SUMMARY  Diazoxide failed to safely relieve cerebral vasospasm in monkeys despite in vitro documentation of arterial relaxation with this agent. Administration of the drug frequently produced hypotension and, in the presence of vasospasm, was associated with a high mortality rate.

Introduction

CEREBRAL VASOSPASM is a common, frequently devastating sequela of subarachnoid hemorrhage. In this laboratory it has been shown that pretreatment with reserpine or Kanamycin protects dogs and monkeys from the development of vasospasm. However, clinical drug trials designed to reverse established vasospasm have been disappointing. Diazoxide, a rapidly acting non-diuretic benzothiadiazine derivative, has been used extensively in the treatment of hypertensive emergencies. It has been shown that diazoxide reverses the contractions produced in isolated vascular segments by agents with such diverse mode of action as norepinephrine, vasopressin and barium chloride and that the action of diazoxide is not modified by beta-blockade with propranolol; therefore, it has been postulated...
that diazoxide acts at a locus closer to the final common pathway of smooth muscle contraction. At present the two most tenable hypotheses are that diazoxide acts as a specific phosphodiesterase inhibitor and thus allows for an increase in cyclic AMP which may mediate in the process of relaxation, or, alternatively, that diazoxide may compete with calcium for membrane sites where the cation is required for contraction. In clinical practice, diazoxide usually does not lower systolic blood pressure below normotensive levels and experimentally it appears that it is effective in reducing systemic arterial pressure in rats with artificial hypertension. This implies that the action of diazoxide may be more pronounced in abnormally "spastic" vascular beds. These pharmacological properties suggested that diazoxide could be a useful agent in the treatment of established cerebral vasospasm.

Methods

Two different experiments were conducted. In one, anesthetized mongrel dogs weighing 15 to 25 kg were used, as described in a previous report. Following control vertebral angiography, vasospasm was induced by cisternal injection of blood as described by Kuwayama and Zervas. The presence of spasm was confirmed by a second vertebral angiogram. Diazoxide was then injected in the cisterna magna at a dose of 5 mg per kilogram and follow-up angiograms were obtained at hourly intervals for four hours.

In the second experiment five rhesus monkeys weighing 4 to 6 kg were used. Following control carotid angiograms transorbital puncture of the middle carotid artery was carried out as described by Roy et al. After confirming the presence of spasm by a second carotid angiogram, diazoxide was injected in the ipsilateral internal carotid artery at a dose of 2.5 mg per kilogram of body weight, and after demonstration of persistent spasm, at a dose of 5 mg per kilogram. Preliminary experiments had indicated that the animals would tolerate 2.5 mg per kilogram without significant change in systemic blood pressure, whereas 5 mg per kilogram was usually associated with a 20% to 40% fall in mean systemic arterial pressure. Follow-up carotid angiograms were obtained hourly for four hours and at 18 hours in the one surviving animal. Systemic blood pressure was recorded continuously throughout the first few hours of the experiment from a femoral arterial catheter connected to a strain gauge.

Results

Severe vasospasm was consistently produced in all animals. It was more severe in the basilar artery and its branches in the dogs and in the ipsilateral internal carotid artery and its branches in the monkeys. In the dogs, relief of the spasm was evident only in the most proximal portions of the arterial tree where the highest concentration of diazoxide would be expected. However, the animals invariably had respiratory irregularities and hypotension and all died within the first 18 hours. In the monkeys, intracarotid diazoxide failed to produce any relief of the spasm, which persisted unchanged throughout the experiment in all cases. Four of the five monkeys died overnight; in two, hemiparesis had become obvious after the second injection of diazoxide. The higher dose of diazoxide usually produced hypotension within seconds of injection to a mean systemic pressure of approximately 60% to 70% of control value. The blood pressure gradually returned to normal over a one-hour period.

Discussion and Conclusions

Although no control animals were used specifically for these experiments, in previous experiments the large majority of the animals survived subarachnoid hemorrhage without permanent ill effects. Since the doses of diazoxide used in the experiments were previously found to be safe in intact animals, we infer that diazoxide must be peculiarly toxic to animals with severe cerebral vasospasm. We suspect that the hypotension induced by the higher intracarotid dose and the single intracisternal injection was the most important factor responsible for the poor survival of our animals. Fein and Boulos have found evidence of breakdown of cerebral autoregulation in some animals with severe vasospasm, and if this occurs the additional decrease in cerebral perfusion pressure during the hypotensive state may well not be tolerated. The development of hemiparesis in two of our monkeys specifically during the hypotensive period strongly implicates hypotension as a factor responsible for the deterioration of the animals. The high pH of diazoxide (11.6) may account for some of its toxicity by the intracisternal route. We were unsuccessful in our attempts to lower the pH with a buffer volume sufficiently small for intracisternal injection without producing crystallization of the compound. The relief of spasm observed after subarachnoid injection of diazoxide in those dependent arterial segments about which the drug would be expected in higher concentrations suggests that topical diazoxide is effective in relieving vasospasm. This indeed had been our previous finding in an in vitro experiment designed to test the effect of several drugs applied topically to arterial segments after strong contractions were produced by serotonin, blood, and norepinephrine. The ineffectiveness of intra-arterial diazoxide may be related to its inability to cross the blood-cerebrospinal fluid barrier and interact with the vascular smooth muscle membranes at the "other side" of the barrier. We have documented a similar gradation of action of papaverine with intracisternal administration being more effective in reversing vasospasm other than intra-arterial injection.

Although our results with diazoxide were consistent enough to discourage a broader, better controlled study with this drug, we feel that in view of the almost certain multifactorial etiology of vasospasm it is appropriate to continue to test in the laboratory agents that, like diazoxide, act at a locus in the contractile process distal to all the commonly implicated spasmodenic factors such as catecholamines, serotonin and prostaglandins.

References

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Hypertension as an Important Factor for Cerebrovascular Atherogenesis in Rats

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SUMMARY A new model for studies on atherogenesis in the cerebrovascular system was obtained by using recently established stroke-prone spontaneously hypertensive rats (SHRSP). SHRSP on a hypercholesterolemic diet (20% suet, 5% cholesterol, and 2% cholic acid) had ring-like fat deposits in the circle of Willis, which were detected within a few weeks by new techniques for the macroscopical demonstration of fat deposits "as a whole" and were proved to be good quantitative indices for the initiation of atherogenesis.

Introduction
EMPHASIS has been placed on atherosclerosis in the cerebrovascular system for the etiology and pathogenesis of stroke in man, but a suitable experimental model for the study of cerebral atherosclerosis related to stroke has not yet been obtained. Above all, rats rarely have atherosclerosis or arterial fat deposition in cerebral vessels, even when on a hypercholesterolemic diet for a long period of time. However, spontaneously hypertensive rats (SHR), especially the strain of SHR, were noted to be exceptionally susceptible to arterial fat deposition. The successful establishment of stroke-prone spontaneously hypertensive rats (SHRSP) in more than 80% of which cerebrovascular lesions developed spontaneously, prompted us to try experimental atherogenesis in this new strain. An extremely rapid development of ring-like fat deposition in the mesenteric vessels of SHRSP on a high-fat cholesterol (HFC) diet was reported by Yamori. The significance of this model for the study of the pathogenetic mechanism of atherosclerosis was investigated. In the present study, we examined the arterial fat deposits in the circle of Willis and basilar arteries in SHRSP on an HFC diet and confirmed the importance of hypertension as the most influential factor on fat deposition in the major cerebral intracranial arteries.

Methods
SHR and SHRSP were F12-14 generations of the original colony of SHR kept in the Department of Pathology, Faculty of Medicine, Kyoto University. These SHRSP were the offspring, one or both parents of which died with cerebral lesions for the preceding six or seven generations. Blood pressures were more than 200 to 210 mm Hg in adult rats (more than four months of age). Normotensive rats of the Wistar-Kyoto strain (WK), from which SHRderived, were used as control rats. Renal infarction hypertension was produced in the WK rats soon after the weaning period or at the age of 30 days. Six SHRSP and seven WK rats were treated at the age of 40 days and thereafter with an antihypertensive agent, Apresoline (8 mg/dl in drinking water).

More than 200 rats including SHRSP, experimental hypertensive rats (renal infarction hypertension) and WK rats, fed a hypercholesterolemic diet with 1% salt in the drinking water for 1 week, 2 weeks, 10 weeks and more than 10 weeks, revealed that the arterial fat deposition in the brain was affected by BP, serum cholesterol level, strain difference and age. High BP was confirmed to be more important than the other factors by the quantitative analysis of sudanophilic rings in relation to BP.
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R C Heros, M H Lavyne and N T Zervas

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