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 indomethadn 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 lwata, 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.
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: P_{O_2}, 90 ± 1 mm Hg; P_{CO_2}, 31 ± 0.3 mm Hg; and pH, 7.494 ± 0.008. Topical pial arteriolar application 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 89%, 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
to inhibit kallikrein activity (Fig. 2), had no effect on bradykinin-induced dilation. This demonstrates that aprotinin's inhibition of kallikrein-induced dilation is specific, and not due to aprotinin inhibition of bradykinin-induced dilation.

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-
Concentration (M)

spond 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-
Kamitani et al. / Kallikrein-Induced Cerebral Vasodilation

FIGURE 5. The effect of indomethacin on adenosine-induced pial arteriolar dilation. The effect of adenosine alone (O) was studied in nine arterioles in three rabbits where the control diameter of the arterioles was 52 ± 3 μm. The effect of adenosine in the presence of indomethacin (Δ: 3 μg/ml) was studied in another group of four rabbits where the control pial arteriolar diameter of 10 arteries was 64 ± 5 μm. The results clearly show that this concentration of indomethacin has no effect on adenosine-induced dilation, and therefore imply that indomethacin is not a nonspecific inhibitor of cerebral arteriolar dilation.

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...
are indeed capable of inducing the degree of vaso-
56% dilation of cat cerebral arterioles, respectively,
at 3 \times 10^{-5} \text{ M}. This demonstrates that prostaglandins
ular prostaglandin which induces pial arteriolar vas-
relaxation by prostaglandin-dependent mechanisms
have 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
message RNA. Kininogen, the substrate for kalli-
krein, 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 kini-
gen may be due to species differences, or perhaps
differences in the techniques used to detect kinino-
gen. 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 ob-
servations 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 oc-
curs as the result of cyclooxygenase activity, since
both indomethacin and meclofenamic acid, structur-
ally dissimilar cyclooxygenase inhibitors, blocked
bradykinin-induced vasodilation. Our finding of
prostaglandin mediation of bradykinin-induced cer-
bral 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 partic-
ular prostaglandin which induces pial arteriolar vas-
odilation. 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 $3 \times 10^{-5}$ \text{ M}. This demonstrates that prostaglandins
are indeed capable of inducing the degree of vaso-
dilation 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 kalli-
krein. Our data (Fig. 2) also show that we were able
to attain a major inhibition of the activity of exogene-
tous tissue kallikrein with aprotinin. The observa-
tions 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 in-
hibiting the effect of kallikrein on kininogen.

With respect to the location of the kininogen that
was acted upon by exogenous kallikrein, we rea-
soned 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 brady-
kinin. A subsequent normal response to bradykinin
following the second application of kallikrein
demonstrated 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 Pash-
inska and Levitsky (1979), if all the kininogen pres-
ent in normal rabbit plasma is converted to brady-
kinin, the maximum attainable plasma concentration
of bradykinin is approximately $10^{-7}$ to $10^{-6}$ \text{ M}. From
our results (Fig. 3), it can easily be seen that this
concentration of bradykinin will produce approxi-
ately 20–28% dilation of cerebral arterioles. Since
kallikrein (1 KU/ml) induced over 44% dilation (Fig.
1), this provides additional evidence that the arteri-
olar dilation in response to kallikrein cannot be due
merely to the conversion of plasma kininogen to
bradykinin. Because the dilation produced by kali-
krein is approximately equal to that produced by
$10^{-5}$ \text{ M} bradykinin, at least an equally high molar
concentration of kininogen must exist in close prox-
imity 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 hypocapnia, 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 with resultant generation of bradykinin may be one of the links between the damaging insult and the stimulation of arachidonate metabolism.

Moreover, the kallikrein-kinin system may play a role in the generation of vasogenic brain edema (Czermicki, 1979; Unterberg and Baethmann, 1984; Maier-Hauf et al., 1984). Unterberg and Baethmann (1984) have shown that intraventricular infusion of bradykinin causes brain edema. However, 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 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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