Experimental evaluation of the spasmogenicity of dopamine on the basilar artery

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Arteriograms of the basilar artery reveal that dopamine given intracisternally to dogs can generate cerebral vasospasm. This finding supports a recent hypothesis of others that dopamine may play a role in the pathogenesis of vasospasm, especially since many substances are known which fail to produce such spasm. Compared to blood or prostaglandin E₂, however, the spasm induced by dopamine was delayed in onset, less in incidence, and usually less intense. Possible explanations for such experimental differences are discussed.

KEY WORDS · cerebral vasospasm · dopamine · prostaglandin E₂

Experimental studies indicate that a large number of substances could be responsible for the phenomenon of cerebral vasospasm. Prominent among these are an unknown platelet factor, prostaglandins, and serotonin. Recently Wurtman and Zervas conjectured that dopamine might be the cause of this phenomenon and that blockade of dopaminergic receptors might be of clinical value in the initial treatment of stroke. These authors suggested that monoamines might be released from damaged neurons in sufficient quantity to compromise cerebral circulation. The loss of dopamine ipsilaterally in animals subjected to unilateral ischemia and the turning movements observed in such animals were considered evidence that dopamine was released to produce excitation. Such a loss of brain dopamine could be associated with abnormal amounts in the cerebrospinal fluid (CSF) which in turn might engender a vasospasm. To test this hypothesis, the present study was performed with a procedure used by many authors to reveal the spasmogenicity of substances suspected of being involved in the genesis of cerebral vasospasm.

Methods and Materials

Mongrel dogs of both sexes were anesthetized with pentobarbital sodium (30 mg/kg) intravenously and given additional amounts as needed. Tracheostomy and the recording of femoral blood pressure and respiratory rate were performed routinely. Single x-ray films of the basilar artery and posterior portion of the circle of Willis were obtained by the rapid injection of 5 ml of Hypaque 60 into the right vertebral artery where it enters the transverse foramen. Several x-ray films were obtained before and at 5, 15, 30, and 60 minutes after the injection.
Fig. 1. Arteriograms obtained before (left) and 60 minutes after (right) injection of dopamine into the cisterna magna. Mild spasm of the basilar artery can be seen (arrows). Dopamine was mixed in 2 ml of CSF at a concentration of $1 \times 10^4$M prior to injection.

of experimental substances into the cisterna magna and hourly thereafter for at least 3 hours. These substances were administered by means of an 18-gauge spinal needle. Further details of the procedures used have been published elsewhere.*

Three experimental substances (blood, dopamine, and prostaglandin $E_2$) were compared for spasmogenicity and administered in the following manner. First, 2 ml of CSF was collected from the cisterna magna. In the experiments using blood, this CSF was discarded and 2 ml of autogenous arterial blood injected intracisternally. In experiments using dopamine hydrochloride* and prostaglandin $E_2$† concentrated stock solutions were prepared. From these, 0.2 ml was added to 1.8 ml of CSF. Thus, all animals in each group of experiments shown in Table 1 received equimolar doses of the agents studied. Prostaglandin (PG) $E_2$ was initially dissolved in 95% ethanol of which 0.1 ml, containing 500 mg of PGE$_2$, was added to 13.6 ml of saline and used as the stock solution. The molar dosage for dopamine was computed from the active base. The degree of spasm of the basilar artery was independently assessed by the authors, quantified by use of a standard comparator‡ and with a surgical microscope.

Results

Dopamine, in the doses studied, generated cerebral vasospasm in approximately 60% of the animals (Table 1). This spasm was mild in

*Dopamine hydrochloride supplied by Nutritional Biochemicals Corporation, Cleveland, Ohio 44128.
†Prostaglandin $E_2$ supplied by courtesy of Dr. John E. Pike, Upjohn Pharmaceutical Co., Kalamazoo, Michigan 49001.
‡Comparator manufactured by Edmond Scientific Company, Barrington, N.J.
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FIG. 2. Arteriograms obtained before (left) and 60 minutes after (right) injection of dopamine into the cisterna magna. There is a severe spasm of the basilar artery (arrows). Dopamine was administered in 2 ml of CSF at a concentration of $1 \times 10^{-4}$M prior to injection.

some animals (Fig. 1) and severe in others (Fig. 2). Compared to blood, however, the spasm induced by dopamine was less in incidence and significantly delayed in onset, most evident at 60 minutes. Moreover, the incidence and onset of spasm appeared unrelated to the dose of dopamine administered, although the duration of the spasm was obviously longer with the larger dose. The delayed spasm produced by dopamine suggests it was caused by an indirect action, perhaps a metabolite.

In contrast to dopamine, blood and PGE$_2$ caused vasospasm early in their course of action (Table 1). The spasm generated by PGE$_2$ was severe and lasted longer than that produced by blood, which usually disappeared between 60 and 120 minutes. The latter is a common finding.$^{3,7,8,9}$

The spasm generated by all three of these substances spontaneously lysed, indicating that the duration of spasm depends upon the maintenance of a critical level of spasmogen around the vasculature. Intracisternal injections of CSF alone failed to produce spasm.

Systemic changes induced by the experimental substances intracisternally were surprisingly absent in many of the animals, or ephemeral in some, regardless of the material injected. Prostaglandin never altered blood pressure and only reduced respiratory rate slightly in two animals for about 40 seconds. Dopamine also failed to change systemic blood pressure in seven animals, but in four lowered it 10 to 15 mm Hg for less than 80 seconds and transiently elevated this pressure 5 to 20 mm Hg in the remaining animals. In 11 of 16 animals, dopamine reduced respiratory rate about 20% to 50% for 30 to 100 seconds. The onset of these effects occurred 12 to 15 seconds after injection. Dopamine changed CSF pH at most only 0.07 units so that the systemic effects seen were not apparently due to such changes. Blood, like dopamine, produced variable transient systemic blood pressure effects and reduced respiratory rate in most animals. The incidence, onset, and duration and severity of
the vasospasm observed was, therefore, unrelated to the systemic recordings. This has been commonly reported with blood.\(^7,8\)

**Discussion**

The present report supports the hypothesis of others\(^9\) that dopamine may be important clinically in the genesis of cerebral vasospasm. The brain may be the source of dopamine following hemorrhage, when its release could reach high concentrations around adjacent vessels, especially if entrapped by blood where its removal by the normal flow of CSF would be impaired. Moreover, dopamine might potentiate the actions of other spasmogens released from brain and blood, a possibility as yet unexplored. On the other hand, the onset, incidence and duration of the spasm produced by PGE\(_2\) more closely resemble that induced by blood. This finding and others discussed below indicate that further studies are needed before concluding that dopamine plays an important role in the phenomenon of vasospasm.

The fact that many substances will induce cerebral vasospasm clearly indicates that this phenomenon involves more than dopamine. Among these are serotonin,\(^1,6,8\) prostaglandin F\(_{2\alpha}\),\(^8,9\) prostaglandin E\(_2\),\(^9\) histamine,\(^6,9\) platelets, and platelet extracts.\(^6,9\) Moreover, since many of these, such as prostaglandin F\(_{2\alpha}\), prostaglandin E\(_2\), serotonin, and histamine, are also synthesized by brain tissue,\(^9\) the brain may be the source of numerous spasmogens following hemorrhage in addition to dopamine. On the other hand, many substances are not vasoactive when introduced into the cisterna magna, such as vasopressin,\(^12\) prostaglandin E\(_1\),\(^9\) and norepinephrine.\(^9\) This finding with norepinephrine suggests that the delayed spasm obtained with dopamine is not due to its metabolism to norepinephrine. Also, norepinephrine brain levels are not altered after occluding one carotid artery, whereas dopamine concentration notably decreases\(^9\) so that dopamine appears to be more involved in pathophysiological phenomena than norepinephrine.

The hypothesis that dopamine may be released from the brain to cause vasospasm of adjacent arteries\(^13\) was based upon the findings that unilateral ligation of the carotid artery causes a selective ipsilateral decrease in brain dopamine and circus movements in animals. The circus behavior was presumed to be due to the release of dopamine in excessive quantities, which in turn caused excitation. However, the circus movements reported were contraversive in some animals and ipsiversive in others,\(^5\) and such movements are produced experimentally by cholinergic excitation of the caudate nucleus\(^10,11\) and the thalamus,\(^11\) respectively. In contrast, dopamine is inhibitory to neurons of the basal ganglion,\(^2,4\) Hence, the loss of brain dopamine reported after carotid ligation\(^13\) may simply mean loss of the molecule permitting cholinergic excitation. In contrast, ischemia associated with vasospasm may cause a rise in dopamine synthesis not evident in ligation-ischemia. Nevertheless,
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the present report shows that dopamine is experimentally spasmogenic as hypothesized by others13 and is apparently the first to demonstrate an effect of dopamine on cerebral arteries which had not been previously characterized.13

References


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