INVOLVEMENT OF CENTRAL ADRENERGIC MECHANISMS IN THE INDUCTION OF CARDIAC ARRHYTHMIAS BY ACONITINE NITRATE ADMINISTERED INTRAVENTRICULARLY

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Summary: Aconitine, 10 μg, administered intraventricularly in cats produced cardiac arrhythmias. Intraventricular administration of phenoxybenzamine, propanolol and practolol abolishes the centrally induced cardiac arrhythmias. Intraventricular reserpinization also abolished these cardiac arrhythmias whereas intraventricular administration of 6-hydroxydopamine and tetrabenazine had no effect. Brain stem noradrenaline probably plays a role in these centrally induced cardiac arrhythmias by aconitine.

Key words: aconitine cardiac arrhythmias central adrenergic mechanisms

INTRODUCTION

In our previous papers (22, 23) we have shown that introduction of 10 μg aconitine nitrate into the lateral cerebral ventricles of cats evoked pressor responses and cardiac arrhythmias and the target area for these arrhythmias is the floor of the fourth ventricle; no cardiac arrhythmias were produced in vagotomized, sympathectomized and reserpinized cats.

This study has been undertaken in an attempt to throw light on the role of brainstem noradrenaline and the role of central alpha and beta receptors in cardiac arrhythmias induced by intraventricular injection of aconitine nitrate.

MATERIALS AND METHODS

Thirty cats of either sex weighing between 2 and 4 *kg* were anaesthetized with ether followed by chloralose, 80 *mg/kg*, intravenously. Cannulation of the lateral ventricle was carried out by the method of Feldberg and Sherwood (10) and a Collison cannula implanted into the ventricle.

In three cats, anaesthetized with pentobarbitone Collison's cannulae were implanted into the lateral ventricles under strict aseptic precautions. The cats were allowed to recover and were utilised for the experiment after an interval of one week.

The mean blood pressure was recorded from the common carotid artery using a mercury manometer attached to a smoked drum kymograph. Electrical activity of the heart was recorded

by means of a Cardiopan-2 electrocardiograph using lead II. The cats were maintained on artificial respiration throughout the experiment. Rectal temperature was recorded and maintained between 36-37°C throughout the experiment.

The intraventricular (lateral ventricle) injection of drugs for the purposes of pre-treatment is referred throughout as "central pre-treatment". Phenoxybenzamine in a dose of 500 μg was administered intraventricularly to cats. Central pre-treatment was also carried out with propranolol (500 μg), practolol (1 mg), tetrabenazine (500 μg), and 6-hydroxydopamine (500 μg). Aconitine was administered intraventricularly one hour after central pre-treatment except for tetrabenazine and 6-hydroxydopamine where the waiting period after central pre-treatment was two hours.

Reserpine in a dose of 500 μg was administered intraventricularly 24 hours before starting the experiment in three cats chronically implanted with Collison's cannulae.

Administration of 10 μg aconitine nitrate intraventricularly was carried out only after a stabilising period of not less than one hour after noting that the electrocardiogram was completely normal.

Control experiments were carried out by injection of 0.9% w/v NaCl intraventricularly and as reported previously (22) no cardiac arryhthmias were seen in any of these experiments.

The criteria on which a disturbance of cardiac rhythm were based was outlined in our last paper (22). The position of the intraventricular cannula was verified by dissection after each experiment.

The standard error of means and test of significance (unpaired 't' test) with determination of probability for the data obtained were calculated according to Mahajan (18).

All injections were given in a volume of 0.2 ml. Drugs were dissolved in normal saline before administration with the exception of practolol. Practolol was dissolved in 5 drops of hydrochloric acid (0. 1. N) and the excess of hydrochloric acid was neutralized with sodium hydroxide (0. 1. N). The solution then made up to the required volume with normal saline.

Drugs: The following drugs were used :

Reserpine (Ciba), tetrabenazine (F. Hoffman-La Roche & Co. A. G.), 6-hydroxydopamine (K and K Laboratories Inc.), phenoxybenzamine bitartrate (Smith, Kline and French), l-propranolol hydrochloride (ICI), practolol (ICI-50172) as the base. The doses were calculated as the base of the substance.

RESULTS

Effect of intraventricular administration of 10 μg aconitine nitrate and heart rate an E.C.G.:

The intraventricular dose of aconitine nitrate required to produce cardiac arrhythmias in 100% of the animals was 1/10th of that required to produce arrhythmia by intravenous route (22). Thus 10 μg of aconitine administered intraventricularly within four minutes produced cardiac arrhythmias, tachycardia and hypertension which persisted for an average of 15 minutes (Fig. 1A and 1B).

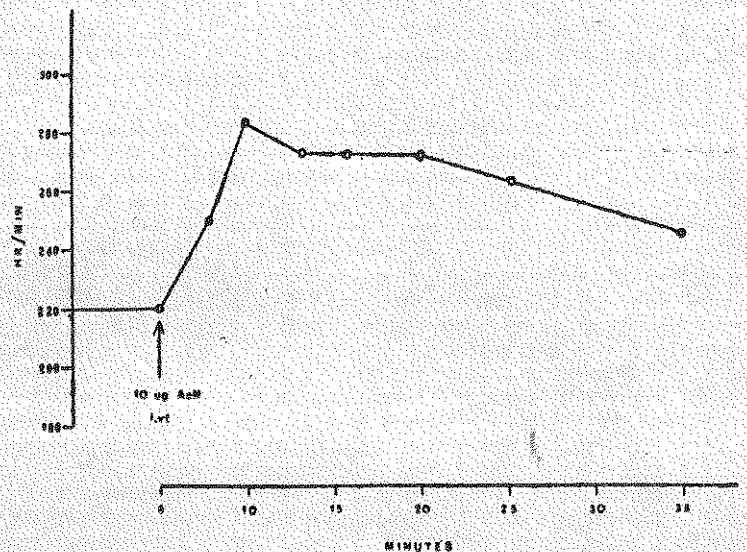
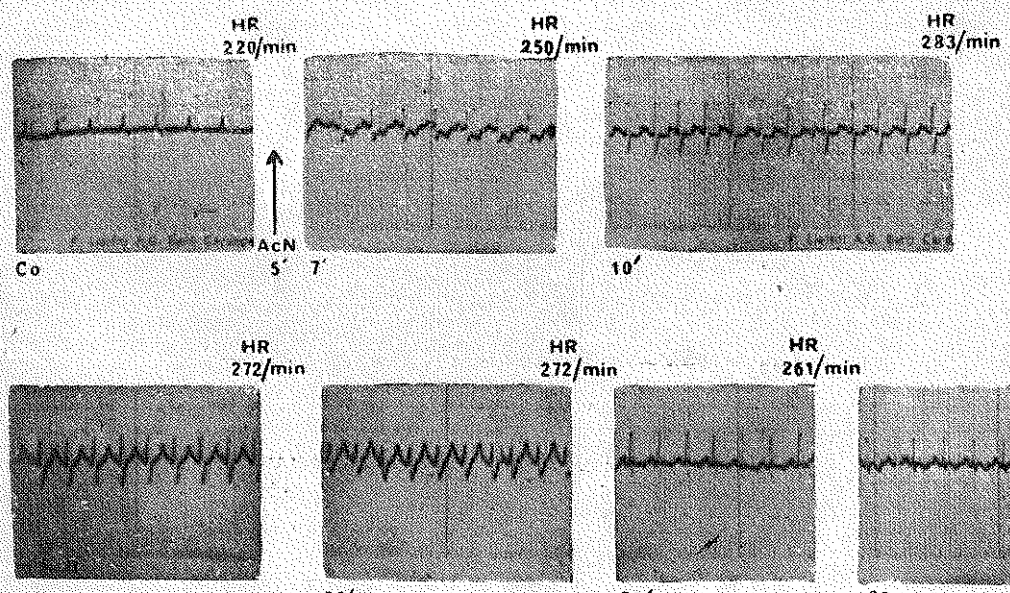


Fig. 1: Cat 2.9 *kg*; Chloralose anaesthesia (80 *mg/kg*) intravenously.

A. Changes in the heart rate (HR/min) induced by intraventricular administration of aconitine nitrate (10 μg. AcN.i.Vt) in a cat.



B. Electrocardiographic changes in heart rate related to Fig. 1A before (Co) and 2,5,10,15, 20 and 30 minutes after AcN.

Central pre-treatment with phenoxybenzamine:

TABLE I: Effect of central pretreatment with phenoxybenzamine (PHE) on the incidence of cardiac arrhythmias induced by intraventricular administration of aconitine nitrate (10 μg).

Drug and dose	*Heart rate per minute*		*Incidence of cardiac arrhythmia**	*P value*
	Control	*Maximum increase Mean + S.E.*		
Aconitine (10 μg)	220	48 +16.96	7/7	—
PHE-Aconitine (500 μg) (10 μg)	187	11 +11.86	0/3	<0.01

*Number of cats in which arrhythmia seen/total number of cats
SE : Standard Error.
The legend is common to all subsequent tables.

Aconitine nitrate, 10 μg, administered intraventricularly in cats centrally pre-treated with phenoxybenzamine (500 μg) did not produce cardiac arrhythmias in any of the three cats tested, whereas the same dose of phenoxybenzamine administered intravenously in a cat of average weight 3 kg did not prevent cardiac arrhythmia after intraventricular administration of aconitine. The degree of cardioacceleration after intraventricular aconitine was significantly less in centrally pre-treated cats than in the control group (Fig. 2A and 2B).

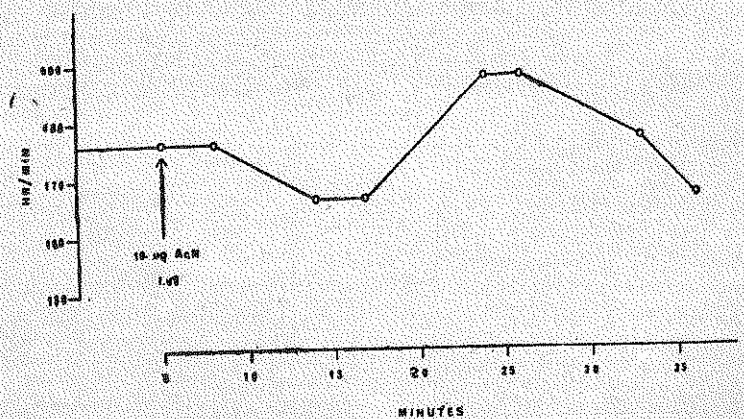
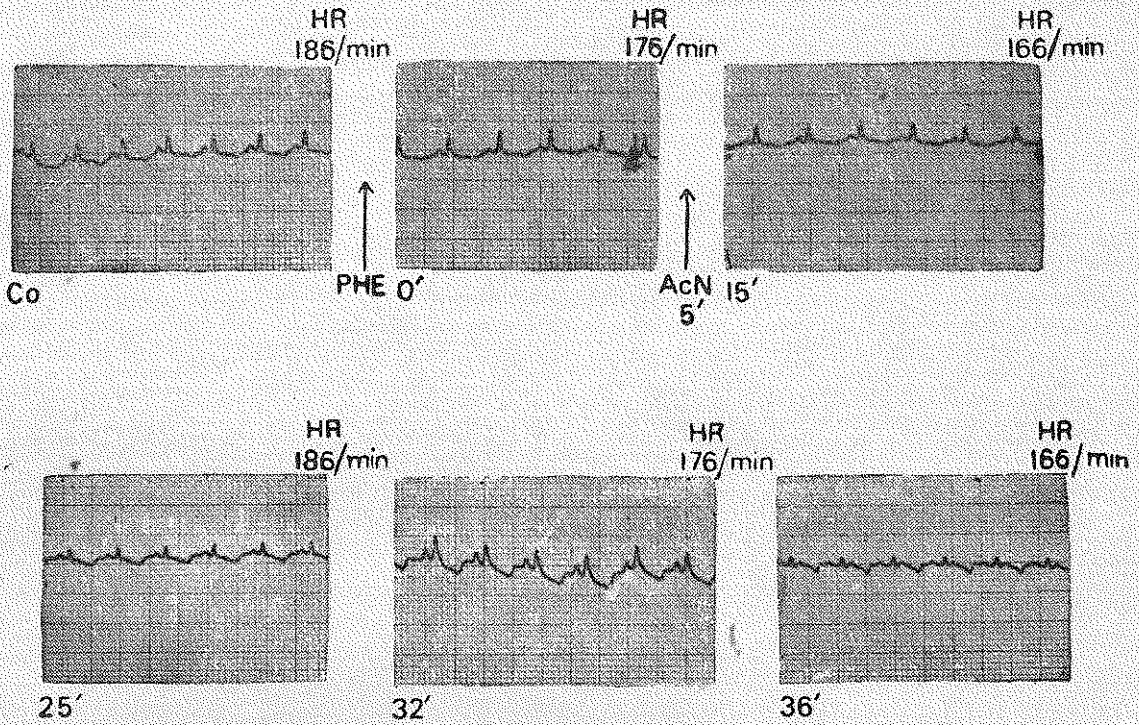


Fig. 2: Cat 3 kg; chloralose anaesthesia (80 mg/kg intravenously.
A. Changes in the heart rate (HR/min) induced by intraventricular administration of aconitine nitrate (10 μg AcN. i.vt) after "central pretreatment" with phenoxybenzamine (PHE) in a cat.



B. Electrocardiographic changes in heart rate related to Fig. 2A before (Co) and after 10,20,27 and 31 minutes after AcN.

Central pre-treatment with beta adrenergic blocking agents:

TABLE II: Effect of central pretreatment with beta-blockers on the incidence of cardiac arrhythmias induced by intraventricular administration of aconitine nitrate.

Drug and dose	*Heart rate per minute*		*Incidence of cardiac arrhythmias*	*P value*
	Control	*Maximum increase Mean ± S.E.*		
Propranolol (500 μg)—	186	19		
Aconitine (10 μg)		± 7.6	0/5	<0.01
Practolol (1 mg)—	230	25		
Aconitine (10 μg)		± 6.2	1/5	<0.05

Propranolol, in a dose of 500 μg intraventricularly, blocked the tachycardia and cardiac arrhythmias induced by intraventricular aconitine. The degree of cardioacceleration was

significantly less than in the control group in all five cats. (Fig. 3A and Fig. 3B). The same dose of propranolol administered intravenously in a cat of average weight 3 *kg* did not block the aconitine induced cardiac arrhythmia. Again, centrally administered practolol in a dose of 1 *mg* completely blocked the aconitine induced cardiac arrhythmia in four out of five cats. The dose of practolol required to block the cardiac arrhythmias was twice that of propranolol.

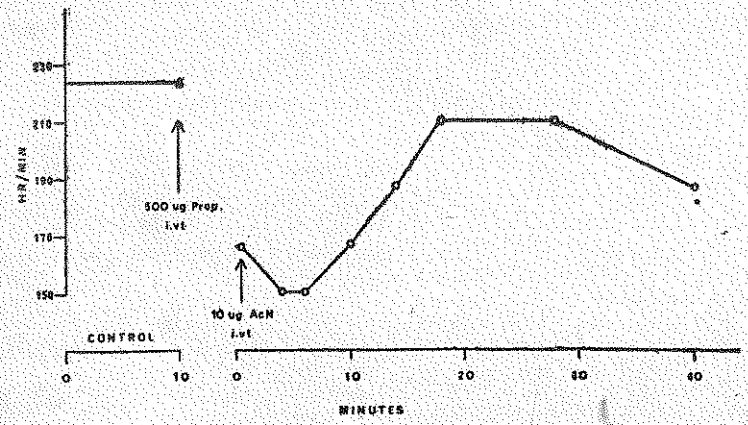
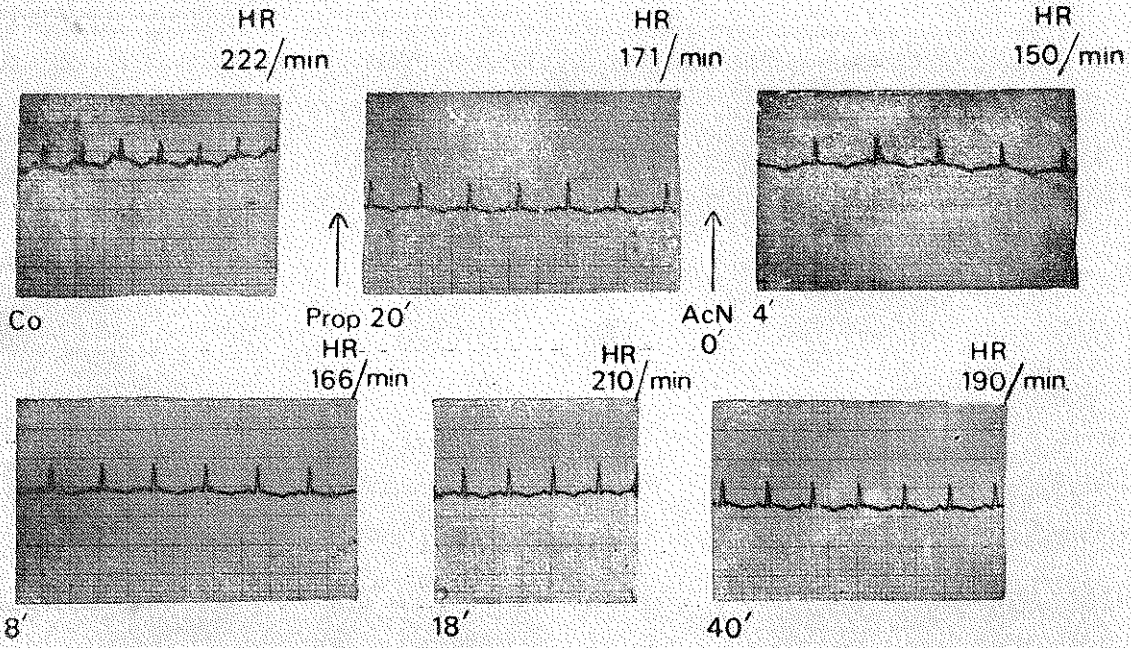


Fig. 3: Cat 3 *kg;* chloralose anaesthesia (80 *mg/kg*) intravenously.

A. Changes in the heart rate (HR/min) induced by intraventricular administration of aconitine nitrate (10 μg AcN i.vt) after "central pretreatment" with propranolol (500 μg Prop i.vt) in a cat.



B. Electrocardiographic changes in heart rate related to Fig. 3A before (Co) and 4,8,18, and 40 minutes after AcN.

Central pre-treatment with reserpine, tetrabenazine and 6-hydroxydopamine:

TABLE III: Effect of central pretreatment with reserpine, tetrabenazine and 6-hydroxydopamine on the incidence of cardiac arrhythmias induced by intraventricular administration of aconitine nitrate.

Drug and dose	*Heart rate per minute*		*Incidence of cardiac arrhythmia*	*P value*
	Control	*Maximum increase Mean ± S.E.*		
Reserpine (500 μg)	136	18 ± 11.0	0/3	<0.01
6-hydroxydopamine (500 μg)	174	34 ± 7.3	3/3	<0.1
Tetrabenazine (500 μg)	197	56 ± 3.0	3/4	—

Central pre-treatment with reserpine in a total dose of 500 μg 24 hours before the commencement of the experiment blocked the cardiac arrhythmias and reduced the tachycardia after intraventricular administration of 10 μg aconitine nitrate in three cats. The central depletion catecholamines was complete as shown by the absence of rise in blood pressure after carotid clamping. 6-hydroxydopamine (500 μg) and tetrabenazine (500 μg) did not block the cardiac arrhythmia and tachycardia induced by aconitine nitrate, 10 μg, administered intraventricularly.

Effect of pre-treatment with drugs and its relation to blood pressure:

Intraventricular injection of 10 μg aconitine nitrate under chloralose anaesthesia was followed in each instance by a rise in blood pressure. Blood pressure rose steeply reaching a peak in about three minutes. The mean maximum increase in blood pressure to intraventricular aconitine after central pre-treatment with drugs is shown in Table IV.

TABLE IV: Effect of pretreatment with drugs and its relation to blood pressure after intraventricular administration of aconitine nitrate (10 μg)

Drug and dose	*Mean maximum increase in blood pressure (mm Hg) Mean ± S.E.*	*P value*
Aconitine (10 μg)	64 ± 4.3	—
Phe-Aconitine (500 μg) (10 μg)	70 ± 10	—
Propranolol-Aconitine (500 μg) (10 μg)	47 ± 8.4	<0.05
Practolol-Aconitine (1 mg) (10 μg)	46 ± 8.0	<0.01
Reserpine-Aconitine (500 μg) (10 μg)	46 ± 8.0	<0.01
6-hydroxydopamine Aconitine (500 μg) (10 μg)	65 ± 5.0	—
Tetrabenazine Aconitine (500 μg) (10 μg)	49 ± 9.0	<0.05

DISCUSSION

Central mechanisms involving catecholamines are thought to play a role in the control of cardiovascular function (2, 7, 8, 11, 12, 20, 21, 26).

Central pre-treatment with Phenoxybenzamine:

In cats centrally pre-treated with phenoxybenzamine intraventricular injection of aconitine (10 μg) induced a pressure response which was attenuated and no cardiac arrhythmias. The same dose of phenoxybenzamine when administered intravenously was unable to block the centrally induced cardiac arrhythmias by aconitine. Thus it follows that blockade of alpha receptors by phenoxybenzamine was central rather than peripheral in origin. This has been amply confirmed by Share and Melville (20). They attributed the absence of E.C.G. changes to a small rise in blood pressure and cardioacceleration to beta receptor stimulation with picrotoxin.

In our experiments central alpha receptor blockade could be achieved with a very small dose of phenoxybenzamine. Although there was no attenuation of the pressor response, there was absence of E.C.G. changes and the degree of cardioacceleration was significantly decreased; there was no significant reduction in hypertensive response. This suggests that in all probability a small dose of phenoxybenzamine is capable of blocking the beta receptors with less increase in cardioacceleration.

It is normally assumed but not validated that catecholamine receptors in the C.N.S. have the same general characteristics as the alpha and beta receptors in the peripheral tissues. Indeed, studies on simple neuronal system in the rabbit olfactory bulb suggest that the specificity of blockade of adrenergic and 5-HT receptors may be quite different from that found in the periphery (4).

Central pre-treatment with beta adrenoceptor blocking agents:

Propranolol in a dose of 500 μg intraventricularly blocked the tachycardia, pressor response and cardiac arrhythmias induced by intraventricular aconitine. The same dose of propranolol administered intravenously in a cat of average weight 3 kg did not block the cardiac arrhythmias. This suggests that beta receptor blockade was central, rather than peripheral in origin and that central beta receptors are responsible for cardiac acceleration.

This has been confirmed by administration of another beta-blocker, practolol administered intraventricularly. Practolol is a selective beta-blocker with no local anaesthetic activity (9) and in a dose of 5 mg/kg intravenously blocks only the excitatory and not the inhibitory responses associated with beta receptors. Propranolol on the other hand possesses a local anaesthetic action and it is thought that beta-adrenergic blocking effect may be due to this property (13, 15, 16, 17). It is therefore speculated that excitatory beta receptors may be present in the central nervous system as they are present in the periphery.

Central pre-treatment with reserpine, 6-hydroxydopamine and tetrabenazine:

Share and Melville (21) have shown that brain stem noradrenaline is possibly involved in centrally mediated sympathetic stimulation by intraventricular picrotoxin. They have further shown that intraventricular administration of reserpine 500 *μg*, 24 hours before the commencement of the experiment was sufficient to deplete the brain stem noradrenaline.

In our experiments "Central reserpinization" prevented cardiac arrhythmias and tachycardia induced by aconitine nitrate administered intraventricularly; the central reserpinization was complete as shown by absence of rise in blood pressure after carotid occlusion. Again, chronic administration of 6-hydroxydopamine intraventricularly causes a long lasting reduction of cerebral noradrenaline and dopamine (1, 3, 6, 24, 25). In our experiments central pre-treatment with 6-hydroxydopamine 500 *μg* did not abolish the cardiac arrhythmias, tachycardia and hypertension by aconitine nitrate. Two possible explanations could be put forward:

1. Acute administration of a small dose of 6-hydroxydopamine causes a release of endogenous noradrenaline. This has been confirmed by recent studies *in vitro* (14) and *in vivo* (5). Intraventricular administration of aconitine may cause further release of brain stem noradrenaline leading to stimulation of post-ganglionic neurones.

2. Acute administration of a small dose of 6-hydroxydopamine is converted into "False transmitter" which initially may evoke stimulation of post-ganglionic neurones.

Similarly, Pletscher (19) has shown that tetrabenazine depletes brain noradrenaline and 5-hydroxydopamine when administered intravenously in a dose of 50 *mg/kg* as a single injection. In present experiments prior central pre-treatment with tetrabenazine (500 *μg*) two hours before did not abolish the cardiac arrhythmias and tachycardia but reduced the hypertension induced by intraventricular aconitine. It probably appears therefore that intraventricular administered tetrabenazine is unable to penetrate completely into the ventricular ependyma and reach the crucial central sites to cause complete depletion of brain noradrenaline.

In conclusion we state that intraventricular aconitine acts by releasing brain stem catecholamines possibly noradrenaline.

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