Prevention of Serotonin-Produced Cerebral Vasospasm
An Evaluation of Blocking Agents

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The symptomatology following subarachnoid hemorrhage from aneurysm or arteriovenous malformation is often more severe than would be expected from the location or size of the lesion. Pool has postulated a vascular etiology secondary to vasospasm for some of these symptoms. Cerebral arteriography has demonstrated the frequent presence of vasospasm in the acute phase following the hemorrhage.

Previous work has shown that serotonin (5-hydroxytryptamine) is a potent cerebral vasoconstrictor when applied topically in small concentrations. Since serotonin is a normal constituent of platelets that is released whenever the platelets are traumatized or disrupted, it was postulated that serotonin might be an etiologic mechanism in the cerebral vasospasm seen so often after subarachnoid hemorrhage. Other workers have investigated different compounds for antiserotoninc action. Woolley and Shaw have constructed specific antagonists to serotonin. The effectiveness of these compounds has been measured on the isolated uterus of the rat and on the pressor action of serotonin. Whether or not these compounds would block the constrictor effects of serotonin in the intact animal and, more specifically, in the cerebral arteries was unknown. A screening of the most effective compounds was undertaken with plans to pursue the investigation further into any promising ones.

Method

The middle cerebral artery and surrounding cortex were exposed in 16 cats unselected as to size, sex, or age. A Zeiss operating room microscope with robot camera attachment was used to record photographically the size of vessels. Pictures were taken at appropriate intervals and later projected onto a large screen where the size of the vessel was measured and recorded. The details of the method have been described previously.

A 1½-in. No. 25 hypodermic needle was mounted in a 3-coordinator manipulator so that its point was a few mm. above a branch of the middle cerebral artery. The testing substance was dropped onto the exposed artery and cortex through the needle. One animal was given reserpine, 15 mg., intravenously 16 hrs. before the experiment. Just before the experiment a sample of blood was removed from the femoral vein and allowed to clot for 2 hrs. while the middle cerebral vessel was exposed. The clotted sample was centrifuged and the serum was decanted; 0.05 ml. of serum was dropped onto the exposed artery and cortex and serial photographs were taken. The remaining serum was refrigerated for 2 days and then used again on a second animal. In a third animal 5 mg. of reserpine was given intravenously simultaneously with the application of topical serotonin.

Chlorpromazine was used in 4 animals. The artery was exposed and 0.05 ml. of 1/1,000,000 solution of serotonin was dropped onto the vessel and surrounding cortex; 1½ to 4 min. later 5 mg. of chlorpromazine was given intravenously. This procedure usually was repeated if the vessel returned to normal size within 15 min. Serial photographs were taken at appropriate intervals.

In six animals BAB† (1-benzyl-2, 5-dimethylbufotenin hydrochloride) was used. In 3 animals, it was applied topically to the vessel from 1 to 5 min. before serotonin, and in 4 animals after the serotonin. The drug was given intravenously in 2 animals from 3 to 5 min. after serotonin, and 30 to 45 min. before serotonin in 2 cases. BAB was injected into the carotid artery 1 min. after serotonin in 2 cases. One to 5 mg. of BAB were used in the intravenous and intra-arterial injections. Some animals were used for more than one type of test. In these cases an adequate time interval for

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the artery to return to normal size was allowed between tests.

**BAS**\(^1\) (1-benzyl-2, 5-dimethyl serotonin) was used in 2 animals. The drug was applied topically in 1 animal 1½ min. before serotonin. In the second animal 1 mg. was given intravenously 30 min. before serotonin and again intra-arterially (1 mg.) 1 min. after serotonin was applied.

Isoxsuprine hydrochloride\(^2\) was tested in 1 animal. It was applied to the vessel and surrounding cortex 3 min. before serotonin, and again 17 min. after the serotonin.

**Results**

Arterial spasm lasted 18 min. when reserpine was given intravenously. Serum from animals treated with reserpine 16 hrs. previously caused local arterial spasm lasting 6 min. and lasting 12 to 15 min. when the serum was stored for 2½ days and then used.

Chlorpromazine-treated animals all had spasm of 3 to 12 + min. in duration. Seven observations were made and only once, in a repeated test in 1 animal, did serotonin fail to produce spasm.

In the 6 animals in which BAB was used 17 observations were made in a variety of combinations to afford adequate screening. Topical testing was done 11 times. It made no difference whether serotonin or BAB was used first. Arterial spasm lasted from 3 to 33 min. with spasm lasting 6 to 15 min. in most cases. Intravenous or intra-arterial injection produced approximately the same results in 6 tests. It also made no difference whether BAB was given before or after serotonin.

BAB was tested in 2 animals 4 times. Topical application was done twice and intravenous and intra-arterial drug was given once each. No difference in the duration of spasm was observed since it lasted for more than 10 min. in each case. In 1 case of topical application of BAS (after previous intravenous injections of BAS) the artery first dilated to size greater than normal but 6 min. later it again went into spasm and remained that way for the duration of the observation period of 15 min.

Topical application of isoxsuprine twice in 1 animal failed to prevent spasm of 17 and 30 min. in duration.

\(^1\) Supplied as Vasodilan, Mead Johnson & Co.

**Discussion**

Serotonin applied topically, in the concentration used here, causes cerebral vasospasm lasting at least 2 min. and usually much longer.\(^8\) It was felt that any compound effective against serotonin-induced spasm should be able consistently to reverse the spasm in less than 5 min., or prevent it when used before the serotonin was applied. No compound tested here fulfilled these criteria.

BAB, designed by Shaw and Woolley as a specific antagonist of serotonin, was felt by them to be the most potent agent available for intravenous use when tested against the pressor effects of serotonin. It was also extremely effective topically in blocking serotonin-induced contractions of the isolated uterus of the rat.\(^1\) BAS is a similar compound found by Shaw and Woolley\(^10\) to be the best oral antagonist of serotonin.

Chlorpromazine has been found to be an effective antagonist of serotonin when tested in the isolated uterus of the rat or against the pressor action of serotonin.\(^1,3\)

Reserpine exerts its antiserotonic action by removing the readily available source, serotonin of platelets, and blocking further uptake of serotonin into platelets.\(^4,5\) There does not seem to be any evidence that reserpine is a direct antagonist of serotonin and the findings here confirm this. The residual constrictor action of serum found after previous administration of reserpine is inconclusive since it appears to take from 1 to 3 days to achieve a significant fall in the level of serotonin of platelets in man.\(^4\) In some animals the fall is more rapid, however.\(^5,6\) Of interest is Wilkins and Hollander’s\(^12\) finding that prolonged oral administration of reserpine does not counteract intravenous serotonin.

**Summary and Conclusions**

1. Some of the symptomatology following subarachnoid hemorrhage from aneurysm and arteriovenous malformations may be caused by cerebral vasospasm.

2. Previous work has shown that serotonin is a potent cerebral vasoconstrictor. Blood platelets provide a ready source of serotonin
that can be released even without destruction of the platelets.

3. BAB, BAS, chlorpromazine, and reserpine have proved to be effective antiserotonergic agents when tested in vitro or against the pressor effects of serotonin in vivo.

4. None of these agents proved effective in preventing or shortening significantly cerebral vasospasm caused by topical serotonin.

References


