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Role of catecholamines in centrogenic cardiac arrhythmia induced by aconitine

K. P. BHARGAVA, R. P. KOHLI, J. N. SINHA AND G. TAYAL

Neuropharmacology Unit of the Council of Scientific and Industrial Research, Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow—3, India

1. Injection of 20 μg of aconitine into the lateral ventricle of dogs anaesthetized with pentobarbitone regularly induced cardiac irregularities and hypertension. The cardiovascular changes appeared within 5 min and lasted for about 90 min. Tachyphylaxis to the aconitine-induced cardiovascular effects was observed.

2. The aconitine-induced arrhythmia and hypertension were centrogenic, for they were abolished or prevented by spinal transection (C_2) or ganglionic blockade.

3. Bilateral vagotomy as well as bilateral stellate ganglionectomy merely raised the threshold for arrhythmia without affecting the blood pressure response. The neural supply to the heart, therefore, does not seem to be the major pathway concerned in the genesis of the centrogenic cardiovascular effects of aconitine.

4. The centrally evoked release of endogenous catecholamines from the adrenal glands was responsible for the aconitine-induced arrhythmia, since the arrhythmia could be blocked or prevented by prior reserpinization, bilateral adrenalectomy or thoracic splanchnic nerve section.

5. α- and β-adrenoceptive receptor blocking agents prevented or abolished the aconitine-induced arrhythmia in a manner similar to the catecholamine-induced arrhythmia.

The attention of most investigators concerned with the genesis of cardiac arrhythmias is generally focused on the tissues within the heart itself. The importance of the central nervous system in controlling the activity of the heart has been relatively neglected because the heart is capable of autonomous activity independent of neural control. There is, however, ample evidence for centrogenic cardiac arrhythmias. Clinically, cardiac arrhythmias occur when there is stimulation of the central neural structures by mechanical means (Pool & Kessler, 1958). Cardiac arrhythmias of central origin have been more clearly demonstrated in experimental studies using electrical stimulation of different areas of the brain, particularly the hypothalamic and other diencephalic and midbrain structures (Purpura, Pool, Housepian, Girado, Jacobson & Seymour, 1958; Weinberg & Fuster, 1960; Manning & Cotton, 1962; Kenneth, Melville, Blum & Shister, 1963; Attar, Gutierrez, Bellet & Ravens, 1963). Chemical stimulation of foci concerned with cardiac function has proved successful in eliciting centrogenic arrhythmias, and attempts have been made to study the

underlying mechanism. Wang and co-workers have favoured a medullary origin of arrhythmias induced by pentylenetetrazol, picrotoxin and deslanoside (Bircher, Kanai & Wang, 1962; Bircher, Kanai & Wang, 1963). A hypothalamic site has been suggested for the centrogenic arrhythmia induced by intracerebroventricular injection of caffeine (Dikshit, 1934). It appears that different chemicals may act at a number of central sites to generate cardiac arrhythmia.

In delineating the mechanism of centrogenic arrhythmia it is important to determine the contribution of various neural as well as humoral factors concerned in the genesis of the arrhythmia. The catecholamines are capable of producing cardiac arrhythmias, particularly during hydrocarbon-induced anaesthesia (Dipalma, 1956; Nickerson & Nomaguchi, 1949). Selective liberation of catecholamines from the adrenal glands is possible by electrical stimulation of specific areas in the central nervous system (Folkow & von Euler, 1954). The role of catecholamines in the genesis of centrogenic arrhythmias induced chemically, however, has not been determined. When applied to the surface of the heart, aconitine consistently produces cardiac irregularities, possibly due to a powerful membrane-depolarizing action (Scherf, 1947). In the present study a similar action, but induced via a central mechanism by the intracerebroventricular administration of aconitine, was utilized for evoking centrogenic cardiac arrhythmia and hypertension.

Further investigation of the mechanism of the arrhythmia and the concomitant blood pressure increase was made using surgical and chemical methods for abolishing neural and humoral influences on the heart.

Methods

Sixty mongrel dogs (10–20 kg) of both sexes were used in the present study. The animals were anaesthetized with pentobarbitone sodium (30 mg/kg intravenously) and maintained on positive pressure artificial respiration. Drug solutions were injected through a cannula inserted into the right femoral vein. Blood pressure was recorded from the right femoral artery by means of a pressure transducer (Statham P 23). The e.c.g. (lead II) was recorded on a Grass Model 5 Polygraph. Intracerebroventricular (i.c.v.) injections of aconitine were made through a stainless steel cannula introduced into the lateral ventricle according to the method described by Bhargava & Tangri (1959). Aspiration of cerebrospinal fluid indicated the proper placement of the cannula, which was confirmed at necropsy. Some experiments were done using conscious dogs in which cannulae had been implanted in the lateral ventricles under pentobarbitone anaesthesia 2 or 3 days previously. The volume of aconitine solution injected into the lateral ventricle did not exceed 0·25 ml. and was followed by 0·25 ml. of normal saline.

Surgical procedures

Surgical interruption of neural pathways was effected in acute experiments to study the mechanism of aconitine-induced cardiac arrhythmias. Bilateral vagotomy was performed in the cervical region, and spinal transection at the level of the second cervical vertebra. Skin incision, laminectomy and exposure of the cord in some cases was done before the induction of aconitine arrhythmias and the cord was transected during the course of the arrhythmias. Similarly, prior exposure of the adrenal glands by the lumbar route was made in some experiments in order

to observe the effects of bilateral adrenalectomy on the aconitine-induced arrhythmia.

For removal of stellate ganglia an incision about 7.5 cm long was made in the third intercostal space extending anteriorly from the posterior axillary line. The muscles in the line of incision were cut and retracted to expose the parietal pleura. The pleura was then carefully cut so that the underlying lung was not damaged. The lung was retracted antero-inferiorly and the sympathetic chain lying paravertebrally was seen shining through the posterior parietal pleura. The pleura was cut and the sympathetic chain dissected *in situ* to expose the stellate ganglion, which was found lying over the head of the first rib. The stellate ganglion, along with its branches, was excised together with 3·0 cm of the sympathetic chain.

The thoracic splanchnic nerves, which are the major sympathetic supply to the adrenal glands (Mizeres, 1955), were transected in the thorax on both sides at the level of the ninth rib before their entry into the abdominal cavity.

Pharmacological procedures

Ganglionic blocking agents or reserpine were used to block neural impulses. Reserpine pretreatment was accomplished by the intramuscular administration of reserpine 0·5 mg/kg for 2 successive days before the experiment. Chlorisondamine (Ecolid) and mecamylamine were given intravenously either before or after induction of cardiac arrhythmias. Blockade of α- or β-adrenoceptive receptors was achieved by the use of specific blocking agents.

Results

Experiments on dogs anaesthetized with pentobarbitone

Control experiments

In fifteen dogs the effect of 5, 10, 15 and 20 μg of aconitine introduced into the lateral cerebral ventricle was observed on the e.c.g. pattern and the systemic arterial blood pressure. The first observable change in the e.c.g. was sinus tachycardia, which gradually became more marked. This was followed by the appearance of occasional ventricular extrasystoles and atrioventricular dissociation culminating in ventricular tachycardia and fibrillation. Together with the e.c.g. changes, the systemic arterial blood pressure gradually showed a rise of 125 to 250 mm Hg and suddenly dropped with the appearance of ventricular fibrillation. The intracerebroventricular dose of aconitine which consistently induced cardiac arrhythmia was found to be 20 μg. Inconsistent changes in the e.c.g. were seen with the lower doses of aconitine. In some experiments, when recovery of cardiovascular effects (cardiac arrhythmia and marked hypertension) occurred following the first dose of aconitine, subsequent injection of the same or higher dose of aconitine failed to elicit the e.c.g. and blood pressure changes. It appears that the phenomenon of tachyphylaxis to cardiovascular effects occurs with intraventricular aconitine.

Effect of bilateral vagotomy

In two dogs the dose of aconitine which usually produced arrhythmias (20 μg) was ineffective in inducing cardiac irregularities, but a marked rise of blood pressure was still observed. Injection of twice the usually arrhythmic dose of aconitine (40 μg), however, induced cardiac abnormalities in two out of three vagotomized dogs.

Effect of spinal transection

Acute spinal transection at C_2 in three dogs effectively prevented the development of aconitine-induced cardiac arrhythmia and the hypertensive response. Injections of aconitine 20, 40 and 80 μg were found ineffective for eliciting the cardovascular effects in these animals. Furthermore, acute spinal transection performed during the course of arrhythmia abolished the aconitine-induced cardiac irregularities in one dog. The results of this experiment are shown in Fig. 1. The control electrocardiograph (A) was converted into sinus tachycardia at 10 min (B) following intraventricular injection of aconitine (20 μg). At 30 min (C), typical arrhythmic changes characterized by ventricular extrasystoles were seen. Spinal transection (C_2) immediately converted the arrhythmia to regular rhythm (D).

Effect of bilateral stellate ganglionectomy

Acute bilateral stellate ganglionectomy was performed in four animals to study the role of the sympathetic supply to the heart in aconitine-induced arrhythmia.

The results of one such experiment are shown in Fig. 2. The first panel is control record. The lower tracing is record of blood pressure and the upper tracing is the electrocardiogram. A period of 2 hr was allowed to elapse after bilateral stellate ganglionectomy before any further experimental procedures were undertaken. Record B was obtained 90 min after ganglionectomy. The intraventricular injection of aconitine (20 μg) did not elicit any change in the e.c.g. in the first hour. Record C, taken 40 min after the injection of aconitine, shows a marked rise in blood pressure but no change in the e.c.g. Subsequently, twice the uniformly arrhythmic dose of aconitine (40 μg) was injected. The arrhythmia appeared after

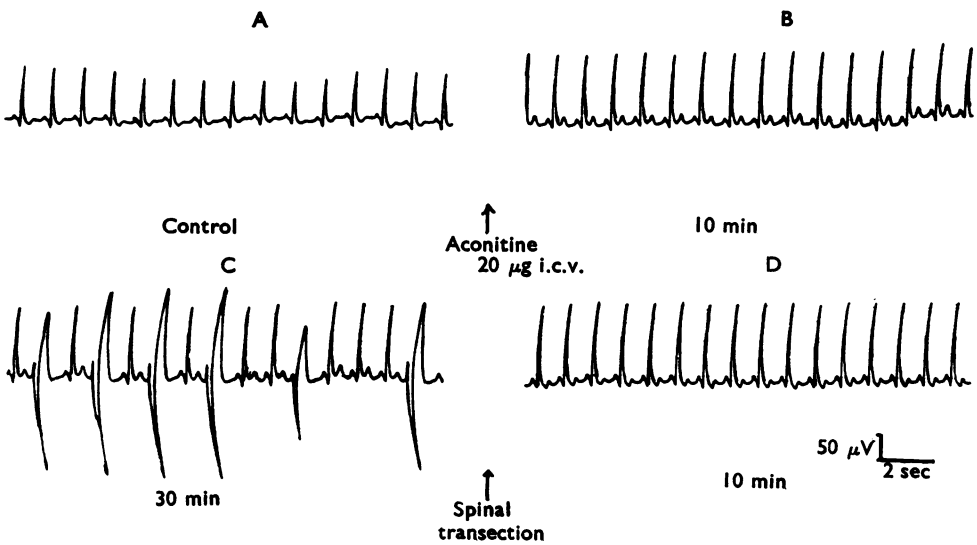

FIG. 1. Effect of aconitine (20 μg i.c.v.) on the e.c.g. pattern of dogs anaesthetized with pentobarbitone. Note the sinus tachycardia at 10 min (B), ventricular extrasystoles at 30 min (C). Spinal transection at C_2 converted the cardiac arrhythmia into normal sinus rhythm (D) within 10 min.

a longer latency and was not well sustained. No change in e.c.g. was observed 10 min after this dose of aconitine (D), but ventricular extrasystoles appeared after 30 min (E) and the e.c.g. returned to normal after 50 min (F). The blood pressure, however, remained high throughout the experiment, following the first injection of aconitine.

Effect of bilateral adrenalectomy

The adrenals were removed in four dogs to study the part played by catecholamine release from these glands. In three dogs adrenalectomy was performed before the injection of the arrhythmia-inducing dose of aconitine. In none of the animals could arrhythmia be induced by intraventricular aconitine in doses up to 40 μg. In one of these dogs, which failed to exhibit arrhythmia with aconitine, adrenaline (100 μg/kg) injected intravenously immediately elicited the arrhythmic response, which was of short duration. In one dog adrenalectomy was performed during the course of aconitine-induced cardiac arrhythmia. The results of the experiment are shown in Fig. 3. The upper record is of blood pressure and the lower record is the e.c.g. Injection of aconitine (20 μg) induced the usual tachycardia at 10 min (B) and ventricular arrhythmia at 30 min (C). The blood pressure was elevated in both records. At this time the adrenals were carefully removed from the previously exposed lumbar region. The abnormal cardiac rhythm and the elevated blood pressure returned to normal immediately after bilateral adrenalectomy. The recovery of blood pressure and e.c.g. is shown in D at 10 min following bilateral adrenalectomy.

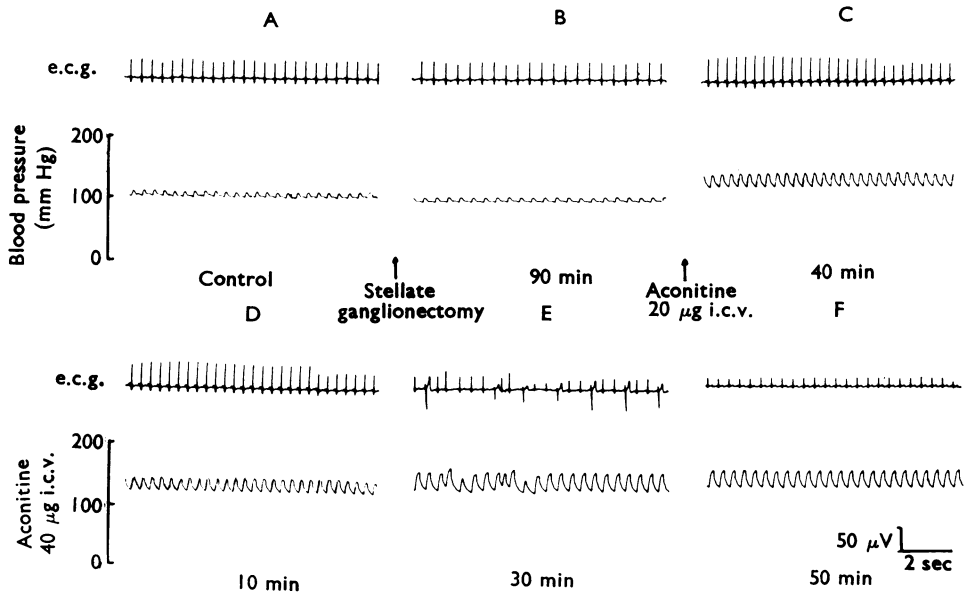

FIG. 2. Effect of bilateral stellate ganglionectomy on the aconitine-induced e.c.g. and blood pressure changes. Note that aconitine (20 μg i.c.v.), 90 min after stellate ganglionectomy, induced a rise in blood pressure without any change in e.c.g. pattern up to 40 min (C). A second injection of aconitine (40 μg), however, induced tachycardia after 10 min (D) and ventricular extrasystoles at 30 min (E). Recovery from the drug was seen at 50 min (F).

Effect of thoracic splanchnic nerve section

The thoracic splanchnic nerves, which constitute the major nerve supply to the adrenals, were transected in two animals at the level of T_9 in the thorax to eliminate the central neural impulses for catecholamine release. The neurectomy was found to be quite adequate in converting the aconitine-induced arrhythmia to normal sinus rhythm, and the blood pressure was also lowered by the procedure. In two dogs prior neurectomy prevented the development of cardiac irregularities to intraventricular injection of aconitine (20 and 40 μg), although a rise in blood pressure was observed.

Effect of ganglionic blockade

Ganglionic blockade was effected by chlorisondamine chloride (Ecolid) 5·0 mg/kg intravenously (three dogs) and mecamylamine hydrochloride 5·0 mg/kg intravenously (two dogs), given before the intraventricular injection of aconitine (20 μg). The resting blood pressure following ganglionic block was about 50 mm Hg. Aconitine injection was without effect on the blood pressure or on the e.c.g. In one dog the aconitine-induced cardiac irregularity and the hypertension were converted to normal cardiac rhythm and hypotension after mecamylamine (5·0 mg/kg intravenously).

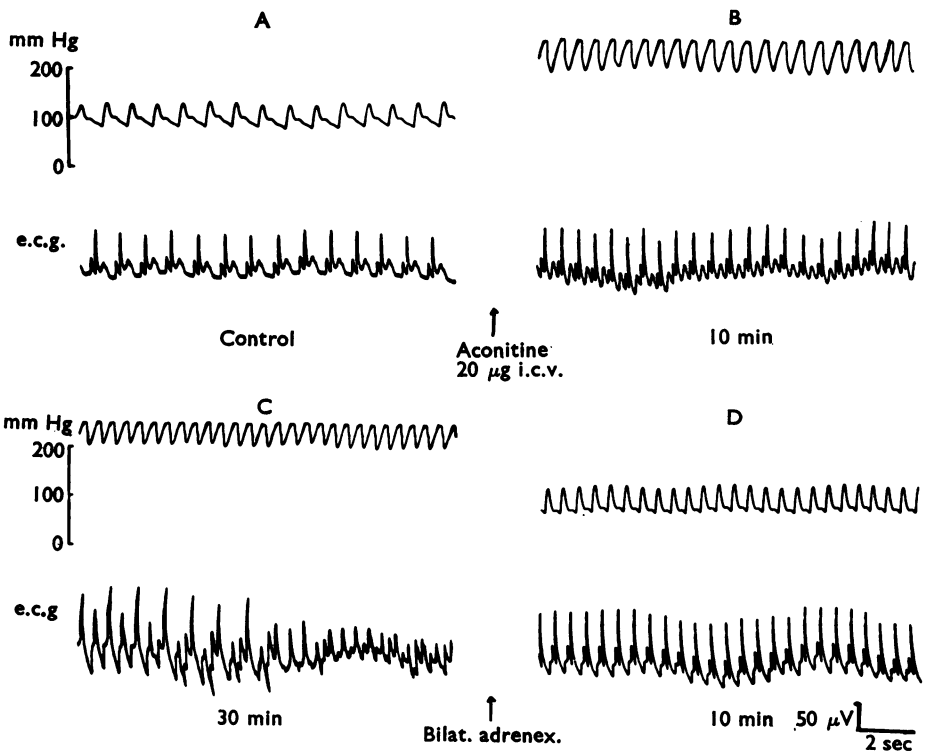

FIG. 3. Effect of bilateral adrenalectomy on aconitine-induced cardiovascular changes. Intracerebroventricular injection of aconitine (20 μg) induced sinus tachycardia at 10 min (B) and ventricular tachycardia at 30 min (C). Note that removal of the adrenals during the course of arrhythmia immediately restored the normal rhythm of the heart and lowered the blood pressure (D).

Effect of reserpinization

In two dogs intramuscular injections of reserpine (0·5 mg/kg) were given daily for 2 days and subsequently aconitine (20–40 μg) was introduced into the lateral cerebral ventricle. The usual arrhythmia, produced by aconitine in normal animals, could not be obtained in the reserpinized animals with twice the arrhythmic dose of aconitine (40 μg). There was no rise in systemic arterial blood pressure with aconitine in the reserpinized dogs.

Effect of α-adrenoceptor blockade

The α-adrenoceptive receptors were blocked by intravenous injection of phenoxybenzamine, 10 mg/kg (two dogs) and yohimbine 1·0 mg/kg (two dogs). Subsequent intraventricular injection of aconitine (20 μg) failed to elicit the usual arrhythmia and rise in blood pressure.

Effect of β-adrenoceptor blockade

In six dogs blockade of the β-adrenoceptive receptors was effected by the intravenous injection of pronethalol (3·0 mg/kg), propranolol (3·0 mg/kg) or INPEA

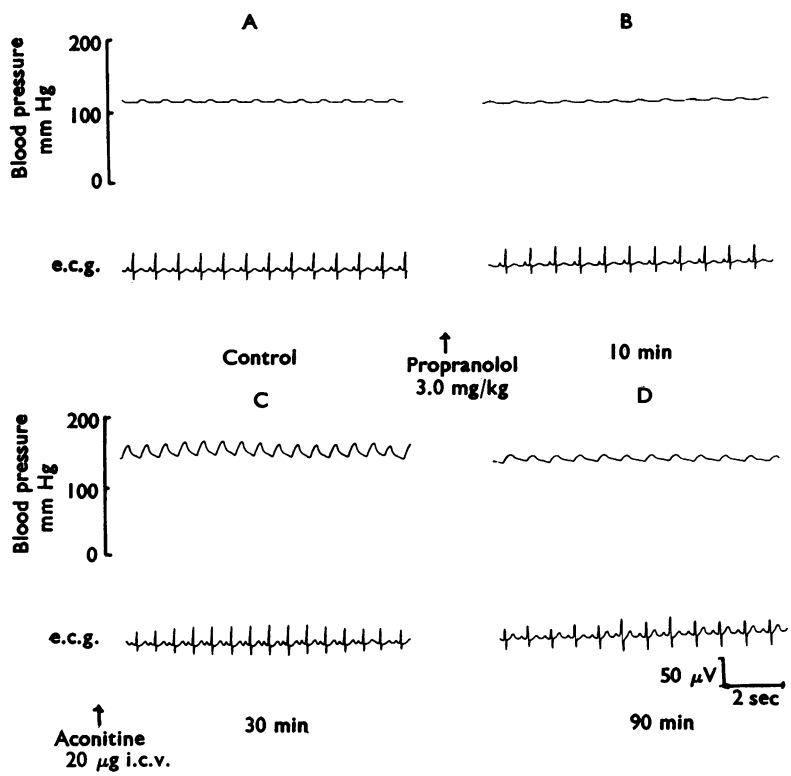

FIG. 4. Effect of propranolol on the cardiovascular effects of intracerebroventricular aconitine. Pretreatment with propranolol (3·0 mg/kg intravenously) did not produce significant changes in the e.c.g. and blood pressure (B). After propranolol, aconitine (20 μg i.c.v.) induced the rise in blood pressure without any cardiac irregularities (C). Recovery from the aconitine effect was seen at 90 min (D).

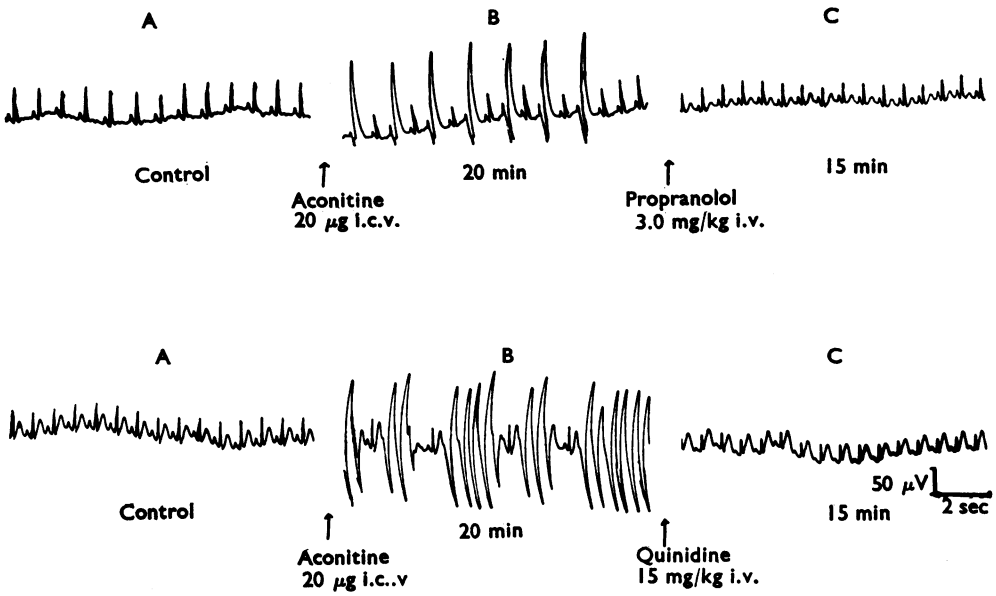

FIG. 5. Effect of propranolol (upper panel) and quinidine (lower panel) on the aconitine-induced cardiac irregularities. Only 3·0 mg/kg of propranolol was required to abolish the cardiac arrhythmia induced by aconitine, but quinidine 15 mg/kg was required.

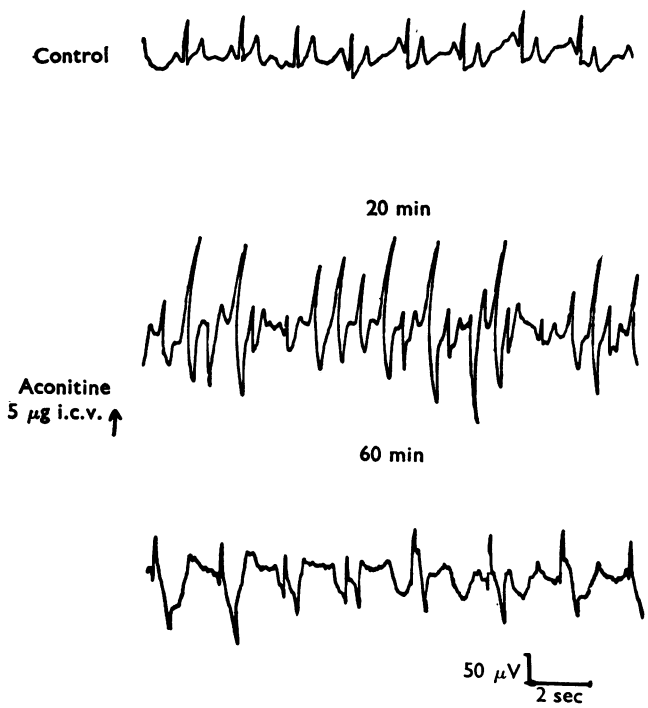

FIG. 6. Electrocardiograph changes induced by intracerebroventricular aconitine (5 μg) in a conscious unanaesthetized dog. At 20 min, aconitine-induced ventricular tachycardia, which was reduced after 60 min.

(3·0 mg/kg), each drug being used in two dogs. Subsequent intraventricular injection of aconitine (20 μg) consistently elicited a rise in blood pressure, but there was no cardiac irregularity. Figure 4 shows the results of an experiment in which the β-adrenoceptive receptors were blocked by propranolol. There was no significant effect of propranolol on the e.c.g. or the blood pressure level. Injection of aconitine (20 μg) into the lateral ventricle (see lower panels) elicited the usual rise in blood pressure, but there was no irregularity in the e.c.g. except slight tachycardia. At 90 min, following the aconitine injection, the blood pressure level returned to the control level and there was no tachycardia at this stage.

Effect of quinidine

In two dogs cardiac arrhythmia was induced by the usual intraventricular injection of aconitine (20 μg). A slow intravenous injection of quinidine sulphate was given to abolish the arrhythmia. The total dose of quinidine required to convert the arrhythmia to a normal sinus rhythm was found to be 15 mg/kg. A record of the comparative anti-arrhythmic activity of propranolol and quinidine is shown in Fig. 5. In both dogs the arrhythmia obtained with intraventricular injection of aconitine (20 μg) was recorded 20 min after giving the drug. Subsequently, a slow intravenous injection of propranolol 3·0 mg/kg (upper record) and quinidine 15·0 mg/kg (lower record) abolished the aconitine-induced arrhythmia within 15 min.

Experiments in conscious unanaesthetized dogs

In three dogs with chronically implanted cannulae in the lateral cerebral ventricles the effects of injections of aconitine (1·0, 2·5 and 5·0 μg) on the e.e.g. and the general behaviour were observed. Clear cardiac irregularities were observed with the 5 μg dose of aconitine at 20 min (see Fig. 6). The animals were unrestrained and behavioural effects were characterized by rapid respiration, pupillary dilatation, piloerection, salivation, increase in muscle tone with extension of the hind legs and a dazed appearance.

Discussion

Previous investigators have observed cardiac arrhythmias following the introduction of chemical agents into the ventricular system of dogs, cats and rabbits. Centrogenic cardiac arrhythmias can be elicited by certain analeptics; pentylenetetrazol (Bircher *et al.*, 1962, 1963), picrotoxin (Bircher *et al.*, 1962; Varma, Share & Melville, 1962; Bircher *et al.*, 1963) and caffeine (Dikshit, 1934), cardioactive drugs; digitalis glycosides (Bircher *et al.*, 1962, 1963) strophanthidin (Haley & Weinberg, 1955), quinidine and procainamide (Weinberg & Haley, 1955) and autonomic agents; acetylcholine and nicotine (Dikshit, 1934). A central origin of these arrhythmias was inferred because the agents were localized to restricted regions of the central nervous system and they induced the arrhythmia in doses which were ineffective on peripheral administration. The arrhythmia was abolished by decentralization of the heart by either spinal transection or bilateral vagotomy or both and the arrhythmia was abolished by pharmacological agents which are known to block the peripheral autonomic transmission.

In the absence of a clear understanding of the central control of cardiac activity it is difficult to localize the central site for the genesis of cardiac arrhythmia induced by intracerebroventricular injection of chemicals. Attempts have been made, however, to localize the central site of action of chemical agents in the production of centrogenic arrhythmias. Wang and his co-workers have ascribed the medullary region to be the most sensitive target area, since arrhythmia was induced by the injection of pentylenetetrazol, picrotoxin and deslanoside into the fourth ventricle in doses lower than those required when they were injected into the third or lateral ventricles (Bircher *et al.*, 1962, 1963). Dikshit (1934) has suggested a hypothalamic site of action for caffeine-induced centrogenic arrhythmia in cats.

In the interpretation of the results of centrogenic arrhythmias it is important to consider the species, the state of the animal (conscious or anaesthetized), the anaesthetic used and the route of administration of the inducing agent. It is known that barbiturates and other anaesthetics may prevent or even abolish certain centrogenic arrhythmias (Haley & Weinberg, 1955). The relative importance of the parasympathetic (vagus) and the sympathetic nerves in the elicitation of centrogenic arrhythmias is debatable. Wang and his group favour a dominant role of the vagus, whereas Melville and co-workers attribute a major role to the sympathetics in the causation of arrhythmia. It is, however, indisputable that centrogenic arrhythmias can be comptelely abolished by decentralization of both the divisions of the autonomic nervous system. Probably the nature of the chemical employed to induce centrogenic arrhythmia also determines the predominance of sympathetic or parasympathetic divisions in causing arrhythmia.

The present study deals with the intracerebroventricular administration of aconitine to induce cardiac arrhythmias. Aconitine is a powerful depolarizer of membranes. Local application of aconitine to the heart also induces arrhythmia (Scherf, 1947; Brown & Acheson, 1952). The results of the present study are summarized in Tables 1 and 2. From these results it is clear that the action of aconitine was confined to structures within the central nervous system. The centrogenic arrhythmia induced by aconitine is largely of a ventricular type, whereas the arrhythmia due to local application of aconitine is of the atrial type. Furthermore, the centrogenic arrhythmia induced by aconitine was abolished by spinal transection and ganglion blockade. It appears that the sympathetic outflow is responsible for the production of aconitine-induced centrogenic arrhythmia.

It is interesting to note that independent bilateral stellate ganglionectomy, or bilateral vagotomy, merely raised the threshold for the induction of arrhythmia. The most important factor concerned in the production of aconitine-induced arrhythmia originates from the adrenal glands, since bilateral adrenalectomy was adequate to prevent or abolish the arrhythmia. Release of catecholamines from the adrenals may be responsible for the aconitine-induced arrhythmia. This is supported by the occurrence of tachyphylaxis in the effects produced by intraventricular injection of aconitine, and that prior reserpinization prevented them, possibly by depleting the adrenal catecholamine stores (De Schaepdryver & Preziosi, 1959). The thoracic splanchnic nerves are the major neural supply to the adrenal glands (Mizeres, 1955). Transection of these nerves prevented or abolished the aconitine-induced arrhythmia, which suggests that it excited neurones in the central nervous system concerned with the release of catecholamines from the adrenal glands. There is physiological and anatomical evidence for the existence

of such neurones in the hypothalamus (Beattie, Brow & Long, 1930). Folkow & von Euler (1954) have demonstrated selective activation of noradrenaline- and adrenaline-producing cells in the suprarenal gland by electrical stimulation of the hypothalamus. Exogenous administration of adrenaline or endogenous release of catecholamines are known to induce arrhythmia in conscious as well as anaesthetized animals (Somani & Lum, 1965; Somani, Fleming, Chan & Lum, 1966). Thus, it seems that aconitine excites the neurones in the central nervous system concerned with the release of catecholamines from the adrenals, which accounts for the cardiac irregularities that it induces.

TABLE 1. *Effect of various surgical procedures on the cardiac arrhythmia and pressor responses induced by intracerebroventricular aconitine in anaesthetized dogs*

Surgical procedure	Dose of aconitine (μg)	No. of dogs	Cardiac arrhythmias		Blood pressure changes		
			Present	Absent	Increased	Decreased	No change
Control	10	5	2	3	5	0	0
	15	5	3	2	5	0	0
	20	5	5	0	5	0	0
Bilateral vagotomy	20	2	0	2	2	0	0
	40	3	2	1	3	0	0
Spinal transection							
Before	20						
	40	3	0	3	0	0	3
	80						
During	20	1	0	1	0	1	0
Stellate ganglionectomy	20	2	0	2	2	0	0
	40	2	2	0	2	0	0
Bilateral adrenalectomy							
Before	20	3	0	3	3	0	0
	40						
During	20	1	0	1	0	1	0
Thoracic splanchnic nerve section	20	2	0	2	2	0	0
	40						

TABLE 2. *Effect of various blocking agents on the cardiac arrhythmia and pressor responses induced by intracerebroventricular aconitine in anaesthetized dogs*

Blocking agents	Dose of aconitine (μg)	No. of dogs	Cardiac arrhythmias		Blood pressure changes		
			Present	Absent	Increased	Decreased	No change
Ganglion blocking agents							
Chlorisondamine chloride During	20	2	0	2	0	0	2
Before	20	1	0	1	0	1	0
Mecamylamine	20	2	0	2	0	0	2
Reserpine	20						
	40	2	0	2	0	0	2
α-Adrenoceptor blocking agents							
Phenoxybenzamine	20	2	0	2	0	0	2
Yohimbine	20	2	0	2	0	0	2
β-Adrenoceptor blocking agents							
INPEA	20	2	0	2	2	0	0
Propranolol	20	2	0	2	2	0	0
Pronethalol	20	2	0	2	2	0	0
Quinidine	20	2	0	2	0	2	0

The rise of blood pressure associated with the aconitine-induced arrhythmia is likely to be the result of sympathoadrenal discharge caused by the central action of aconitine, since it was abolished by spinal transection, bilateral adrenalectomy or reserpinization. The rise of blood pressure and cardiac arrhythmia were prevented by prior ganglionic block as well as by α-adrenoceptive receptor block. The α-adrenoceptor blocking agents prevent the cardiac arrhythmia induced by catecholamines in two ways; first, by preventing the rise of blood pressure and, second, by a direct depressant action on the myocardium (Moe, Malton, Rennick & Freyburger, 1948; Nickerson & Smith, 1949; Nickerson, 1949). The β-adrenoceptor blocking agents, on the other hand, blocked the aconitine-induced arrhythmia without preventing the rise in blood pressure. These findings suggest a role for catecholamines in the genesis of aconitine-induced arrhythmia. It is significant to note that INPEA, which is a β-adrenoceptor blocking agent, devoid of local anaesthetic and direct myocardial depressant activity (Somani & Lum, 1965; Sinha, Srimal, Jaju & Bhargava, 1967), also blocked the aconitine-induced arrhythmia in doses which selectively block catecholamine-induced arrhythmia (Somani & Lum, 1965; Somani *et al.*, 1966). The relatively smaller dose of β-adrenoceptor blocking agents, as compared with quinidine, required to antagonize the aconitine-induced arrhythmia indicates the involvement of specific β-adrenoceptive receptors similar to those shown for the catecholamine-induced arrhythmia (Somani & Lum, 1965; Somani *et al.*, 1966).

The findings that the cardiac arrhythmias could be induced with one fourth of the dose of intracerebroventricular aconitine in the conscious dog as compared with the dog anaesthetized with pentobarbitone probably indicates a greater release of catecholamines in the former case (De Schaepdryver, 1959). The cardiac arrhythmia induced in anaesthetized animals was consistently observed following a dose of 20 μg of aconitine introduced into the lateral ventricle. The effect began within 5–10 min and persisted for at least 90 min. These characteristics make the aconitine-induced arrhythmia a suitable method for the screening of anti-arrhythmic agents.

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