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ANTIFIBRILLANT ACTION OF THE SERPAJMALINE COMPLEX AND ITS CONSTITUENT ALKALOIDS

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In the preceding communication the pharmacological action of the alkaloidal complex serpajmaline,[3,9,10] isolated by S. Siddiqui, [23,24] from the fresh undried roots of *Rauwolfia serpentina* has been described. Serpajmaline, which is free from reserpine and other weaker bases, has a hypotensive action without central side effects. With reference to the antifibrillant cardiac action of serpajmaline,[3] it was considered of interest to study the action of the various alkaloidal and non-alkaloidal constituents of the complex, and the present paper deals with the results obtained from this study.

The fraction serpajmaline includes ajmaline, serpentine and serpentinine, two unknown compounds and a carbohydrate-like substance. Ajmaline belongs to the tertiary indoline alkaloids; serpentine and serpentinine belong to the quarternary and hydronium bases. The three alkaloids ajmaline, serpentine and serpentinine were isolated by S. Siddiqui and R. H. Siddiqui.[20,21,22] These alkaloids have been studied extensively by many workers and there are wide differences of opinion regarding their sites and modes of action. It is generally agreed that serpentine reduces blood pressure,[14,16,11,7,19] is a more active substance than ajmaline[13] and more toxic than ajmaline and serpentinine.[5] Its hypotensive activity is probably due to acute vasodilatation.[19] The pressor effect of adrenaline was reduced to about the same extent as after equal doses of ajmaline.[2] There is a discrepancy in the description of the blood pressure effect of serpentinine and ajmaline. Chopra and coworkers [5,6,11] observed that ajmaline and serpentinine raised the blood pressure, while other workers found that both alkaloids have a weak hypotensive action [1,15,16,17] and do not contribute much to the hypotensive activity of an alkaloidal mixture.

Method

The importance of potassium concentration for the occurrence of heart fibrillation became evident both for auricular and ventricular fibrillation. The fibrillation occurs when the potassium concentration of the solution is reduced.[12]

Isolated Rabbit Heart (Langendorff method).—After fixing the electrodes on the tip and the base of the heart, ventricular fibrillation was produced by electric stimulus: stimulation for 2 to 4 minutes, frequency 200-400, 5-10 mA, sharp rectangular impulses. If the fibrillation was not arrested by itself within 5 minutes after that, the fibrillation lasted for a longer period (40-60 minutes). After 10 minutes fibrillation a control solution was injected and 5 minutes later a solution of the drug was introduced via a polythene cannula opening near the coronary arteries to the perfusion fluid.

Perfusion Fluid.—McEwen solution with lower potassium chloride content and without sodium dihydrogen phosphate: sodium chloride, 7.6 g.; potassium chloride, 0.24 g.; calcium chloride, 0.19 g.; sodium bicarbonate, 2.1 g.; dextrose, 2.0 g.; sucrose, 4.5 g.; aqua dest., 1000 ml.

Isolated Dog Heart.—After perparing carotid artery and jugular vein of an anaesthetised dog (narcosis: chloralose 80 mg./kg. i.v., or pentothal 15 mg./kg. + phenobarbitone 25 mg./kg. i. v., and phenobarbitone 75 mg. / kg. intraperitoneal),

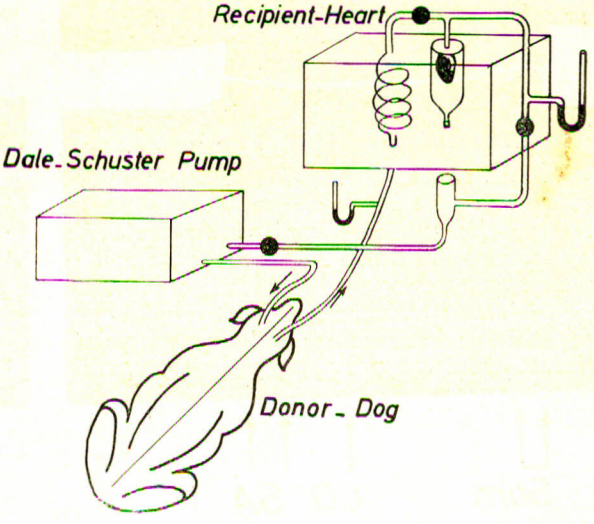

Fig. 1.—Arrangement of an isolated perfused dog heart connected with the circulation of second anaesthetised dog. The blood flow coming from the carotid artery passes: (1) mercury manometor; (2) spiral in isolated organ bath; (3) isolated dog heart; (4) blood reservoir; (5) Dale - Schuster pump; and (6) jugular vein. A second direct connection is between isolated heart and blood reservoir, passing a second mercury manometer registering the pressure in the aorta of the isolated heart.

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the aorta of an isolated dog heart is connected with the circulatory system of the anaesthetised dog between the carotid artery and the jugular vein (see Fig. 1). The blood then circulates from the carotid artery of the donor dog and passes a spiral of the organ bath (37 °C.) via a two way cannula either to the isolated heart through the coronaries, blood reservoir, Dale-Schuster pump and back to the jugular vein of the donor dog (=way I), or directly to the blood reservoir (=way II). Two mercury manometers are connected in this system, the one showing the blood pressure of the anaesthetised dog (donor dog), and the other the pressure in the recipient heart.

The preparation is done in the following manner:

(1) The two cannulas of the system are connected with the carotid artery and the jugular vein. The whole system is closed, except for the blood pressure manometer which is kept open.

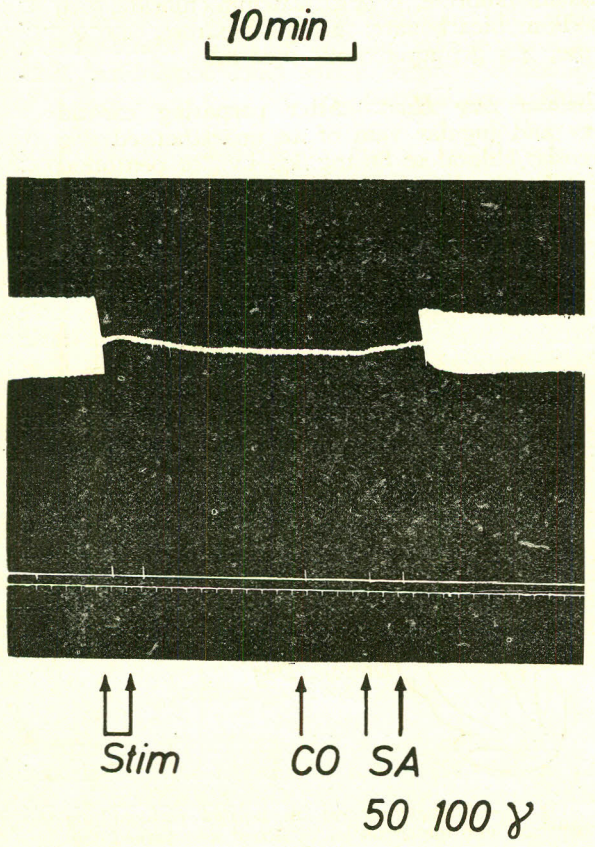

Fig. 2.—The effect of serpajmaline (SA) on a fibrillating rabbit heart after electrical stimulation (STIM). Thirteen minutes after fibrillation has started, a control solution (CO) was injected, afterwards serpajmaline was given, 100 γ was effective. Above: isolated heart. Below: signal and time (1 min.).

(2) The way II of the recipient system is then opened slowly to the extent the Dale-Schuster pump 1.5 ml. at a frequency of 80/min. can pump away by steady level in the blood reservoir. (3) After 10 minutes, the isolated heart (recipient heart) is prepared and immediately connected with the heart cannula. As the way I through the recipient heart is opened, the way II is simultaneously reduced to bring the pressure in the aorta of the recipient heart to 50-60 mm. Hg.

The recipient heart is connected with an isometric writing lever. Fibrillation is induced in the perfused beating recipient heart by electrically stimulating the ventricle. Fibrillation always appeared after short stimulation (10-30 seconds). Frequency, 200-700/sec.; duration, 0.75 msec.; 1-10 mA.; stimulus, sharp rectangular. The fibrillation persisted for periods of 60-120 min.

Results

As already described[3] serpajmaline arrested the fibrillation of the isolated rabbit heart immediately after the injection of 100-300 γ (see Fig. 2), average value 182 γ (14 hearts). Repeated attemps to reinduce fibrillation by electrical stimulation during the first hour after the injection of serpajmaline were unsuccessful.

Following the technique described above, fibrillation was induced in the isolated dog heart by electric stimulus, and about 10 minutes later a solution of serpajmaline (4 mg./kg.) was injected into the V. femoralis of the donor dog. After a

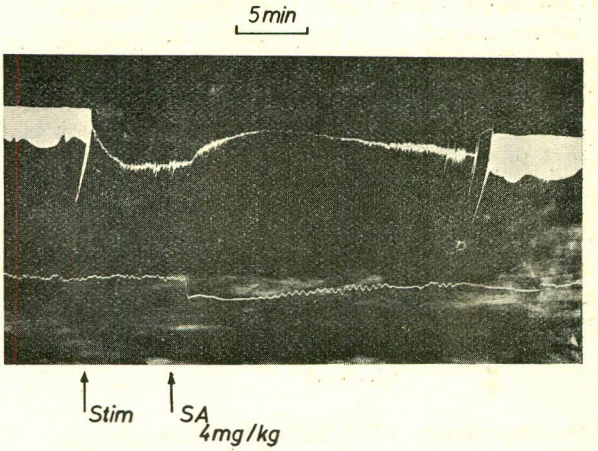

Fig. 3.—The effect of serpajmaline on the fibrillating isolated dog heart injected intravenously to the donor dog. The isolated dog's heart is connected with the circulation of a second anaesthetised dog. The isolated dog heart was electrically stimulated (STIM) till fibrillation appeared. Seven minutes after fibrillation started, serpajmaline (SA) 4 mg./kg. was injected intravenously to the donor dog. Twenty minutes after injection the fibrillation of the isolated heart was arrested. Above: isolated dog heart (recipient). Below: blood pressure in the system.

latent period of 20-25 minutes the fibrillation was completely arrested. The latent period may be taken as the time the drug takes to flow into the recipient heart after passing the artificial circulatory system. This finding shows that serpajmaline exercises its antifibrillant action well within the range of therapeutic dosage (see Fig. 3).

During a few of these experiments the recipient heart showed irregularity and partial block on its own without any artificial manipulation. After injection of 2 mg. serpajmaline into the heart via cannula, the heart in such cases recovered immediately and the rhythm was normalised.

It was of further interest to clear up the question if any of the alkaloids in serpajmaline is responsible for the heart action. The following bases and combinations have been investigated: (1) the total basic fraction of the serpajmaline complex; (2) the non-basic fraction of serpajmaline containing sugars and sugar acids and chlorides; (3) the alkaloids: ajmaline, serpentine and serpentinine; and (4) serpajmaline with the addition of 10-20% of ajmaline.

The following results were obtained on the isolated rabbit heart:

The basic fraction of serpajmaline showed an antifibrillant action with 50 to 100 γ (8 hearts).

The non-basic fraction of serpajmaline arrested fibrillation in an average dose of 217γ (ranging 100-300 γ) (6 hearts).

Ajmaline in an average dose of 63 γ, ranging 25-100 γ (8 hearts), and serpentine in an average dose of 200 γ (9 hearts) have both got an antifibrillant action. Serpentinine was ineffective even in doses of 600γ. K. J. Child [4] could confirm the results with ajmaline, serpentine and serpentinine. He also found ajmaline and serpentine to exercise an antifibrillant action on the isolated auricle.

In experiments with serpajmaline with added ajmaline it was observed that this combination arrests fibrillation in an average dose of 26 γ ranging between 6.125 and 75γ (16 hearts).

Discussion

Recently it was found that the combined activity of the known alkaloidal constituents of serpajmaline, (ajmaline, serpentine and serpentinine) cannot account for all its actions.[3] In the present investigation also it has been observed that the antifibrillant action of serpajmaline is not only due to ajmaline and serpentine, as its non-basic fraction has this action too. Ajmaline is 2-3 times more active than serpajmaline. Serpentine acts quantitatively similar to serpajmaline. The alkaloid content of serpajmaline is 35 to 40% depending upon the age of the root. From the results obtained so far on the chemical side of investigations, it would appear that, if ajmaline and serpentine only were to be responsible for the antifibrillant action, this action should be still stronger in comparison with that of serpajmaline. It has moreover been shown that the non-basic fraction of serpajmaline has likewise an antifibrillant action in a dose of 100 to 200γ , and the action of serpajmaline is intensified with the incorporation of 20% ajmaline. In fact this combination arrests fibrillation in most cases with a dose of 6.125 to 12.25 γ as against 182γ of serpajmaline, and this intensification of action cannot be accounted for on a merely addition basis.

Conclusion

Serpajmaline and the alkaloids ajmaline and serpentine contained in this complex have an antifibrillant action on the isolated rabbit heart. Ajmaline is more active than serpentine. Serpentinine is inactive.

The heart action of serpajmaline does not depend only on its alkaloidal content ajmaline and serpentine.

The non-basic fraction and the basic fraction of serpajmaline have both an antifibrillant action on the isolated perfused rabbit heart. The basic fraction was more active than the non-basic fraction of serpajmaline.

The addition of ajmaline to serpajmaline strongly potentiates its antifibrillant action.

With a newly developed method for testing the heart action, which consists in connecting the isolated dog heart with the circulatory system of a second anaesthetised dog, it has been demonstrated that serpajmaline arrests the heart fibrillation in therapeutic dosage (4 mg./kg. intravenously).

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