

PHARMACOLOGICAL INVESTIGATION OF SERPAJMALINE, AN ALKALOIDAL FACTOR OF RAUWOLFIA SERPENTINA

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Recently S. Siddiqui¹ reported the discovery of a pharmacologically active *Rauwolfia* alkaloidal fraction which was named 'serpajmaline'. This fraction includes the alkaloids serpentine, serpentinine and ajmaline, two unknown substances and a carbohydrate-like substance, and possesses remarkable blood pressure reducing properties without any sedative action, as recently described by us.² It has long been known that the *Rauwolfia Serpentina* alkaloids, reserpine³ and rescinnamine,⁴ have a greater blood pressure reducing action than the other alkaloids but it has not hitherto been possible to answer the question whether the hypotensive action is primarily inherent or whether it depends only on its central depressive action. It thus seems noteworthy that serpajmaline, which contains no reserpine, has a strong blood pressure reducing action without central side effects. In the present work we have therefore extended our previous results on the blood pressure reducing action of serpajmaline and have investigated more closely various peripheral effects of this fraction.

Methods

Blood Pressure Experiments on Dogs.—Using a *bloodless method*, we prepared the art. carotid externally looped in a skin sheath, following Wezler and Thauer.⁵ The blood pressure was measured as by Riva Rocci on the non-anaesthetised animal.

For the *sanguinous method* we used a Hg manometer for recording the arterial pressure from the carotid. To prevent coagulation we injected 500 I.U./kg. Vetren with a preliminary 500 I.U. in the supply tube. Heart frequency was recorded with the ordinate recorder developed by Heuwing. Narcosis; Pentothal 15 mg./kg. and phenobarbitone 25 mg./kg. intravenous, phenobarbitone 75 mg./kg. intraperitoneal. Injections in the V. Femoralis.

Blood Pressure Experiments on Cats.—Recording of the arterial pressure from the carotid with a Hg manometer. As regards preventing coagulation see dogs. Injection in the Femoralis. Narcosis: Chloralose 80 mg./kg. intraperitoneal. Injections in the V. Femoralis.

Intestine and Spleen in situ.—With cats under the above Chloralose narcosis or with spinal cats, a bubble sonde was introduced into the jejunum through the oesophagus and the stomach, and this was connected to a water manometer. The recording of the spleen volume was made pethysmographically and connected to a piston recorder.

Isolated organs.—Terminal ileum of guinea-pigs was used in the usual arrangement following Magnus.

Temperature Monitoring.—For recording the body temperature of rabbits we used Hartmann and Braun's apparatus.

Preparation.—The serpajmaline was isolated by Dr. S. Siddiqui in the Chemical Research Division of the Central Laboratories.

Experiments

(1) **Action of Serpajmaline on the Circulation.**—Serpajmaline has a blood pressure reducing action on dogs and cats, dogs being more sensitive than cats. The magnitude of the blood pressure reduction depends on the condition of the experimental animal, the depth of narcosis, and the dosage.

(a) *Effect on the Blood Pressure of Anaesthetised Dogs*

Small doses of serpajmaline, 0.25-1 mg./kg., injected intravenously, produce a transient fall of blood pressure of a few mm. Hg. After 2 mg./kg., however, the blood pressure was reduced by 40 mm. Hg for about 20 min. on the average. Figure 1 shows the effect on the blood pressure of repeated injections of serpajmaline at intervals of 10 min. From this figure it can be seen that serpajmaline is still capable of depressing the blood pressure even after it has been greatly reduced by repeated injections.

Reserpine has no effect after repeated injections. After a reduction of the blood pressure has been produced once, reserpine is incapable of depressing the blood pressure even once more. The bradycardiac action of serpajmaline can be

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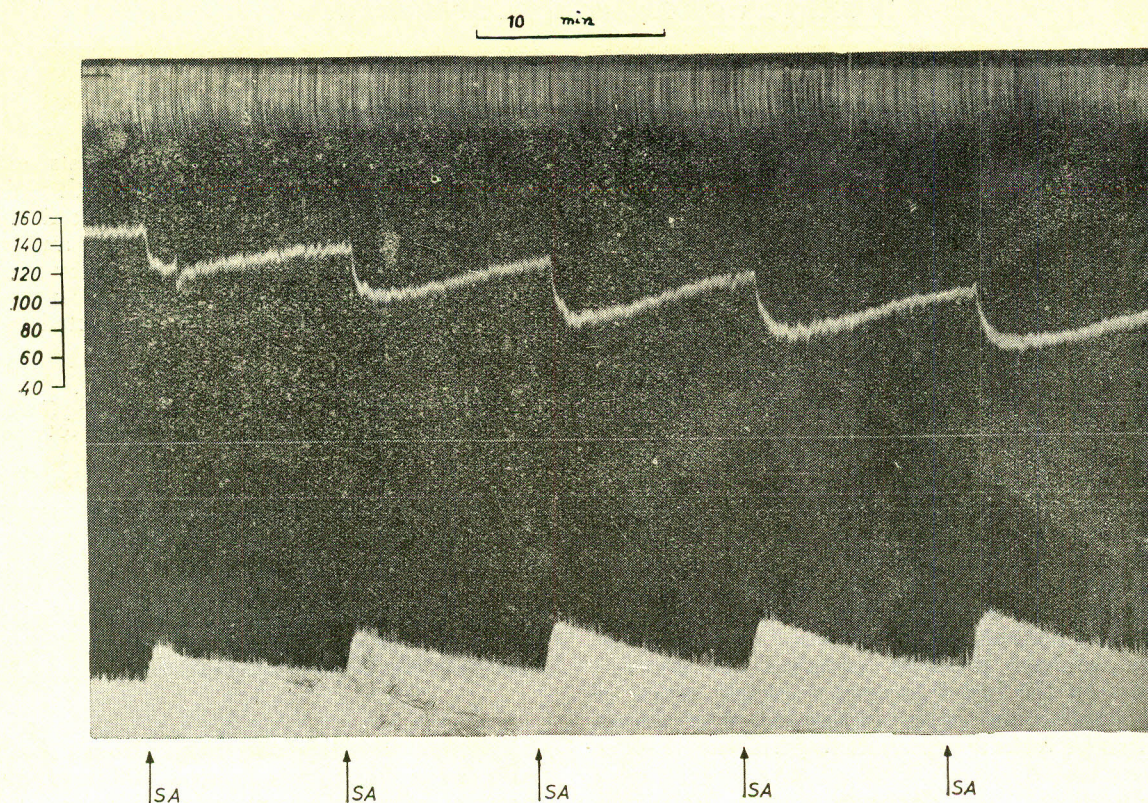


Fig. 1.—The effect on the blood pressure and heart frequency after repeated injections of serpajmaline. Dog 25 kg., Pentothal-phenobarbitone anaesthesia. Recording of blood pressure with Hg manometer from the carotid. Above: respiration; middle: blood pressure; and below: heart frequency. Time in minutes. After repeated injections of serpajmaline, 2 mg./kg. i.v., at ten-minute intervals, the blood pressure falls in steps. The bradycardia increases.

seen clearly from Fig. 1; this action is also cumulative.

At this dosage (2 mg./kg.) reserpine has no acute blood pressure reducing action. A transient blood pressure reduction of short duration is obtained in the control test (0.5% acid acetic) (see Fig. 2). The hypotensive action of reserpine does not show until 1-2 hours after the injection, and the magnitude of the reduction is 20-40 mm. Hg. Because of these circumstances, a quantitative comparison is very difficult, if not impossible. It may however be stated that, in comparison with reserpine, serpajmaline has a much stronger acute depressive action on the blood pressure (see Fig. 2).

(b) *Effect on the Conscious Dog with Carotid in External Skin Sheath*

In the experiments on the conscious dog with carotid in external skin sheath there was general concordance with the results on anaesthetised animals. The effect of serpajmaline was stronger

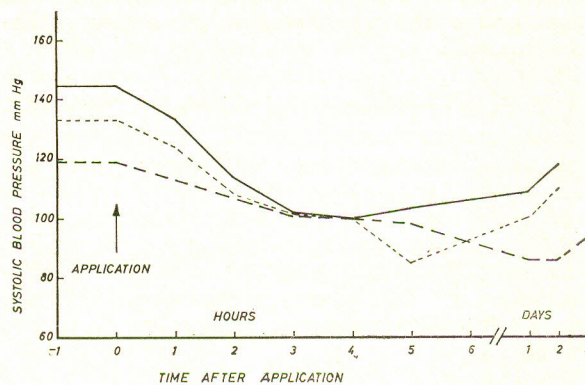


Fig. 3.—The effect of single applications of serpajmaline or reserpine on systolic blood pressure in conscious dogs. Dogs with carotid in external skin sheath.

—: Serpajmaline 5 mg./kg. intramuscularly. Average values of 3 dogs.
: Serpajmaline 5 mg./kg. orally. Average values of 6 dogs.
 - - - -: Reserpine 1 mg./kg. intramuscularly. Average values of 3 dogs.

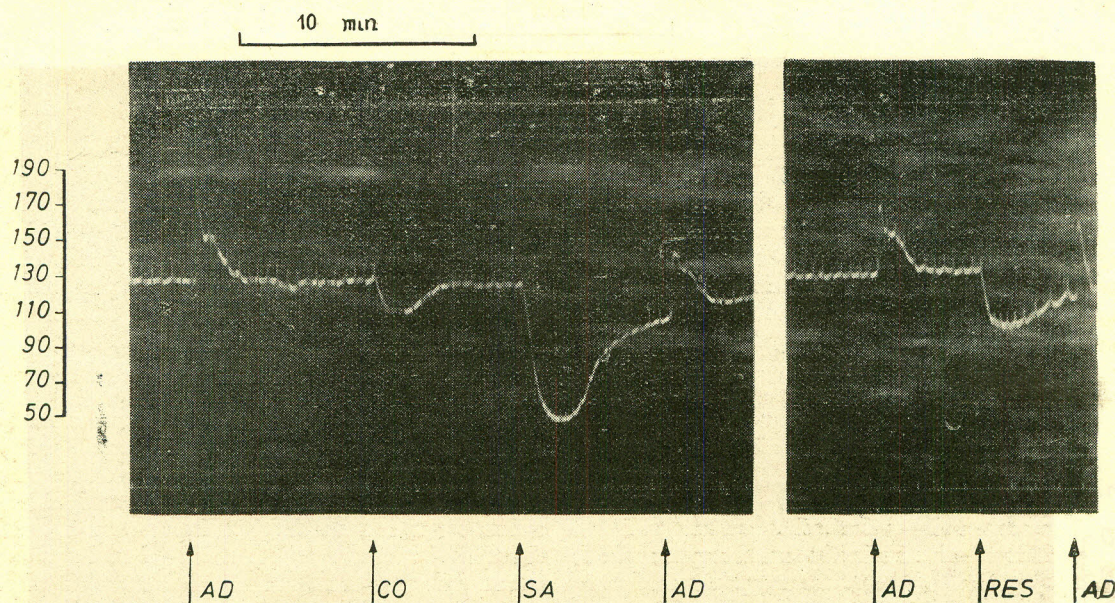


Fig. 2.—Comparison of the acute blood pressure effect of serpajmaline and reserpine. Dog 15 kg., pentothal-phenobarbitone anaesthesia. Recording of blood pressure with Hg manometer from the carotid. Above: respiration; below: blood pressure. Time in minutes. The acute fall of blood pressure after 1 mg./kg. reserpine (RES) corresponds to the control (CO) whereas serpajmaline (SA) 1 mg./kg. depresses the blood pressure clearly and reduces the effect of adrenalin (AD) 12γ.

and more enduring on conscious animals than on anaesthetised ones. In all cases, 5 mg./kg., was given orally and intramuscularly. This dose resulted in a reduction of 40-60 mm. Hg in the blood pressure. After oral application of 5 mg./kg., serpajmaline also has a definite long-term action, up to 24 hours. During the period of hypotension there was no miosis, no relaxation of the nictitating membrane, and no diarrhoea or sedative action. In comparison with serpajmaline, the effect of reserpine, 1 mg./kg. intramuscular, can be seen in Fig. 3. Orthostatic collapse did not occur after

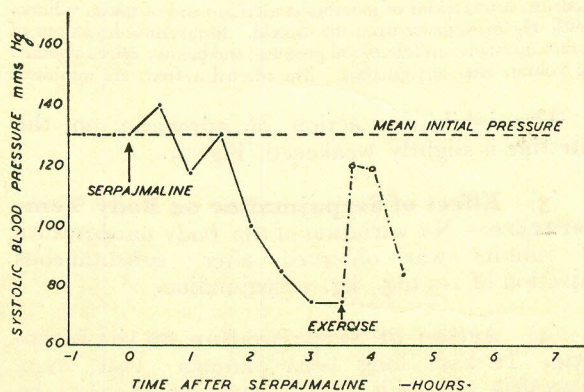


Fig. 4.—The effect of exercise on the hypotension produced in a conscious dog by a single oral dose of serpajmaline. (Dose 5 mg./kg.). Dog 20 kg., with carotid in external skin sheath.

serpajmaline when the dog jumped from the table, and a rise in blood pressure could still be obtained when the dog was given exercise (Fig. 4).

(c) *Effect of Serpajmaline on the Blood Pressure and Spleen Volume of Anaesthetised and Decapitated Cats*

The effect of serpajmaline on the blood pressure of anaesthetised cats is weaker than on dogs. Five mg./kg. serpajmaline injected intravenously into the anaesthetised cat had little effect on blood pressure. On the spinal cat there is sometimes a short-term rise of blood pressure. Rothlin⁶ has described a rise of blood pressure with various ergot alkaloids. However, notwithstanding the rise in blood pressure, there is an increase in the spleen volume of the spinal cat (Fig. 5).

(2) **Adrenergically Inhibiting Effects of Serpajmaline.**—In anaesthetised and decapitated cats, serpajmaline inhibits the pressor action of adrenalin and noradrenalin. Similarly, the contraction of the nictitating membrane after adrenalin is inhibited (Figs. 5,6). On the other hand, the contraction of the nictitating membrane after pre-ganglionic stimulation is inhibited to only a small degree (Fig. 6). The block which is to be seen in Fig. 6 after peripheral vagus stimulation is discussed elsewhere. The contraction of the spleen volume after adrenalin is inhibited by serpajmaline (Fig. 5).

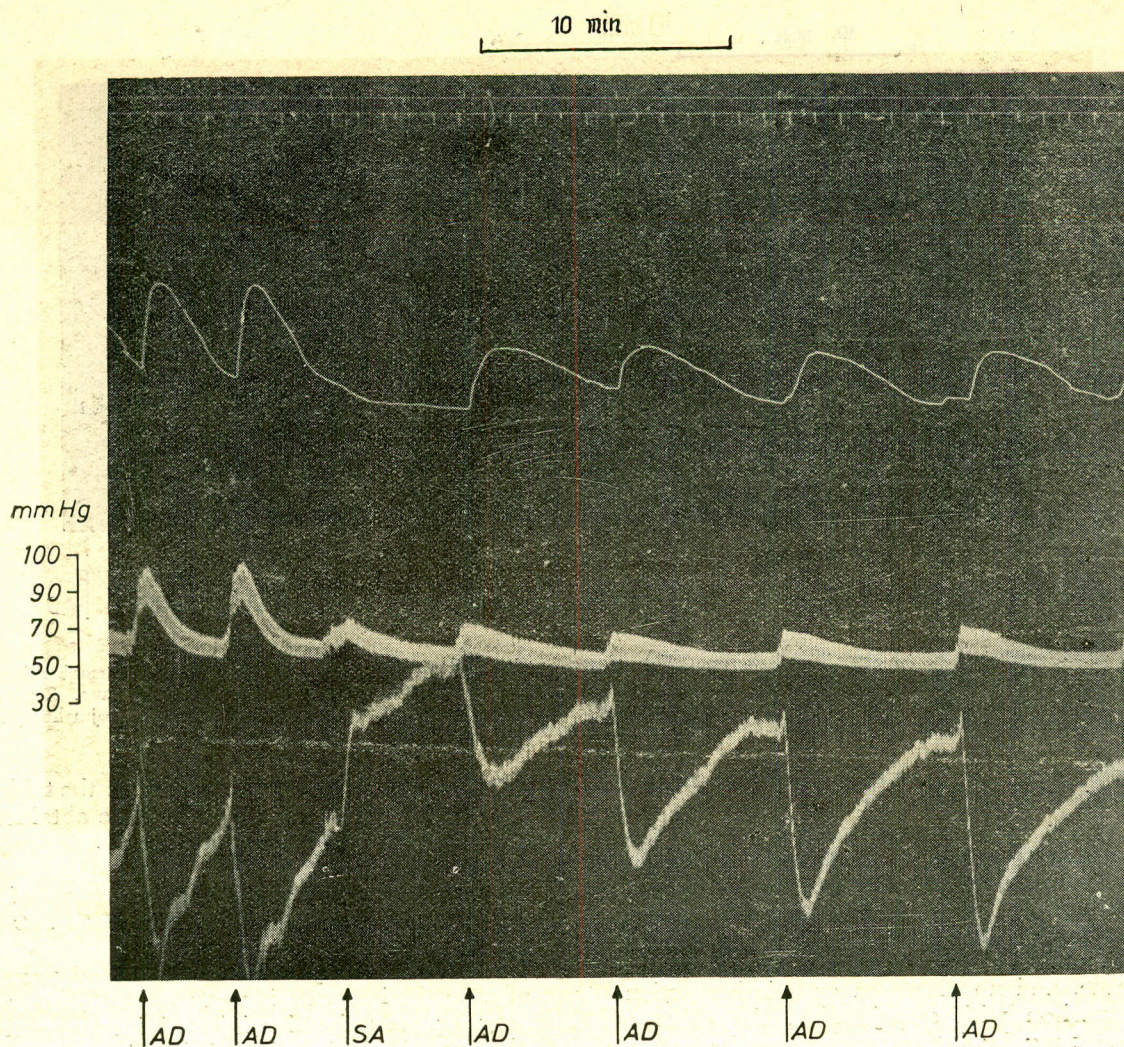


Fig. 5.—Inhibition of the increase of blood pressure caused by adrenalin, contractions of membrana nictitans and of spleen volume. Spinal cat, 2.2 kg., artificial respiration. Recording of blood pressure with Hg manometer from the carotid. Intravenous injections of adrenalin (AD) 10 γ after serpajmaline 10 mg./kg. i.v. (SA). Above: membrana nictitans; middle: blood pressure; and below: spleen volume. Time in minutes. Transient rise of blood pressure and increase of spleen volume after serpajmaline. The adrenalin effects are inhibited.

The tachycardiac effect of adrenalin and noradrenalin on anaesthetised dogs is definitely reduced, the inhibiting effect for noradrenalin being greater than for adrenalin, as can be seen from Table I.

TABLE I

Frequency rise after	Adrenalin	Nor-adrenalin
	30%	26%
After serpajmaline 2 mg./kg. i.v.	19%	9.5%

The inhibitory action of adrenalin on the intestine is slightly weakened (Fig. 7).

(3) **Effect of Serpajmaline on Body Temperature.**—No variation of the body temperature of rabbits was observed after subcutaneous injection of 1-5 mg./kg. serpajmaline.

(4) **Action of Serpajmaline on the Intestine.**—It has long been known that some *Rauwolfia* alkaloids have an exciting effect on the stomach intestinal tract.⁷ With serpajmaline also, after injection of 10 mg./kg. i.v. in cats there is an increase of motility and tone in the intestine

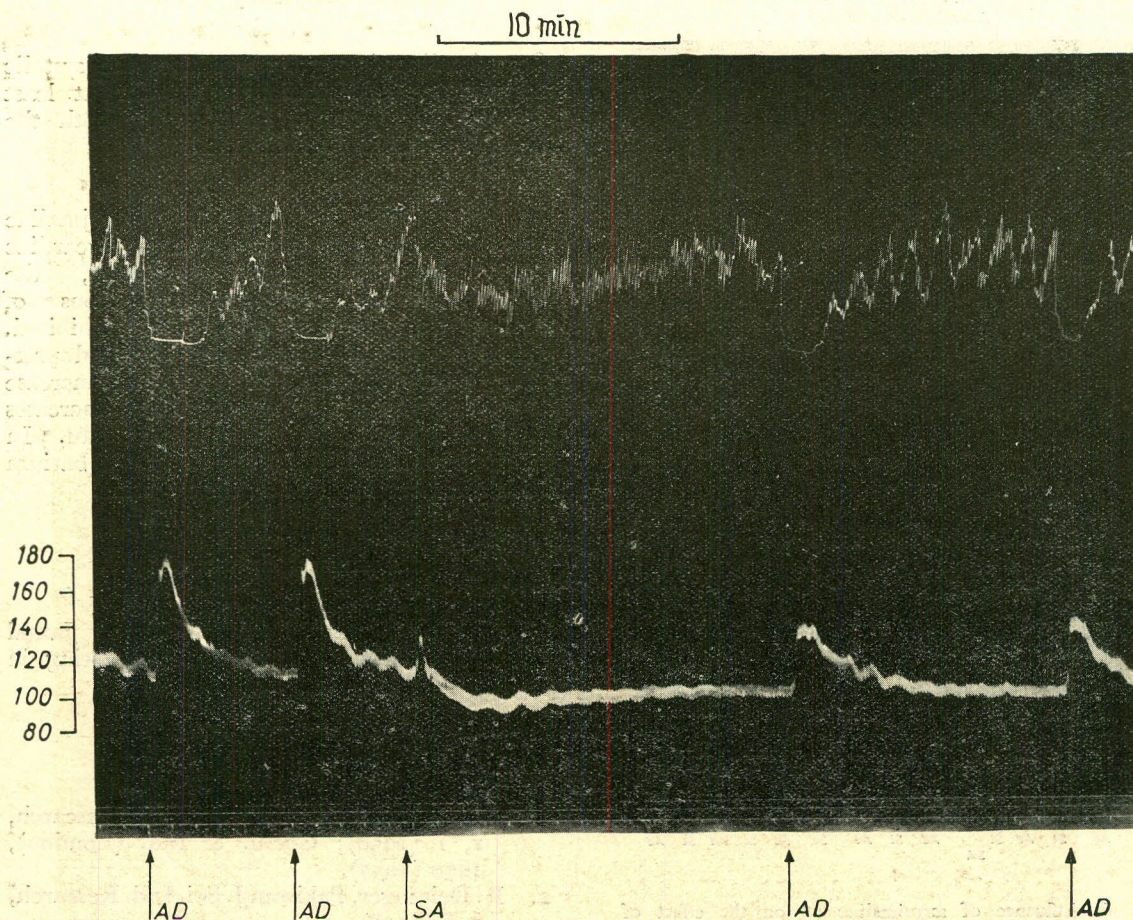


Fig. 7.—Influence of serpajmaline on the contractions of the jejunum in situ. Cat 13 kg. Chloralose anaesthesia. Recording of blood pressure with Hg manometer from the carotid. Above: volume of jejunum; and below: blood pressure. Time in minutes. After serpajmaline 10 mg./kg. (SA) the pressor effect of adrenalin (AD) on the blood pressure is reduced. The inhibitory effect of adrenalin on the intestine is slightly reduced. The intestine reacts with enhanced tone and contractions.

in situ. On the isolated ileum of guinea-pigs serpajmaline in concentrations of 1×10^{-5} inhibits contractions induced by barium chloride and acetylcholin.

Discussion

The hypotensive action of serpajmaline is not complicated by any of the side effects encountered with compounds such as reserpine or rescinnamine, the ganglion blockers or the anti-adrenalin drugs. Thus there is no sedative action, anorexia or diarrhoea or postural hypotension. Serpajmaline induces a bradycardia of the sinus. On the basis of the anti-adrenergic activity it is to be assumed that the inhibition of the adrenergic innervation of the vessels is the cause of the effect on the

circulation. However, this inhibition is certainly not necessarily or exclusively the sole cause. The action of the serpajmaline on the relieving reaction of the carotid sinus² provides evidence that not only the periphery of the vessels but also central mechanisms of the circulation are affected by the action. But it is difficult to draw conclusions as to central activity of a drug known to possess anti-adrenalin activity. Spinal animals show a transient rise of blood pressure after serpajmaline. Dihydro ergot alkaloids raise the blood pressure in spinal animals and lead to reductions of blood pressure only when there is an intact connection between medulla and the upper thoracic marrow,⁸ which points to medullary centres being involved. The fact that serpajmaline is a mixture of five bases

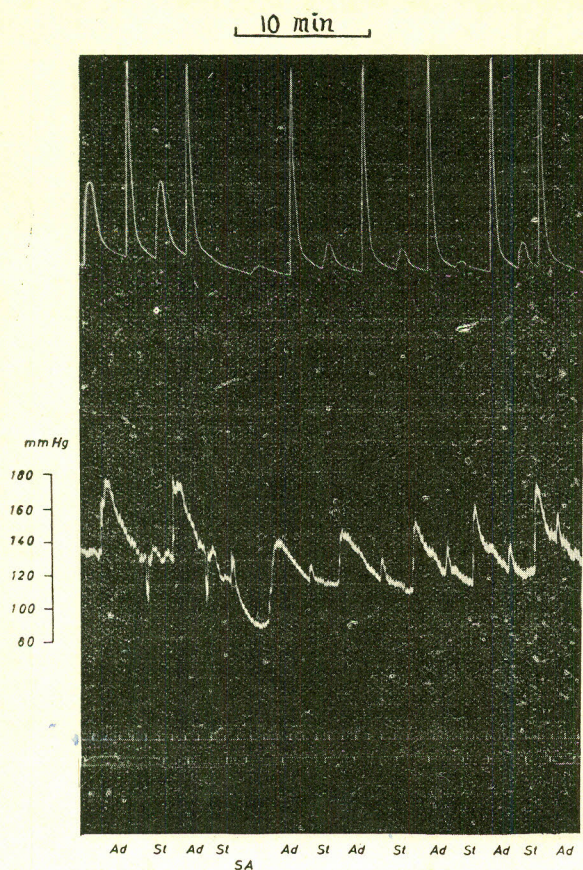


Fig. 6.—Influence of serpajmaline (a) on the effect of adrenalin on the membrana nictitans and the blood pressure, (b) on the contractions of the nictitans and the blood pressure after supramaximal stimulation of the vago-sympathicus. Cat 2.3 kg. Chloralose anaesthesia. Recording of blood pressure with Hg manometer from the carotid. Above: membrana nictitans; and below: blood pressure. Intravenous injections of adrenalin (AD) 10 γ , stimulation of the vago-sympathicus (ST). After serpajmaline 8 mg./kg., lowering of the blood pressure and inhibition of the contractions of the membrana nictitans and pressor effect produced by adrenalin. Blockage of the peripheral vagus effect. No effect on the nictitans membrane after preganglionic stimulation.

and carbohydrates renders more difficult the pharmacological interpretation of the complex mechanism producing the action. Further experiments for elucidating the pharmacology and toxicology of serpajmaline will be treated in greater detail in a separate paper.

Summary

Serpajmaline (5 mg./kg.) reduces the systolic blood pressure of conscious dogs for at least 24 hours. The drug is effective by both the oral and the intramuscular routes.

In anaesthetised animals, serpajmaline reduces blood pressure and has a bradycardiac action. The nictitating contraction, the pressor, and the tachycardiac actions of adrenalin and noradrenalin are inhibited. In spinal animals, transient rises of blood pressure are observed, together with an increase of spleen volume. Serpajmaline increases motility and tone of the intestine in situ. In vitro, serpajmaline inhibits the action of barium chloride and acetylcholine on the intestine.

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