these factors has a therapeutic function in cerebral injury. Our current experimental results have clear clinical implications because they demonstrate that the inhibition of a specific pathophysiological mechanism involved in the formation or enhancement of brain edema may be beneficial. The findings provide an experimental basis for a clinical trial.

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