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Reserpine and Cerebral Vasospasm

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SUMMARY Cerebral vasospasm was produced in the dog basilar artery by topically applied five-day-old clotted autologous blood, but not by freshly drawn blood. The spasm was reversed by methysergide, an antiserotonin agent. However, vasospasm was not produced by five-day-old clotted autologous blood from dogs pretreated with reserpine.

Introduction

CEREBRAL VASOSPASM often complicates the management of patients with intracranial aneurysms and is usually associated with blood in the subarachnoid space.1 It has been concluded that the predominant vasoconstrictor elements of blood are contained in the platelet fraction.2 The storage in platelets of certain vasoactive amines liberated during normal clotting is influenced by reserpine,3 a phosphodiesterase inhibitor.4 The present study was undertaken to ascertain the vasoactive effect upon the basilar artery of clotted autologous blood from dogs pretreated with reserpine.

Methods

The basilar artery was exposed in 13 mongrel dogs using a translaterial approach under intravenous pentobarbital anesthesia with endotracheal intubation and spontaneous, unassisted respiration. A Zeiss operating microscope was used to open the dura and remove the arachnoid membrane. Observations of the ventral brain stem and the basilar artery and its branches were made continuously through the operating microscope. The changing diameter of the basilar artery was measured through the microscope by a micrometer calibrated to the nearest 0.1 mm.

There were three experimental groups. Group A contained three dogs. The basilar artery of each dog was bathed in fresh autologous blood for 30 minutes and then washed briefly with normal saline at 37.5°C. The diameter of the artery was measured immediately before and after treatment.

Group B contained six dogs. They were treated as were the dogs in Group A. The blood used, however, had been drawn from the specific animal tested five days prior to the experiment, allowed to clot, and then stored at 37.5°C until used in the experiment. After the blood was irrigated from around the vessel and the posttreatment diameter was measured, the vessels of three dogs were bathed in a solution of methysergide (1 mg/cc) for 15 minutes. The diameter was again measured.

There were four dogs in Group C. Each dog received reserpine, 0.1 mg per kilogram intramuscularly, daily for four days. Then blood was drawn from each animal, allowed to clot, and stored at 37.5°C for five days. At the end of that period, the basilar artery of each dog was exposed as noted above and then treated with autologous blood, as in Group A.

Results

The results are summarized in table 1. In Group A, no vasospasm was produced in any animal by the treatment of the basilar artery with fresh autologous blood.

Vasospasm was seen in the basilar artery of each animal in Group B. These vessels were treated with five-day-old
TABLE 1 Results of Cerebral Vasospasm in Three Experimental Groups

<table>
<thead>
<tr>
<th>Group and treatment</th>
<th>Animal</th>
<th>Resting diameter (mm)</th>
<th>Diameter after treatment</th>
<th>% Spasm</th>
<th>Diameter after methysergide</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Fresh autologous blood</td>
<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.3</td>
<td>1.4</td>
<td>0</td>
<td>—</td>
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<tr>
<td></td>
<td>3</td>
<td>1.5</td>
<td>1.5</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>B Old autologous blood</td>
<td>1</td>
<td>1.5</td>
<td>1.2</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.5</td>
<td>1.1</td>
<td>27</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.5</td>
<td>1.2</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>Plus methysergide</td>
<td>4</td>
<td>1.3</td>
<td>0.9</td>
<td>31</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1.0</td>
<td>0.8</td>
<td>20</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1.8</td>
<td>1.4</td>
<td>23</td>
<td>1.9</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td>23 ± 4</td>
<td></td>
</tr>
<tr>
<td>C Old reserpined autologous blood</td>
<td>1</td>
<td>1.3</td>
<td>1.4</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
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<td>2</td>
<td>1.1</td>
<td>1.1</td>
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<td></td>
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<td>1.5</td>
<td>0</td>
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</tr>
</tbody>
</table>

Discussion

One of the major problems confronting the neurosurgeon in the management of intracranial aneurysms is cerebral vasospasm, which often complicates their postbleed state or surgical treatment. This phenomenon is usually, though not always, associated with blood in the subarachnoid space. Cerebral vasospasm has been produced experimentally by the topical application of blood on large cerebral arteries of animals such as cats, dogs, and monkeys. Kapp, Mahaley, and Odom have concluded that the platelet fraction of blood carries the predominant vasoconstrictor elements of blood. Mammalian platelets are able to store several vasoactive substances such as catecholamines, histamines, prostaglandins and serotonin. It has been reported, however, that dog platelets bind very little, if any, histamines and catecholamines. The primary action of reserpine on blood is to prevent the storage of vasoactive amines by platelets.

Most investigators report that fresh autologous blood applied to exposed major vessels experimentally will produce a transient vasospasm lasting several minutes. Since we measured the basilar artery after 30 minutes, we may have failed to observe this phenomenon in our control animals. We did note, however, that the topical application of five-day-old autologous blood upon the basilar artery of the dog did produce vasospasm. These findings suggest that a vasoconstrictor element exists in blood which is released slowly during the clotting process. Blood from reserpinized dogs did not produce vasoconstriction of the dog basilar artery. Zervas and co-workers produced vasoconstriction in reserpinized dogs with normal blood. This indicated to them that the prevention of spasm by reserpine was due to an effect upon blood rather than upon the nervous system. It also suggests that the prevention of spasm is not related to a phosphodiesterase inhibitor-induced (such as reserpine) local enhancement of cyclic 3',5'-adenosine monophosphate (cAMP), as has been suggested. This in turn tends to negate the importance of the vasoactivity of certain blood prostaglandins in the present experimental model, since they also increase smooth muscle cAMP.

Serotonin has been shown to produce cerebral vasospasm when applied topically in the cat and the dog. Methysergide is an antiserotonin drug for which there is experimental evidence that it antagonizes the effects of serotonin on blood vessels. Daily and Moulder demonstrated that methysergide antagonized the vasoconstrictor activity of serum on pulmonary vessels, as measured by perfused wedge technique. Karlsberg, Elliott, and Adams showed that methysergide both prevented and reversed the increase in carotid perfusion pressure induced by intra-arterial serotonin. Moncy, Watts, and Clark revealed that serotonin-induced vasospasm of the basilar artery of the dog could be readily reversed by topical methysergide. They also noted that although the drug did not prevent vasospasm by topical serotonin, it did lessen the severity of it. The present study demonstrated that the vasospasm produced by topically applied five-day-old clotted blood in the dog could be reversed readily by the topical application of methysergide.

Our findings together with the above-summarized experimental data suggest that the primary vasoactive substance in dog blood responsible for the production of experimental vasospasm is serotonin, or a very similar but as yet unidentified substance.

While the cause of cerebral vasospasm remains an enigma, a workable theory concerning its etiology has evolved in light of recent experimental data. Cerebral vasospasm noted initially following the rupture of intracranial aneurysms might be induced by the simple mechanical effects or force of the rupture. Vasospasm seen within a few days thereafter could be due to the release of some vasoconstrictor substance from the blood in the subarachnoid space such as serotonin. If an aneurysm is operated on early following rupture, particularly in the presence of mild vasospasm, severe vasospasm is likely to occur. Mechanical stimulation combined with the topical application of serotonin has been shown to produce rather...
severe vasospasm in the dog. The combination of mechanical stimulation by the surgeon in the presence of serotonin in the subarachnoid space released from blood could do the same thing. It is well known that unless a second rupture occurs, surgery has much less chance of producing vasospastic complications the longer it is delayed following the rupture. This delay would result in the presence of less serotonin in the subarachnoid space.

Investigations concerning the prevention and treatment of cerebral vasospasm related to subarachnoid hemorrhage must take into account these experimental findings. They suggest that an antiserotonin drug such as methysergide should be investigated concerning its applicability in the treatment of this condition.

Acknowledgment

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References

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