Evidence for a Possible Role of the Brain Kallikrein-Kinin System in the Modulation of the Cerebral Circulation

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SUMMARY. Experiments by others have shown that exogenous bradykinin dilates cerebral arterioles and that the brain contains kininogen and kallikrein, the latter being the enzyme which converts kininogen to bradykinin. The objective of these experiments was to determine if bradykinin produced from endogenous brain kininogen can affect the cerebral microcirculation.

Rabbit pial arteriolar diameter was measured with a microscope using the closed cranial window technique. Topical application of bradykinin (10^{-8}-10^{-5} M) induced a dose-dependent vasodilation (8—46%) which was completely inhibited by the cyclooxygenase enzyme inhibitors indomethacin and meclofenamic acid. Topical application of 1 U of tissue kallikrein per milliliter of artificial cerebrospinal fluid induced 43% dilation, which could be prevented by local treatment with indomethacin or the proteinase inhibitor aprotinin. The action of aprotinin and indomethacin was specific, since aprotinin did not affect the dilation produced by bradykinin, and indomethacin did not affect dilation produced by adenosine. A second application of kallikrein had no effect on cerebral diameter, yet the arterioles still responded normally to exogenous bradykinin, indicating that the first application of kallikrein depleted brain kininogen. We suggest that activation of brain kallikrein and subsequent formation of kinin from brain kininogen may be important in modulation of cerebral blood flow or generation of cerebral edema. (Circ Res 57: 545–552, 1985)

BRADYKININ has been reported to exert a concentration-dependent relaxation of isolated cerebral vessels from a wide variety of species including the human (Toda, 1977; Wahl et al., 1983a), rabbit (Toda, 1977; Whalley et al., 1983), and cat (Wahl et al., 1983a, 1983b; Whalley and Wahl, 1983). Cerebral vasodilation has also been observed in situ cat pial vessels (Wahl et al., 1983a, 1983b; Kontos et al., 1984). It is known that bradykinin activates phospholipase A₂ and releases arachidonic acid, the precursor of prostaglandins, from membrane phospholipids (Nasjletti and Malik, 1979). In the renal, mesenteric, and coronary vasculature, the vasodilator response to bradykinin is mediated by the formation and action of prostaglandins (McGiff et al., 1972; Needleman et al., 1975; Blumberg et al., 1977; Cherry et al., 1982). Whether the in vivo cerebral arteriolar dilation in response to bradykinin is also due to prostaglandin generation has not been confirmed.

Many investigators have reported a bradykinin-like substance in the central nervous system (Hori, 1968; Correa et al., 1979; Perry and Snyder, 1984). Kinin-generating activity has been detected in homogenates of rabbit (Hori, 1968) and rat (Shikimi et al., 1973; Powers and Nasjletti, 1983) brain. Highest activity was found in the cerebral cortex, with less in the brain stem and cerebellum (Shikimi et al., 1973). Recently, using a monoclonal antibody against purified rat urinary kallikrein, Chao et al. (1983) have shown the existence of an endogenous tissue kallikrein in the central nervous system. Shikimi et al. (1973) have reported that kininogens are present in the rat brain, and kininase, the enzyme which inactivates bradykinin, has also been shown to be present in the brain (Hori, 1968; Shikimi and Iwata, 1970; Camargo et al., 1979; Kariya et al., 1981).

Whereas brain has been reported to contain bradykinin, kininogen, and kallikrein activity, and although the cerebral circulation dilates in response to exogenous bradykinin, it is uncertain whether the cerebral circulation can be influenced by bradykinin formed from endogenous brain kininogen. The purpose of this study was to begin to address the question of whether conversion of brain kininogen to bradykinin can influence the cerebral vasculature.

Methods

A total of 64 male New Zealand white rabbits weighing 2.9—4.4 kg were studied under anesthesia produced by sodium pentobarbital (25 mg/kg, iv), urethane (560 mg/kg, sc), and α-chloralose (38 mg/kg, sc). Supplemental doses of pentobarbital were given as needed to maintain anesthesia. Under this regimen of anesthetic agents, surgical anesthesia is quickly induced with a minimum of respiratory depression, and the need for administration of additional doses of pentobarbital is reduced.
After completion of a tracheotomy, each animal was ventilated with room air. The end-expiratory CO₂ of each animal was continuously monitored with an Anarad Inc. infrared CO₂ analyzer and was maintained at a level of approximately 34 mm Hg throughout each experiment by adjusting the respirator rate and volume. Arterial blood pressure was measured with a Statham P23Db pressure transducer connected to a cannula inserted into the left femoral artery. Arterial blood samples were periodically analyzed with an Instrumentation Laboratory blood pH-blood gas analyzer to ensure a normal range of PaCO₂, PaO₂, and blood pH.

Pial arterioles ranging in diameter between 30 and 94 μm were visualized by the previously described cranial window technique (Lavasseeur et al., 1975). The 12 mm in diameter cranial window was implanted on the midline just caudal to the suture connecting the frontal and parietal bones. Two to four vessels were studied in each animal using a Vickers image-splitting device according to the method described by Baez (1966). The cranial window was equipped with three openings. Two openings were used as an inlet and outlet for filling the space under the cranial window with test solutions. The third opening was connected to a Statham pressure transducer for continuous measurement of intracranial pressure. The intracranial pressure outlet of the window was connected to plastic tubing whose open end was placed at a fixed level to give a constant 5 mm Hg intracranial pressure throughout the experiment. The space under the window and the plastic tubing connected to it were filled with artificial cerebrospinal fluid (CSF) (Lavasseeur et al., 1975). This fluid was equilibrated with gas containing 6.6% oxygen, 5.9% carbon dioxide, and 87.5% nitrogen, which gives gas tensions and a pH in the normal range for CSF. The experiments were conducted using groups of three to nine animals.

Bradykinin triacetate, kallikrein (from porcine pancreas), aprotinin (from bovine lung), sodium-benzoyl-L-arginine ethyl ester (BAEE), sodium-benzyl-L-arginine (BA), adenosine, and indomethacin were purchased from Sigma Chemical Company, and meclofenamic acid was obtained from Parke-Davis. All of these reagents except indomethacin were directly dissolved in CSF. Meclofenamic acid stock solution (10 mg/ml) was made by dissolving in CSF. Bradykinin (0.8 nM to 8 μM) was applied in a cumulative manner (Fig. 3). As shown in Figure 3, topical application of high concentrations of bradykinin (0.8 nM to 8 μM) decreased pial arteriolar diameter. Aprotinin itself had no effect on pial arteriolar diameter in 18 arterioles in four rabbits. Aprotinin almost completely inhibited kallikrein-induced vasodilation. When we assayed this same ratio of kallikrein plus aprotinin spectrophotometrically in vitro, we found that the aprotinin inhibited kallikrein activity by 99%, indicating a good correlation between in vivo and in vitro inhibition of kallikrein activity. To determine whether aprotinin blockade of kallikrein-induced dilation was reversible, we flushed the aprotinin plus kallikrein from under the window and then reapplied kallikrein only. The arterioles responded markedly to kallikrein (1 KU/ml, Fig. 1) and slowly decreased up to 30 minutes. We suggest that the waning response to kallikrein may be due to depletion of kininogen and inactivation of bradykinin. To ensure that the kallikrein-induced vasodilation was due to enzyme activity, and not to a nonspecific activity, we determined the effect of kallikrein (1 KU/ml) on pial arterioles in the presence of aprotinin (30 KIU/ml, Fig. 2). Aprotinin is a proteinase inhibitor which is known to inhibit tissue kallikrein's conversion of kininogen to bradykinin. Aprotinin itself had no effect on pial arteriolar diameter in 18 arterioles in four rabbits. Aprotinin almost completely inhibited kallikrein-induced vasodilation. When we assayed this same ratio of kallikrein plus aprotinin spectrophotometrically in vitro, we found that the aprotinin inhibited kallikrein activity by 99%, indicating a good correlation between in vivo and in vitro inhibition of kallikrein activity. To determine whether aprotinin blockade of kallikrein-induced dilation was reversible, we flushed the aprotinin plus kallikrein from under the window and then reapplied kallikrein only. The arterioles responded markedly to kallikrein (1 KU/ml, Fig. 2); however, the maximum dilation at 2 minutes after kallikrein application was depressed, compared to the 2-minute post-kallikrein effect in preparations not previously treated with aprotinin (Fig. 1). This initially depressed dilation in response to kallikrein after aprotinin washout may be due to residual amounts of aprotinin that were not flushed from the cranial window chamber, or the fact that the first application of kallikrein produced some dilation and depletion of kininogen, despite the presence of aprotinin.

Effect of Cyclooxygenase Inhibitors on Bradykinin- or Kallikrein-Induced Dilation

Increasing doses of bradykinin were applied in a cumulative manner. As shown in Figure 3, topical application of bradykinin (0.8 nM to 8 μM) induced a concentration-dependent increase of pial arteriolar diameter. Aprotinin, at the same concentration used

Results

The mean arterial blood pressure in all animals was 82 ± 1 mm Hg (mean ± se) and therefore similar to that reported for unanesthetized rabbits (Aylward et al., 1983). Arterial blood gases and pH were; PaO₂, 90 ± 1 mm Hg; PaCO₂, 31 ± 0.3 mm Hg; and pH, 7.494 ± 0.008. Topical pial arteriolar administration of the various agents had no effect on systemic arterial blood pressure or blood gases and pH.

The Effect of Kallikrein on Pial Arterioles

The effect of two concentrations of porcine tissue (pancreatic) kallikrein was tested in two different groups of animals (Fig. 1). Kallikrein induced a concentration-dependent vasodilation of the cerebral arterioles. The kallikrein-induced vasodilation was maximal at 2 minutes after kallikrein application and slowly decreased up to 30 minutes. We suggest that the waning response to kallikrein may be due to depletion of kininogen and inactivation of bradykinin. To ensure that the kallikrein-induced vasodilation was due to enzyme activity, and not to a nonspecific activity, we determined the effect of kallikrein (1 KU/ml) on pial arterioles in the presence of aprotinin (30 KIU/ml, Fig. 2). Aprotinin is a proteinase inhibitor which is known to inhibit tissue kallikrein's conversion of kininogen to bradykinin. Aprotinin itself had no effect on pial arteriolar diameter in 18 arterioles in four rabbits. Aprotinin almost completely inhibited kallikrein-induced vasodilation. When we assayed this same ratio of kallikrein plus aprotinin spectrophotometrically in vitro, we found that the aprotinin inhibited kallikrein activity by 99%, indicating a good correlation between in vivo and in vitro inhibition of kallikrein activity. To determine whether aprotinin blockade of kallikrein-induced dilation was reversible, we flushed the aprotinin plus kallikrein from under the window and then reapplied kallikrein only. The arterioles responded markedly to kallikrein (1 KU/ml, Fig. 2); however, the maximum dilation at 2 minutes after kallikrein application was depressed, compared to the 2-minute post-kallikrein effect in preparations not previously treated with aprotinin (Fig. 1). This initially depressed dilation in response to kallikrein after aprotinin washout may be due to residual amounts of aprotinin that were not flushed from the cranial window chamber, or the fact that the first application of kallikrein produced some dilation and depletion of kininogen, despite the presence of aprotinin.

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FIGURE 1. The effect of topical application of kallikrein on rabbit pial arteriolar diameter. Data are the mean percent change ± SE in 18 arterioles in five rabbits for the 0.1 U/ml group (○) and 32 arterioles in nine rabbits for the 1 U/ml group (□). The control mean arteriolar diameter ± SE was 56 ± 3 μm for the 0.1 U/ml group, and 50 ± 2 μm for the 1 U/ml group.

Simultaneous topical application of indomethacin (3 μg/ml, 8.4 μM), a cyclooxygenase inhibitor, completely inhibited the effect of 0.8 μM or lower doses of bradykinin. The vasodilator response to 8 μM bradykinin was 80% inhibited by indomethacin. Indomethacin itself had no effect on pial arteriolar diameter (−0.5 ± 0.9%, mean ± SE of 16 arterioles in six rabbits). In order to demonstrate that the inhibitory effect of indomethacin was due to cyclooxygenase inhibition and not to a nonspecific effect of indomethacin, we also examined the effect of meclofenamic acid, another cyclooxygenase inhibitor which is structurally dissimilar to indomethacin. Meclofenamic acid itself at 3 μg/ml (9.4 μM) induced a slight (7 ± 3%) vasoconstriction in nine arterioles in three rabbits (P < 0.01 vs. vehicle, paired t-test). This new baseline diameter in the presence of meclofenamic acid was used to compute the effect of bradykinin in the presence of meclofenamic acid. Meclofenamic acid completely inhibited the effect of 0.8 nM to 8 μM bradykinin (Fig. 3), further implying that kallikrein-induced vasodilation is dependent on cyclooxygenase metabolism of arachidonic acid. Because of the 7% vasoconstriction produced by meclofenamic acid, we were concerned with the possibility that meclofenamic acid might be injuring the capacity of the arteriolar smooth muscle to re-

FIGURE 2. Aprotinin inhibition of kallikrein-induced pial arteriolar dilation. First aprotinin (30 KIU/ml) plus kallikrein (1 U/ml) was tested in 14 arterioles in five rabbits (△). The cranial window chamber was flushed with CSF, and kallikrein (1 U/ml) alone was applied (○). The control diameter before application of kallikrein plus aprotinin was 60 ± 6 μm and the control diameter before application of kallikrein, after washout of aprotinin, was 61 ± 6 μm.
respond to vasoactive agents. Therefore, after testing the effect of bradykinin plus meclofenamic acid, the meclofenamic acid was flushed from under the window and bradykinin reapplied. We found that the vasculature was still responsive to bradykinin.

Pial arteriolar dilation induced by topical application of kallikrein (1 KU/ml) was also depressed during topical co-treatment with indomethacin (Fig. 4). These data imply that kallikrein produces vasodilation via kallikrein conversion of endogenous kininogen to bradykinin, with subsequent bradykinin stimulation of cyclooxygenase enzyme activity and vasodilation. An alternative explanation of these results might be that indomethacin non-specifically blocks the vasodilation induced by kallikrein or bradykinin. We therefore examined the effect of the same concentration of indomethacin on adenosine, another known dilator of cerebral arterioles (Wahl and Kuchinsky, 1976). As shown in Figure 5, indomethacin did not alter the dilator response to adenosine, further implying that indomethacin's inhibition of kallikrein- and bradykinin-induced dilation was due to the specific cyclooxygenase inhibitory activity of indomethacin.

Kallikrein Depletion of Brain Kininogen

In tests to determine whether the kininogen acted upon by exogenous kallikrein was in the brain or blood, kallikrein was applied repeatedly (Fig. 6). Our rationale for this approach was that topical application of kallikrein would deplete brain kininogen but not plasma kininogen. The first kallikrein appli-
cation was kept on the brain surface for 30 minutes and then was washed out with artificial CSF. Thirty minutes after washout, the same concentration of kallikrein was again applied. Whereas the first kallikrein application induced a marked vasodilation of pial arterioles, the second kallikrein application had no effect. To determine whether the lack of response following the second application of kallikrein might be due to development of tachyphylaxis to bradykinin, we tested the effect of bradykinin 30 minutes after washout of the second dose of kallikrein. We found that bradykinin still induced a dose-dependent vasodilation, implying that the lack of response after the second application of kallikrein is due to depletion of the kininogen and not to tachyphylaxis to bradykinin.

Discussion

Whereas previous studies have shown that exogenous bradykinin induces relaxation of cerebral arteriolar smooth muscle, the present study is the first to provide evidence that conversion of endogenous brain kininogen to bradykinin is capable of altering cerebral vascular resistance. This conclusion is supported by several lines of evidence. First, the literature supports the existence of endogenous brain kininogen, kallikrein, and bradykinin. Second, the effects of exogenous bradykinin are mimicked by kallikrein. Third, agents which specifically prevent bradykinin-induced dilation also prevent kallikrein-induced dilation.

Brain bradykinin has been demonstrated by a
number of investigators (Hori, 1968; Correa et al., 1979; Perry and Snyder, 1984), yet our understanding of its exact cellular distribution and function in the brain is incomplete. Brain bradykinin is likely formed within the brain, since it is known that circulating bradykinin has a very short plasma half-life. In addition, the necessary components for formation of bradykinin by the brain have been demonstrated. Recently, Chao et al. (1983) have used a monoclonal antibody to rat urinary kallikrein, which is a tissue kallikrein, to demonstrate the existence of tissue kallikrein in the rat brain. They found that brain kallikrein is identical to urinary kallikrein and that brain kallikrein can be synthesized by brain messenger RNA. Kininogen, the substrate for kallikrein, has also been reported in rat brain (Shikimi et al., 1973). However, Maier-Hauff et al. (1984) could not detect kininogen in the normal cat brain. This discrepancy in the ability to demonstrate kininogen may be due to species differences, or perhaps differences in the techniques used to detect kininogen. Since our results imply that brain kininogen can easily be depleted we suggest that differences in the capability to demonstrate brain kininogen may be due to varying depletion of kininogen during tissue preparation prior to the measured procedure.

Our results confirm previous observations that bradykinin is a powerful dilator of the cerebral arterial vasculature. For technical reasons, our observations have been limited to the pial vessels in one area of the cerebral cortex. Therefore, we cannot say with certainty that deeper vessels or pial vessels in all parts of the brain behave similarly. However, since bradykinin has been reported in all brain areas (Perry and Snyder, 1984), there is no compelling reason to exclude this possibility. In addition, our data show that bradykinin-induced vasodilation occurs as the result of cyclooxygenase activity, since both indomethacin and meclofenamic acid, structurally dissimilar cyclooxygenase inhibitors, blocked bradykinin-induced vasodilation. Our finding of prostaglandin mediation of bradykinin-induced cerebral arteriolar dilation is highly consistent with the literature on this interrelationship, since bradykinin has been shown to induce vascular smooth muscle relaxation by prostaglandin-dependent mechanisms in the heart, mesentery, and kidney (McGiff et al., 1972; Needleman et al., 1975; Blumberg et al., 1977; Cherry et al., 1982). Bradykinin has also been shown to stimulate prostaglandin formation in vitro (Hong and Deykin, 1982).

Several candidates exist with respect to the particular prostaglandin which induces pial arteriolar vasodilation. In our previous studies (Ellis et al., 1979), we demonstrated that exogenous Prostacyclin (PGI₂), Prostaglandin E₂ (PGE₂), and Prostaglandin G₂ (PGG₂) are capable of inducing a 33%, 44%, and 56% dilation of cat cerebral arterioles, respectively, at 3 x 10⁻⁵ M. This demonstrates that prostaglandins are indeed capable of inducing the degree of vasodilation reported in the current study. The work of Kontos et al. (1984) shows that oxygen-free radicals, formed during the cyclooxygenase metabolism of arachidonic acid, may also be contributing to bradykinin-induced vasodilation. They showed that bradykinin-induced dilation of cat cerebral arterioles is reduced by the free radical scavengers catalase and superoxide dismutase.

In our experiments, indomethacin blocked the effect of topically applied tissue kallikrein. Since we were interested in determining whether bradykinin produced from brain kininogen, as opposed to bradykinin produced from plasma kininogen, was acting on the cerebral circulation, we chose to use tissue kallikrein, which differs from plasma kallikrein. Our data (Fig. 2) also show that we were able to attain a major inhibition of the activity of exogenous tissue kallikrein with aprotinin. The observations that aprotinin itself had no effect on diameter, that aprotinin did not affect the dilator response to bradykinin, and that a large dilation occurred in response to kallikrein after washout of the aprotinin, are evidence that the aprotinin was specifically inhibiting the effect of kallikrein on kininogen.

With respect to the location of the kininogen that was acted upon by exogenous kallikrein, we reasoned that the local stores of kininogen in the brain would be limited and perhaps easily depleted, whereas kininogen in the blood, which is rich in plasma kininogens, would not be depleted by the relatively large, nondiffusible kallikrein molecule applied locally on the brain surface. Our finding that the second kallikrein application had no effect on diameter suggested two possibilities: first, that the brain kininogen was indeed depleted, or, second, that the vasculature was tachyphylactic to bradykinin. A subsequent normal response to bradykinin following the second application of kallikrein showed that tachyphylaxis to bradykinin did not occur under these treatment conditions.

An additional line of reasoning indicates that the blood plasma is not the source of the kininogen and, in fact, suggests that the kininogen may be located in or near the vascular wall. As reviewed by Pashinska and Levitsky (1979), if all the kininogen present in normal rabbit plasma is converted to bradykinin, the maximum attainable plasma concentration of bradykinin is approximately 10⁻⁷ to 10⁻⁶ M. From our results (Fig. 3), it can easily be seen that this concentration of bradykinin will produce approximately 20–28% dilation of cerebral arterioles. Since kallikrein (1 KU/ml) induced over 44% dilation (Fig. 1), this provides additional evidence that the arteriolar dilation in response to kallikrein cannot be due merely to the conversion of plasma kininogen to bradykinin. Because the dilation produced by kallikrein is approximately equal to that produced by 10⁻⁵ M bradykinin, at least an equally high molar concentration of kininogen must exist in close proximity to the vascular bradykinin receptors. Since it
would seem unlikely that such a high concentration of kininogen would exist in all parts of the brain, we suggest that the kininogen may be concentrated in the vascular wall or in close proximity to the vascular wall. Nolly et al. (1981) have demonstrated kallikrein activity in mesenteric arteries; however, to our knowledge, bradykinin or kininogen levels have not been examined in cerebral vascular tissue. We caution, however, that since we have not measured kininogen or kinins directly, we cannot say with absolute certainty that kallikrein-induced dilation is due to the formation of bradykinin. It may be that kallikrein is stimulating cyclooxygenase-dependent dilation by some other, unknown mechanism. Evidence for this possibility does exist, since kallikrein has been shown to stimulate endothelial cell 6-keto-PGF1α formation (Morita et al., 1984) and uterine smooth muscle contraction (Chao et al., 1981) by a mechanism which is not understood, but does appear to be independent of bradykinin formation.

Whether brain bradykinin can regulate blood flow in the normal brain remains untested; however, several lines of evidence suggest that it may be important in brain injury and inflammation or vascular headache. Following acute hypertension or experimental fluid-percussion brain injury in cats, the cerebral arterioles dilate, become unresponsive to arterial hypoxia, and display endothelial lesions (Kontos et al., 1981). In addition, free radical generation (Wei et al., 1981) and increased prostaglandin synthesis (Ellis et al., 1981) are known to occur after these insults. Pretreatment of cats with cyclooxygenase inhibitors or free radical scavengers prevents this triad of arteriolar abnormalities, indicating that oxygen-free radicals produced in association with increased arachidonate metabolism are responsible for this pathology (Wei et al., 1981). The signal which stimulates cyclooxygenase metabolism of arachidonate is unknown. We hypothesize that activation of endogenous kallikrein-kininogen complex and formation of bradykinin causes brain edema. Bradykinin injected intraventricularly into the brain has been shown to have only a 30-second half-life (Kariya et al., 1981). We suggest that in vivo generation of bradykinin by low concentrations of kallikrein may provide more information on the role of bradykinin in the generation of edema and increased vascular permeability. In fact, our unpublished pilot data support such an approach. Maier-Hauf et al. (1984) have reported increased amounts of kininogen in perifocal edematous brain following induction of experimental cold injury. They proposed that the kininogens in injured brain were derived from blood, perhaps as a result of blood-brain barrier breakdown. Since development of cold injury-induced edema requires several hours, one might also consider local induction of protein synthesis and formation and action of brain kallikrein and kininogen. In fact, their very recent data support such a proposal, since they have found that treatment with aprotinin, but not treatment with soybean trypsin inhibitor, an inhibitor which is more specific for plasma kallikrein, decreases edema after experimental cold-injury of the brain (Unterberg et al., 1984).

Migraine, or vascular, headache has been hypothesized by some investigators to be caused by cerebral arterial dilation and stimulation of pain receptors associated with the vasculature (Caviness and O’Brien, 1980). Cyclooxygenase inhibitors such as aspirin and indomethacin often provide relief from headaches, and in one type of cluster headache, indomethacin has been reported to provide relief in 85% of the patients studied (Medina and Diamond, 1981). Also, it is well known that bradykinin can sensitize or stimulate pain receptors (Clark, 1979). These facts and our current results lead us to hypothesize further that conversion of endogenous brain kininogens to bradykinin, with resultant bradykinin-induced cerebral arterial dilation and bradykinin stimulation of pain fibers, may be involved in the etiology of vascular headache.

In summary, our results provide evidence that formation of kinins from endogenous brain kininogens can influence cerebrovascular resistance. Experiments aimed at determining the possible role of kinins in the regulation of blood flow in the normal brain are yet to be performed; however, the literature and our results suggest the possibility that endogenous brain kinins may be critical mediators of cerebrovascular events associated with brain injury or headache.

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