Vasoconstrictor Effect of Angiotensin on Pial Arteries

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SUMMARY The effect of topical application of angiotensin on pial arterioles was examined in anesthetized cats equipped with a cranial window for the direct observation of the pial microcirculation of the parietal cortex. Angiotensin in a dose of 0.01 to 1 µg/ml constricted pial arterioles and arteries strongly. The response of the smaller vessels was greater than that of the larger ones. Intravenous administration of angiotensin in a dose of 0.04-3.8 µg/min raised arterial blood pressure and constricted the larger pial arteries. While the infusion of angiotensin was continued at the same dose, the blood pressure was then reduced to the control level via bleeding into a reservoir. This abolished the vasoconstriction of the larger pial arteries, showing that this effect was due to autoregulatory adjustments to the rise in blood pressure and not due to a direct effect of angiotensin. We conclude that, despite the strong constrictor effect of angiotensin on pial arteries, intravenous angiotensin can be used to study the effects of arterial hypertension on the cerebral circulation.

ANGIOTENSIN has been used extensively to study the effects of raised arterial blood pressure on cerebral blood flow and cerebral vascular resistance as well as on pial vessel caliber.1-4 The use of angiotensin for this purpose is predicated on the premise that it does not have a direct vasoconstrictor effect on cerebral vessels, presumably because it does not cross the blood-brain barrier. This assumption is based on considerable, though indirect, evidence.1,2,4 To our knowledge the direct effect of angiotensin on cerebral vessels in vivo has not been studied.

We report here results which show that angiotensin has a strong vasoconstrictor effect on pial arteries of the anesthetized cat.

Methods

Experiments were carried out in 10 cats, weighing 2.3-4 kg and anesthetized with intravenous sodium pentobarbital (30 mg/kg). The animals were subjected to skeletal muscle paralysis with decamethonium (0.4 mg/kg i.v.) and were ventilated with a positive pressure respirator connected to a tracheostomy tube. The end-expiratory CO2 was monitored with a CO2 analyzer and was maintained at a constant level of about 35 mm Hg throughout the experiment by adjusting the respiratory rate and volume. Arterial blood pressure was measured with a Statham P23Db pressure transducer connected to a cannula introduced into the aorta through the femoral artery. Arterial blood samples were periodically collected for the determination of PCO2, PO2, pH and hematocrit. Blood gases and pH were determined with Radiometer electrodes. Hematocrit was measured with a micromethod. The mean ± (SE) PaCO2 for all the animals studied was 34.9 ± 0.9 mm Hg.

Pial precapillary vessels were visualized through a cranial window acutely implanted just distal to the fronto-parietal suture. The cranial window technique was described in detail previously.5 One of the window outlets was connected to a Statham strain-gauge for continuous measurement of intracranial pressure. The latter was maintained constant at 7 mm Hg throughout the experiment by connecting a second outlet of the window to plastic tubing whose free end was placed at a fixed height. Arterial vessel diameter was measured with a Vickers image-splitting device, closed-circuit TV camera and monitored according to the method described by Baez.7 The space under the cranial window and the plastic tubing connected to it were filled at the beginning of the experiment with artificial CSF having composition identical to normal CSF for cats.8 This fluid was equilibrated with gas containing 6% oxygen, 6.5% CO2 and 87.5% nitrogen to give gas tensions and pH in the normal range for CSF of cats. Angiotensin II amide was dissolved in artificial CSF and equilibrated with the gas mixture described above at 37°C in a water bath. Following equilibration the solutions were stored at 37°C until used.

Two types of experiments were carried out. In the first type, carried out on 5 cats, the effect of angiotensin applied topically on pial arterial caliber was studied. Artificial CSF containing 0, 0.01, 0.1 and 1 µg/ml of angiotensin was used to perfuse the space under the cranial window while measurements of vessel caliber were made. Multiple vessels, covering the range from 30 to 300 µ in diameter, were selected for measurement. The angiotensin solution was infused at the rate of 3.8 ml/min for a sufficiently long period of time to allow the establishment of a steady state. Diameter measurements during the infusion of CSF containing no angiotensin were used as the control values.

The second series of experiments was carried out in 5 cats. In this series, control measurements of the diameter of larger pial arteries, which respond to increases in arterial blood pressure with definite and reproducible reduction in diameter, were made prior to infusion of angiotensin. Subsequently, angiotensin was infused intravenously at a rate of 0.04-3.8 µg/min until a steady level of vessel caliber was achieved. Thus, while angiotensin infusion was continued at the same rate, the animal was bled into a reservoir con-
Results

Fig. 1 shows that angiotensin applied topically had a dose dependent vasoconstrictor effect on pial arterioles and arteries. At the lowest dose used the effect was the same irrespective of vessel size, but at the 2 higher concentrations the response of the smaller vessels was greater than that of the 2 groups of larger vessels. Mean arterial blood pressure averaged 114 ± 9.9 mm Hg before the application of angiotensin and did not change significantly during infusion of angiotensin at any of the doses used. In none of the animals was there more than a 10 mm Hg alteration in blood pressure from the control value. Fig. 2 shows the results of the experiments in which angiotensin was infused intravenously. We deliberately selected vessels of larger size for this study, because these are the vessels which show the larger and most consistent constriction when blood pressure rises. Angiotensin was infused at a dose sufficient to raise arterial blood pressure to about 170 mm Hg, where the maximum pial arterial vasoconstriction was observed by us previously in this preparation. Vessels observed in this study constricted by 7% in response to the rise in arterial blood pressure induced by angiotensin. When the blood pressure was lowered to the pre-infusion level by bleeding, while angiotensin infusion was continued, vessel diameter returned to the control value. This occurred in the absence of any significant change in arterial blood gases.

Discussion

The results show clearly that angiotensin constricts pial precapillary vessels strongly. The effect of angiotensin is more pronounced on the smaller pial arterioles than on larger ones. A similar greater constrictor effect of angiotensin on smaller arterioles has been observed in the mesentery of the cat. It is of interest that the vasoconstrictor effect of angiotensin on the smaller vessels is greater than the effect of reduction in the arterial blood Pco₂ to 10–15 mm Hg, or the vasoconstrictor effect of local severe alkalosis with CSF pH at 8.15. The effectiveness of angiotensin as a vasoconstrictor of pial arterioles contrasts with the inability of norepinephrine to constrict the smaller pial arterioles even when used at an exceedingly high concentration. The larger pial arteries do constrict in response to norepinephrine, but their response to this agent is also less pronounced than to angiotensin.

Altura obtained dose-response curves for the vasoconstrictor effect of angiotensin on mesenteric arterioles of the rat. Comparison of the present findings with his results shows that angiotensin is approximately 10 times less effective as a vasoconstrictor.
degradation in the blood stream, barely reaches a level where significant vasoconstriction of the pial arterioles. There are 2 reasons for the lack of a direct effect of intravenous angiotensin on pial arterioles. The first is that because of its strong vasoconstrictor action on the other vascular beds, its concentration in the blood stream, even at the highest infusion rates used in the present experiments and assuming no significant degradation in the blood stream, barely reaches a level where significant vasoconstriction of the pial arterioles would be expected. A second, and perhaps more important reason, is that the peptide, as pointed out by Joy, may not be able to penetrate the blood-brain barrier. Although no direct evidence exists regarding the ability of angiotensin to pass across the blood-brain barrier, it is well known that polar, non-lipid soluble compounds, in general, cross this barrier poorly. In addition, a similar polypeptide, vasopressin, has been shown not to cross the blood-brain barrier. Although direct effects of circulating angiotensin on the central nervous system have been demonstrated, these are exerted on areas of the brain which lack a blood-brain barrier, such as the area postrema and the hypothalamus. We emphasize that, although angiotensin does not seem to have direct action on cerebral vessels in the doses employed here, the potential for such action exists. It is possible for this action to materialize under conditions of a breakdown on the blood-brain barrier, or in prolonged experiments where, because of the development of tachyphylaxis, very high concentrations of angiotensin are used.

Acknowledgment

This work was supported by grants HL-14251 and HL-21851 from the NHLI and by contract DAMD17-74-C021 from the U.S. Army Research and Development Command.

Dr. Patterson is the recipient of a Research Career Award from the NHLI.

References

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Stroke. 1978;9:487-489
doi: 10.1161/01.STR.9.5.487

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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