A NOTE ON THE PHARMACOLOGY OF ASPIDOSPERMINE

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The alkaloid aspidospermine has been isolated from the barks of *Aspidosperma quirandy* Hassler[1], *A. australe* Mull. Arg.,[2] *A. quebracho-blanco* Schlecht,[3–7], *A. polyneuron* Mull. Arg.[8] and *Vallesia glabra*.[9–13] The chemistry of aspidospermine has received some attention[5,14,15,16].

There is some conflict of opinion in the earlier reports on the pharmacology of aspidospermine. Cow[17] studied the pharmacology of the four principal alkaloids of Quebracho bark (quebrachine, aspidospermine, quebrachamine and aspidosamine), and reported that aspidospermine caused a rapid and well marked fall in the blood pressure which then rose slowly, but did not return again to its former level. This effect was due to a dilatation of the splanchic and limb vessels and was of vasomotor origin. The individual alkaloids all caused an increase in the rate and depth of respiration. There was slowing and weakening of the heart beat of the rabbit and the frog. Intestinal movements were stimulated by small doses; larger doses caused less stimulation and at this stage neither stimulation of the vagus, nor injection of pilocarpine caused peristalsis. The effects of adrenaline were reduced, but the response to barium was unchanged. Floriani[18] found that aspidospermine hydrochloride caused arterial hypertension, peripheral vasoconstriction, diuresis and an increase in the depth and frequency of respiration. Cow[17], using decerebrated frogs, perfused through the aorta, had noted a constrictor effect upon the blood vessels.

Aspidospermine has been used as the sulphate, hydrochloride or citrate in the treatment of various forms of dyspnœa and asthma[19]. It is described by the National Standard Dispensatory (1905)[20] as being either commercial aspidospermine, which is mostly a mixture of six alkaloids of white quebracho bark, or a purified weak base obtained from the former mixture, and melting at 205° C. The same source[20] points out that red quebracho is often substituted for quebracho and that a mixture of the two barks is often encountered. In these circumstances, it was not remarkable that there were wide discrepancies between reports on the therapeutic value of the drug. This may also explain the differing results obtained by pharmacologists using different samples of aspidospermine alkaloid. We have been very fortunate in obtaining an authentic sample of aspidospermine through the courtesy of Dr. Openshaw of the University of St. Andrews, and Dr. G. F. Smith of the University College of North Staffordshire. The melting point of this sample is 210 to 211·5° C.

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Experimental. The alkaloidal base was dissolved in the appropriate saline at *p*H 6·6, hydrochloric acid being used to aid solution. A 0·5 per cent. solution was used throughout, unless otherwise indicated.

On the frog rectus abdominis muscle preparation, using a 10-ml. bath, antagonism was shown to 10 μg. of acetylcholine chloride. The antagonism was proportional to the dose of alkaloid given, which ranged from 0·5 to 2·2 mg. (Fig. 1). Applied to the frog heart *in situ* a solution containing

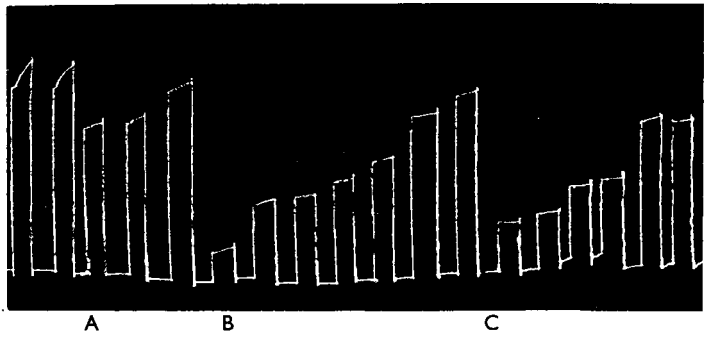

FIG. 1. Antagonism to acetylcholine of aspidospermine on the frog rectus abdominis muscle preparation.

All contractions due to the addition of 10 μg. acetylcholine chloride to the bath, preceded two minutes earlier by the addition of: (A) 0·05 mg.; (B) 0·22 mg.; (C) 0·15 mg. of aspidospermine.

5 mg./ml. of alkaloid slowed the heart rate, then impaired auricular-ventricular conduction, and finally produced a partial block. This was reversible on washing. Perfusion of the isolated frog heart through the *sinus venosus* with a 1 in 200,000 solution of alkaloid in frog Ringer's solution caused similar effects. On the isolated rabbit duodenum 0·10 mg. to 0·25 mg. of aspidospermine depressed peristaltic movements, but

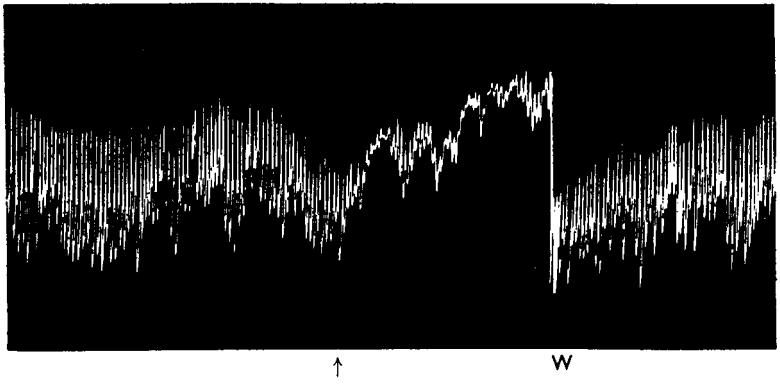

FIG. 2. Action of aspidospermine on the normal movements of the isolated small intestine of the rabbit.

0·2 mg. of aspidospermine added to the bath at the point indicated by the arrow. W = wash.

increased muscle tone. These effects were reversible (Fig. 2). The spasmogenic actions of 1 μg. of acetylcholine chloride were antagonised. the extent of the inhibition was proportional to the dose of alkaloid given. The spasmolytic potency of aspidospermine on this tissue was about one-twentieth of that of atropine sulphate.

Aspidospermine was found to antagonise the spasmogenic actions of 1 μg. of acetylcholine chloride, 1 μg. of histamine acid phosphate and 4 mg. of barium chloride on the isolated guinea-pig ileum. The respective dose ranges were 0·06 mg. to 0·80 mg.; 0·06 mg. to 0·12 mg. and 0·05 mg. to 0·2 mg. The extent of the inhibition was proportional to the dose given. There was no evidence of specificity. On this tissue, aspidospermine appeared to possess about one-thirtieth of the anticholinergic activity of atropine sulphate.

Doses of from 0·5 to 1·0 mg. of aspidospermine caused marked dilatation of the blood vessels of the isolated perfused rabbit's ear. The dilator action of acetylcholine on these vessels was not modified, but the constrictor action of 0·1 μg. of adrenaline hydrochloride was reversed. Similar doses caused slight constriction of the blood vessels of the perfused hind quarters of the rat. In this case the constrictor action of 1 μg. of adrenaline hydrochloride was reversed to a vasodilation, but there was no antagonism to the vasodilator effects of 10 μg. of acetylcholine chloride.

There was antagonism to the inhibitor action of 50 μg. of acetylcholine chloride on the isolated rabbit's auricles by doses of 0·6 mg. of aspidospermine. The auricles were suspended in Ringer-Locke's solution at 29° C.

The spasmogenic action of 10 μg. of adrenaline hydrochloride on the isolated rabbit uterus was antagonised by 0·2 to 0·5 mg. of aspidospermine. A graded antagonism was shown.

In intact chloralosed cats and in spinal cats there was a transient fall in the carotid arterial blood pressure when 5 to 30 mg. of the alkaloid were given by injection into the jugular vein. There was no evidence of reversal of the pressor effects of 5 to 10 μg. of adrenaline hydrochloride. The depressor action of 1 to 2 μg. of acetylcholine chloride was not modified.

In the rabbit anæsthetised with urethane, there was an increase in the frequency of respiration when 2 to 5 mg. of aspidospermine were given by injection into the jugular vein. Gaddum's method of recording was used[21].

Local anæsthetic activity as measured by the frog plexus anæsthesia method[22,23] was not marked. The solutions used contained 0·25, 0·5 and 1·0 per cent. of aspidospermine.

2 mg. of aspidospermine, when injected intraperitoneally into mice weighing 20 to 25 g., did not significantly reduce body temperature.

Discussion. Aspidospermine appears to possess many of the properties found commonly amongst alkaloids. Thus it non-specifically antagonises the spasmogenic properties of acetylcholine, histamine and barium on the guinea-pig ileum, and it is toxic to heart muscle. Like certain other indole derivatives, aspidospermine appears to influence the response of the blood vessels to adrenaline. The adrenaline reversal shown by the blood vessels of the rabbit's ear and rat hind quarters after aspidospermine is of some

interest. Adrenaline reversal could not, however, be shown on the chloralosed or spinal cat and the fall in blood pressure was only transient, in contradistinction to the findings of Cow[17], who noted a rapid and well-marked fall in the blood pressure which did not again reach its former level, and Floriani[18], who observed that the alkaloidal hydrochloride caused arterial hypertension. Aspidospermine does not appear to be a vaso-constrictor of the blood vessels of the rabbit's ear or to cause marked constriction of those of the hind quarters of the rat. On the isolated rabbit duodenum peristaltic movements were depressed; we observed no stimulation of intestinal movements and the response to barium was inhibited. Aspidospermine appears to be a respiratory stimulant and to have atropine-like activity on smooth muscle. Although we have demonstrated antagonism to the actions of acetylcholine on a number of organs, we noted no hypothermic activity and local anæsthetic activity was only slight.

Summary

1. Aspidospermine reverses the constrictor responses of the perfused blood vessels of the rabbit's ear and rat hind quarters to adrenaline.

2. The spasmogenic response of the rabbit uterus to adrenaline is antagonised.

3. The respiratory stimulant properties of aspidospermine have been confirmed.

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