PHARMACOLOGICAL PROPERTIES OF HYDRALLAZINE, DIHYDRALLAZINE AND SOME RELATED COMPOUNDS

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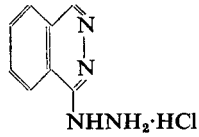
Hydrallazine and dihydrallazine cause adrenaline reversal and antagonise the pressor effects of noradrenaline on the cat blood pressure. Both hydrallazine and dihydrallazine antagonise vasoconstriction caused by adrenaline, noradrenaline, histamine, 5-hydroxytryptamine or barium chloride in isolated perfused preparations of the rat hind quarters or rabbit ear. In isolated aortic strips antagonism is shown to the constrictor action of adrenaline, noradrenaline, histamine and 5-hydroxytryptamine but not to barium chloride. Marked antagonism to 5-hydroxytryptamine is shown only on the perfused rat hind quarters or rabbit ear. Antagonism to pressor reflexes is of moderate potency or is absent. Applied locally to the carotid sinuses of the cat, hydrallazine causes a rise of blood pressure. Hydrallazine and dihydrallazine have mainly a peripheral site of action involving an effect upon the contractile elements of the blood vessel walls. 3-Phenyl-6-hydrazino-pyridazine HCl, 1-hydrazino*iso*quinoline HCl and 3:6-dihydrazino-pyridazine nitrate appear to have similar properties to hydrallazine and dihydrallazine.

HYDRALLAZINE and dihydrallazine have been used in the treatment of hypertension in the United States of America and Europe but they have not been widely used in Britain. Both compounds are potent hypotensive agents probably ranking next to the ganglion-blocking agents and veratrum preparations. They were synthesised by Druey and Ringier[1] in 1950 and early reports of their hypotensive activity were made by Gross, Druey and Meier in 1950[2] and by Craver and his colleagues (1950–1)[3,4]. The introduction of these compounds aroused interest since not only did they lower blood pressure, but they also increased renal blood flow in animals[2,5–7], and in man[8–13]. The mode of action of hydrallazine and dihydrallazine is not clearly understood. Various effects have been described, indicating a partly central action[4,5,14–17], a mainly peripheral point of attack[5,17,18], antagonism to 5-hydroxytryptamine[5,15], to rennin[5,19], to a cerebral vasopressor hormone[15], to adrenaline and noradrenaline[4,5,17,20,21] and inhibition of histaminase[22,23]. Antagonism to various pressor reflexes has been noted[5,14,17], especially in cats[5,17]. There is disagreement about some of the properties of hydrallazine. Erspamer[24] does not, for example, consider it to be a specific antagonist of 5-hydroxytryptamine, whilst, using dogs, Walker and his colleagues[20] could not show blockade of the carotid sinus pressor reflex; and Britton and his colleagues[25] could not inhibit the pressor response to hypoxia.

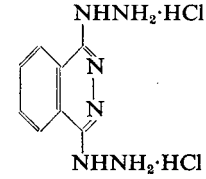
We have repeated some of the earlier investigations and extended them with the object of gaining some insight into the mode of action of these potentially valuable drugs.

MATERIALS AND METHODS

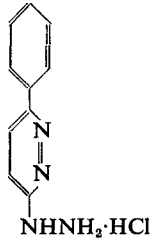
Perfusion fluids. The composition of these in g./litre was as follows. Frog Ringer's solution, NaCl 6·5, KCl 0·14, $CaCl_2$ 0·12, $NaHCO_3$ 0·2, glucose 1·0. Locke's solution, NaCl 9·0, KCl 0·42, $CaCl_2$ 0·24, $NaHCO_3$ 0·5, glucose 1·0. Tyrode's solution, NaCl 8·0, KCl 0·2, $CaCl_2$ 0·2, $MgCl_2$ 0·1, NaH_2PO_4 0·05, glucose 1·0, $NaHCO_3$ 1·0. De Jalon's solution, NaCl 9·0, KCl 4·2, $CaCl_2$ 0·06, $NaHCO_3$ 0·5, glucose 0·5.



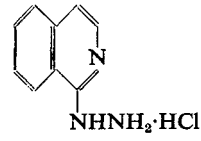
(I) Hydrallazine
(1-Hydrazinophthalazine-hydrochloride)



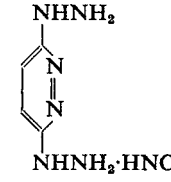
(II) Dihydrallazine
(1:4-Dihydrazinophthalazine-dihydrochloride)



(III) 3-Phenyl-6-hydrazino-pyridazine-hydrochloride



(IV) 1-Hydrazino-*iso*quinoline-hydrochloride



(V) 3:6-Dihydrazino-pyridazine nitrate

Drugs were dissolved in the appropriate saline solution. In studying drug antagonisms the following were used. Acetylcholine chloride (ACh), carbachol, histamine acid phosphate (Hm), (−)-adrenaline hydrochloride (Ad), (−)-noradrenaline bitartrate (NA), 5-hydroxytryptamine creatinine sulphate (5-HT), tubocurarine chloride (TC), decamethonium iodide (C 10), nicotine hydrogen tartrate (NHT), eserine sulphate (eserine), potassium chloride (KCl), barium chloride ($BaCl_2$) and atropine sulphate (atropine). The following drugs were investigated. Hydrallazine (I), dihydrallazine (II), 3-phenyl-6-hydrazino-pyridazine hydrochloride (III), 1-hydrazino-*iso*quinoline hydrochloride (IV) and 3:6-dihydrazino pyridazine nitrate (V). We are indebted to Dr. C. D. Falconer and Dr. F. Gross of Ciba Laboratories for supplies of these compounds.

The following preparations and techniques were used. The frog rectus abdominis muscle suspended in frog Ringer's solution at room temperature. The oestrous uterus of the rat suspended in oxygenated de Jalon's fluid at 29°. The rabbit duodenum in oxygenated Locke's solution at 37°. Isolated strips of the descending aorta of cats or rabbits cut spirally (Furchgott and Bhadrakom[26]) and perfused with Tyrode's solution with

O_2 and 5 per cent CO_2 at 37°. The isolated rabbit heart perfused by Langendorff's method[27] using oxygenated "double glucose" Locke's solution at 37°. The isolated guinea pig auricles in oxygenated "double glucose" Locke's solution at 29°. Strips of the terminal ileum of guinea pigs suspended in oxygenated Tyrode's solution at 34 to 35°. Segments of the diaphragm of the rat with the attached phrenic nerve, set up in "double glucose" Tyrode's solution with O_2 and 5 per cent CO_2 at 29°. The nerve was stimulated with a Dobbie McInnes stimulator, at a frequency of 6 or 8/minute at 6 volts; the pulse width was 1 to 3 msec. Finally the isolated rat hindquarters and rabbit's ear described by Burn[28] and perfused with oxygenated Locke's solution at room temperature.

In anaesthetised cats, constant pressor responses were obtained with (*a*) NA or Ad (1 to 2 μg./kg.), (*b*) clamping for 30 or 40 seconds with bulldog clips both common carotid arteries at a point immediately below the carotid sinuses, (*c*) stimulation of the cut central end of the vagus, (*d*) stimulation of the cut central end of the sciatic nerve, (*e*) stimulation of the splanchnic nerve, (*f*) compression with artery forceps for 15 to 40 seconds of the abdominal aorta at a point just above the coeliac artery, (*g*) anoxia and (*h*) hypoxia by inhalation of 95 per cent N_2 and 5 per cent O_2 for periods of 1 to 3 minutes. In stimulation of nerve square impulses were used at 5 to 125 volts and a frequency of 1200 to 1400/minute. The pulse width was 0·5 to 3 msec. Constant depressor responses were obtained to ACh (0·5 to 2 μg./kg.) or Hm (0·5 to 2 μg./kg.). In some cats a constant hypertension was maintained by intravenous infusion of a solution of 10 to 100 μg./ml. Ad or NA at 1·0 ml./minute. Contractions of the nictitating membrane were obtained in response to 5 to 10 μg./kg. Ad or NA, or to electrical stimulation of the cervical sympathetic. Drugs (1 mg./kg.) were administered once reproducible responses had been obtained.

In spinal cats, reproducible pressor responses were obtained to Ad or NA (1 to 3 μg./kg.) or to anoxia. Reproducible depressor responses were obtained to ACh or Hm (2 to 3 μg./kg.). Drugs (1 mg./kg.) were administered once reproducible responses had been obtained.

Results

Direct Effects

Smooth muscle. Hydrallazine and dihydrallazine (0·5 to 10 μg./ml.), increased the tone and the amplitude of peristaltic movements of isolated strips of rabbit duodenum (Fig. 1). Higher doses, 25 to 50 μg./ml., caused a contraction of the strip. The other compounds tested caused a slight increase in tone at doses of 2·5 to 12·5 μg./ml. Hydrallazine, (400 μg./ml.) and dihydrallazine (500 μg./ml.) caused a slight relaxation of aortic strips. All five compounds, 1 to 100 μg./ml., increased the outflow from the perfused rabbit's ear and rat's hindquarters. When injected into anaesthetised cats, 1 to 2 mg./kg. of hydrallazine, dihydrallazine and 3:6-dihydrazinopyridazine nitrate caused a delayed and gradual fall in the blood pressure with slight stimulation of respiration. One to 2 mg./kg. of 1-hydrazino-*iso*quinoline HCl or of 3-phenyl-6-hydrazino-pyridazine

HCl occasionally failed to produce a fall in the blood pressure, instead there was a gradual rise.

Cardiac muscle. Perfusion of the isolated rabbit heart with hydrallazine or dihydrallazine (1 to 10 μg./ml.) caused an irreversible decrease in amplitude but an increase in the rate, and in the outflow. 1-Hydrazino-*iso*quinoline HCl (10 μg./ml.) irreversibly decreased rate amplitude and

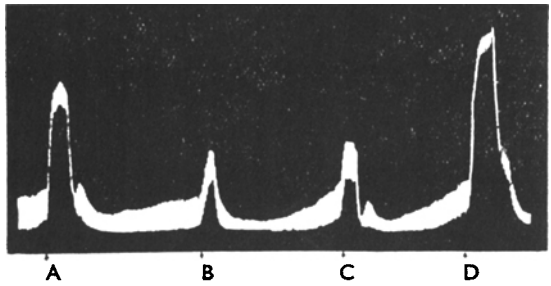


FIG. 1. Isolated rabbit duodenum.
At A, 30 μg./ml. of 1-4-dihydrazinophthalazine.
B, 12·5 ,, ,, 1-hydrazinophthalazine HCl.
C, 25 ,, ,, ,, ,,
D, 50 ,, ,, ,, ,,

outflow. 2·5 to 10 μg./ml. of hydrallazine or dihydrallazine initially increased the amplitude of beat of the isolated guinea pig auricles. This effect was followed by depression. The other compounds, 2·5 to 12·5 μg./ml., were ineffective or caused a fall in rate and amplitude.

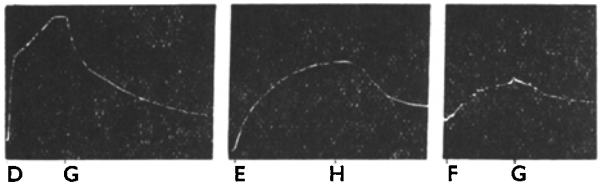


FIG. 2. Influence of hydrallazine on contractions of aortic strips induced by adrenaline, noradrenaline and 5-HT.
At D, 2 μg./ml. of (−)-adrenaline hydrochloride.
E, 5 ,, ,, (−)-noradrenaline bitartrate.
F, 2 ,, ,, 5-HT creatinine sulphate.
G, 400 ,, ,, hydrallazine.
H, 1 mg./ml. of hydrallazine.

Skeletal muscle. Hydrallazine or dihydrallazine (1 to 3 mg./ml.) reduced the twitch amplitude in the rat diaphragm preparation. Complete neuromuscular block was not seen and the muscle continued to respond to direct stimulation. No direct effects were observed on the frog rectus muscle or rat uterus at doses of 10 to 125 μg./ml. The guinea pig ileum showed no direct action unless spontaneous activity was high

when both hydrallazine and dihydrallazine 12·5 to 125 μg./ml. caused a contraction.

Antagonism to Adrenaline and Noradrenaline

Smooth muscle. Hydrallazine (400 μg./ml.) relaxed aortic strips caused to contract with Ad or NA (1 to 10 μg./ml.). Dihydrallazine (400 to 500 μg./ml.) was less effective (Fig. 2). Similar but much weaker effects followed the addition of the other three compounds (100 to 200 μg./ml.). When injected into anaesthetised cats, all five drugs, 1 mg./kg., altered the pressor response to Ad into a biphasic pressor-depressor response (Fig. 3), indicating an effect upon adrenaline vasoconstriction, but no effect upon the stimulant actions of Ad on the heart. When the blood

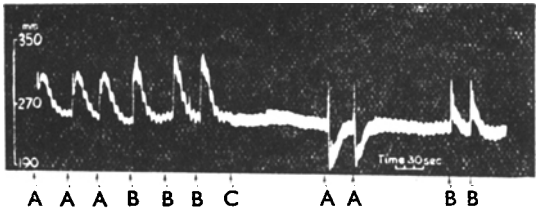


FIG. 3. Blood pressure record of a cat anaesthetised with ether-chloralose.
At A, 5 μg. of (−)-adrenaline i.v.
B, 5 μg. of (−)-noradrenaline i.v.
C, 1 mg./kg. of 1-hydrazinophthalazine HCl i.v.

pressure was raised by continuous perfusion of a solution of Ad or NA at constant rate, all five compounds antagonised the hypertension due to Ad more effectively than that due to NA (Fig. 3). Hydrallazine, dihydrallazine or 3:6-dihydrazinopyridazine nitrate, 1 mg./kg., partially antagonised the pressor response to NA. The other compounds had little or no effect. At doses of 1 to 10 μg./ml. hydrallazine and dihydrallazine antagonised Ad and NA (10 ng. to 1 μg.) vasoconstriction in the perfused rabbit ear or rat hindquarters. This effect was shared by 10 μg./ml. of 1-hydrazino-*iso*quinoline HCl and 3:6-dihydrazino-pyridazine nitrate, but not invariably by 10 μg./ml. of 3-phenyl-6-hydrazino pyridazine HCl. Hydrallazine and dihydrallazine (25 to 50 μg./ml.) showed no, or slight, antagonism to Ad (0·01 to 0·1 μg./ml.) or NA (0·25 to 1 μg./ml.) inhibition of ACh induced contractions of the rat uterus. The other three compounds themselves antagonised ACh and were not therefore tested. Only very slight antagonism to Ad or NA (0·013 to 0·1 μg./ml.) was shown on the rabbit duodenum. Contractions of the nictitating membrane induced by Ad were slightly antagonised by all compounds, excepting 3-phenyl-6-hydrazino-pyridazine HCl at doses of 1 mg./kg. Contractions due to NA or electrical stimulation were not affected.

Cardiac muscle. Hydrallazine and dihydrallazine (10 μg./ml.) caused slight potentiation of the effects of 0·5 to 2 μg. of Ad and NA on the isolated perfused rabbit's heart or of Ad (0·05 μg./ml.) and NA (0·025 μg./ml.) on the isolated guinea pig auricles, but 1-hydrazino-*iso*quinoline HCl and 3:6-dihydrazino-pyridazine nitrate showed no effect or caused slight

potentiation. 3-Phenyl-6-hydrazino-pyridazine HCl had no effect. These three compounds were tested at 2·5 to 12·5 μg./ml.

Vasopressor Reflexes

Pressor responses to compression of the common carotid arteries, stimulation of the central end of the cut vagus and hypoxia (Fig. 4) were either not antagonised or were slightly so by doses of 1 mg./kg. of all five drugs. At similar doses there was antagonism to the pressor response after stimulation of the cut central end of the sciatic nerve. Hydrallazine

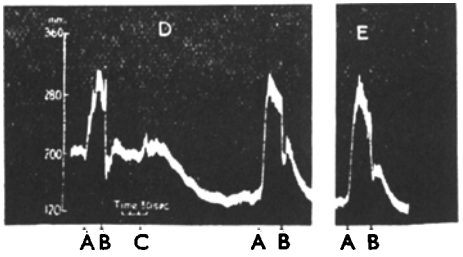


FIG. 4. Influence of hydrallazine on the pressor response to hypoxia. Record D, blood pressure of cat, wt. 2·5 kg., anaesthetised with ether-chloralose. Between A and B, inhalation of gas mixture of nitrogen 95 per cent and oxygen 5 per cent.

At C, 1 mg./kg. of hydrallazine i.v.
Record E, 30 min. after hydrallazine i.v.

and dihydrallazine (1 mg./kg.) antagonised the pressor responses after compression of the abdominal aorta (Fig. 5) or stimulation of the splanchnic nerve (Fig. 6). The other compounds at the same doses did not reliably block these responses. In some preparations no antagonism was shown.

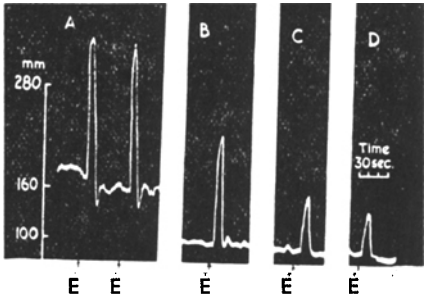


FIG. 5. Influence of hydrallazine on the pressor response to compression of the abdominal aorta. Blood pressure of cat, wt. 4 kg., anaesthetised with ether-chloralose.

A. Before hydrallazine.
B. 10 min. after 1 mg./kg. hydrallazine i.v.
C. 20 ,, ,, ,, ,, ,,
D. 30 ,, ,, ,, ,, ,,

At E, compression of the abdominal aorta for 15 sec.

Antagonism to 5-hydroxytryptamine. Marked antagonism was shown to the vasoconstrictor effects of 10 ng. to 1 μg. of 5-HT on the perfused rat's hindquarters or rabbit's ear by 10 μg./ml. of hydrallazine, dihydrallazine, 1-hydrazino-*iso*quinoline HCl or 3:6-dihydrazino-pyridazine nitrate. 10 μg./ml. of 3-phenyl-6-hydrazino-pyridazine HCl was ineffective. On the other hand, 10 to 125 μg./ml. of hydrallazine or dihydrallazine potentiated the response of the guinea pig ileum to 5-HT (30 ng. to 3 μg./ml.).

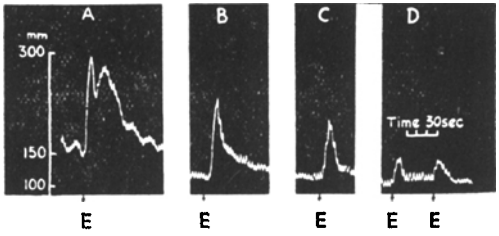


FIG. 6. Influence of hydrallazine on the pressor response to stimulation of splanchnic nerve. Blood pressure of cat, wt. 2·5 kg., anaesthetised with ether-chloralose.

A. Before hydrallazine.
B. 15 min. after 1 mg./kg. hydrallazine i.v.
C. 45 ,, ,, ,, ,, ,,
D. 75 ,, ,, ,, ,, ,,

At E, splanchnic nerve stimulated for 20 seconds (square impulses, 7·5 V., frequency 1400/min., width, 3 msecs.).

3-Phenyl-6-hydrazino-pyridazine HCl or 1-hydrazino-*iso*quinoline HCl (25 to 125 μg./ml.) antagonised 5-HT on this preparation, but 25 to 125 μg./ml. of 3:6-dihydrazino-pyridazine nitrate had no effect. Slight potentiation of 5-HT (1 to 3 μg./ml.) induced contractions of the rabbit duodenum was shown by 10 to 50 μg./ml. of hydrallazine or dihydrallazine. 2·5 to 12·5 μg./ml. of the other compounds had no effect. Hydrallazine and dihydrallazine (10 to 100 μg./ml.) showed slight antagonism to 5-HT (0·1 to 2 μg./ml.) contractions of the rat uterus. Similar effects were shown by 25 to 125 μg./ml. of 3-phenyl-6-hydrazino-pyridazine HCl or 3:6-dihydrazino-pyridazine nitrate but 1-hydrazino-*iso*quinoline HCl (2·5 to 25 μg./ml.) was more potent. Hydrallazine and dihydrallazine (400 μg./ml.) relaxed aortic strips caused to contract by 5-HT 2 to 5 μg./ml. (Fig. 2).

Antagonism to Acetylcholine and Histamine

Smooth muscle. 12·5 to 125 μg./ml. of hydrallazine or dihydrallazine potentiated the response of the guinea pig ileum to ACh (0·1 to 1 μg./ml.). Hm contractions (0·1 to 0·5 μg./ml.) showed initial potentiation followed by antagonism. 25 to 125 μg./ml. of 3-phenyl-6-hydrazino-pyridazine HCl or 1-hydrazino-*iso*quinoline HCl antagonised contractions due to both ACh and Hm but 3:6-dihydrazino-pyridazine nitrate at similar dose levels was ineffective. On the rat uterus 12·5 to 125 μg./ml. of hydrallazine or dihydrallazine caused a slight potentiation of the response

to ACh (0·1 to 0·25 μg./ml.), but 1-hydrazino-*iso*quinoline HCl (5 to 50 μg./ml.), 3-phenyl-6-hydrazino-pyridazine HCl (25 to 75 μg./ml.) and 3:6-dihydrazino-pyridazine nitrate (25 to 75 μg./ml.) antagonised it. 1-Hydrazino-*iso*quinoline HCl was the most potent. On the rabbit duodenum hydrallazine or dihydrallazine (12·5 to 50 μg./ml.) potentiated the contractions induced by ACh (0·02 to 0·1 μg./ml.) or Hm (2 to 20 μg./ml.). ACh induced contractions were slightly antagonised by 2·5 to 12·5 μg./ml. of the other three compounds. Hm or ACh induced contractions of aortic strips (Hm or ACh 1 to 10 μg./ml.) were relaxed by hydrallazine. Hm-induced vasoconstriction of the rat's hindquarters or rabbit's ear (Hm 1 to 10 μg.) was antagonised by 10 μg./ml. of hydrallazine or dihydrallazine. Slight antagonism was shown by the five compounds (1 mg./kg.) to the depressor effects of 0·5 to 2 μg./kg. of Hm and ACh on the blood pressure of anaesthetised or spinal cats. In some cats the depressor effects of Hm and ACh appeared to be slightly prolonged. When administration of Hm was followed by biphasic depressor-pressor response, hydrallazine or dihydrallazine or 1-hydrazino-*iso*quinoline HCl (1 mg./kg.) strongly antagonised the pressor component. A biphasic response to Hm cannot always be obtained. For this reason the effects upon it of the other two compounds have not yet been investigated.

Cardiac muscle. 10 to 25 μg./ml. of hydrallazine or dihydrallazine had no effect upon Hm acceleration of the guinea pig auricles (Hm 0·013 μg./ml.). The same compounds at doses of 10 μg./ml. had no effect upon ACh slowing of the isolated perfused rabbit heart caused by 0·5 to 1 μg. of ACh.

Skeletal muscle. 5 to 50 μg./ml. of hydrallazine or dihydrallazine and 2 to 5 μg./ml. of 1-hydrazino-*iso*quinoline HCl potentiated the response of the rectus muscle to ACh (0·1 to 0·5 μg./ml.). 5 to 25 μg./ml. of 3-phenyl-6-hydrazino-pyridazine HCl or 3:6-hydrazino-pyridazine nitrate showed neither potentiation nor antagonism of ACh.

Other Drug Antagonisms

Skeletal muscle. 5 to 50 μg./ml. of hydrallazine or dihydrallazine potentiated the response of the frog rectus abdominis muscle to 0·25 to 0·75 μg./ml. KCl. 5 to 25 μg./ml. of the other three compounds had no effect or caused slight antagonism. C 10-induced contractions of the rectus (C 10, 2 to 3 μg./ml.) were antagonised by 5 to 25 μg./ml. of 3-phenyl-6-hydrazino-pyridazine HCl, 1-hydrazino-*iso*quinoline HCl and 3:6-dihydrazino-pyridazine nitrate. Hydrallazine and dihydrallazine (50 to 100 μg./ml.) showed similar effects. On the other hand, 50 μg./ml. of hydrallazine or dihydrallazine potentiated the response to 1 to 3 μg./ml. NHT whilst the other three compounds at dose levels of 2·5 to 12·5 μg./ml. showed a slight antagonism. After C 10 had been washed out, 50 μg./ml. of hydrallazine or dihydrallazine and 25 to 50 μg./ml. of 1-hydrazino-*iso*quinoline HCl caused the rectus to contract even though they had no direct action on the tissue prior to C 10. After 5 to 25 μg./ml. of hydrallazine or dihydrallazine, atropine (0·1 to 2 μg./ml.) or TC (0·4 to 0·5 μg./ml.)

did not antagonise ACh induced contractions of the rectus. Eserine (2 to 4 μg./ml.) potentiation of ACh induced contractions was increased after hydrallazine or dihydrallazine (5 to 25 μg./ml.).

Smooth muscle. 12·5 to 125 μg./ml. of hydrallazine or dihydrallazine, 25 to 125 μg./ml. of 1-hydrazino-*iso*quinoline HCl or 3:6-dihydrazinopyridazine nitrate did not modify contractions of the guinea pig ileum induced by 0·2 to 0·5 mg./ml. of $BaCl_2$. 25 to 125 μg./ml. 3-phenyl-6-hydrazino-pyridazine HCl showed slight antagonism. Marked antagonism to vasoconstriction of the rat hindquarters induced by 0·1 to 5 mg. $BaCl_2$ was shown by 1 to 10 μg./ml. of hydrallazine or dihydrallazine and 10 μg./ml. of 1-hydrazino-*iso*quinoline HCl and 3:6-dihydrazinopyridazine nitrate but 10 μg./ml. of 3-phenyl-6-hydrazino-pyridazine HCl had no effect.

Skeletal muscle. Hydrallazine or dihydrallazine (200 to 500 μg./ml.) almost completely antagonised C 10 and NHT block of the rat diaphragm, but had no effect on the block caused by TC.

Discussion

Hydrallazine and dihydrallazine have certain properties in common: both antagonise the stimulant effects of Ad and NA. This is shown by their ability to cause adrenaline reversal and antagonism to NA on the blood pressure of the cat. They also antagonise the pressor component of the biphasic pressor-depressor response to Hm. Antagonism to Ad is also shown in the isolated perfused rat hindquarters and rabbit ear, on the nictitating membrane and on isolated aortic strips. There are wide variations in potency. It is greatest on the isolated perfused rat hindquarters and rabbit ear, moderate on aortic strips and the cat blood pressure, and low on the heart, auricles and nictitating membrane. Hypertension induced and maintained by constant rate infusion of Ad in cats is promptly reduced to normal levels but if NA is used hydrallazine and dihydrallazine are less effective.

Marked antagonism to 5-HT is shown only on the isolated perfused rat hindquarters or rabbit ear; in other preparations, it is weak or absent or there may even be potentiation of the response to 5-HT.

At the doses used none of the pressor reflexes was eliminated; but responses to stimulation of the cut central end of the sciatic nerve, to compression of the abdominal aorta and to stimulation of the splanchnic nerve, were reduced by both compounds. The responses to anoxia, hypoxia, carotid sinus occlusion and stimulation of the cut central end of the vagus were almost unaffected.

Neither hydrallazine nor dihydrallazine antagonises ACh. Potentiation is more usual. Responses to Hm may be potentiated but both drugs are potent antagonists of $BaCl_2$ or Hm vasoconstriction of the isolated perfused rat hindquarters and rabbit ear.

In our view, both hydrallazine and dihydrallazine have mainly a peripheral site of action. They appear to be able to abolish vasoconstriction in isolated vascular beds, irrespective of the nature of the chemical agent

constricting the blood vessels. This is shown in experiments on the perfused rat's hindquarters and rabbit ear when hydrallazine and dihydrallazine antagonise vasoconstriction due to Ad, NA, 5-HT, Hm or $BaCl_2$ and is also indicated by the increased outflow recorded from the isolated perfused heart, and by the direct vasodilator properties which both compounds possess. Hydrallazine and dihydrallazine seem to be adrenergic blocking agents but appear to be neither specific, selective nor potent. An effect upon the carotid body chemoreceptors does not seem likely since the pressor responses to hypoxia and anoxia are not affected. The carotid sinus pressor reflex is not abolished; this seems to rule out an effect upon the pressor receptors of this organ. We have carried out a few experiments similar to those described by Heymans[29] in which 6 mg. of hydrallazine dissolved in 1 ml. of saline were infiltered around both carotid sinuses of the cat. This caused a rise in the systemic blood pressure, an effect similar to that obtained by Heymans using adrenergic blocking agents including the ergot alkaloids. This points to a direct relaxant effect upon the muscle fibres, of the carotid sinus walls. When the walls are relaxed, intrasinusoidal pressure falls and this reflexly causes a rise in the blood pressure.

There is no specific antagonism to any one humoral agent. The effects observed may be due to a direct depressant action upon the contractile elements of the blood vessels. On the other hand they may react with the receptors involved in the process of vasoconstriction, making it impossible for compounds such as Ad, 5-HT, Hm, NA and $BaCl_2$ to exert their effects.

Hydrallazine and dihydrallazine potentiated the effects of KCl, ACh and NHT on the frog rectus. On the other hand, C 10 is antagonised and there is antagonism to TC block of ACh contractions. These effects are contradictory and at the moment we can offer no explanation of their mechanism.

3-Phenyl-6-hydrazino-pyridazine HCl, 1-hydrazino-*iso*quinoline HCl and 3:6-dihydrazino-pyridazine nitrate have some properties in common with hydrallazine and dihydrallazine, but in other respects they differ. All lower the cat blood pressure, 3:6-dihydrazino-pyridazine nitrate being the most potent. All antagonise vasoconstriction due to Ad, NA, $BaCl_2$, Hm and 5-HT in isolated vascular beds. Blockade of the pressor reflexes was weak or absent, but 3:6-dihydrazino-pyridazine nitrate antagonised the pressor response to stimulation of the cut central end of the sciatic nerve. Adrenergic blockage on other preparations was not seen. On the guinea pig ileum the three compounds non-specifically antagonise the contractions of ACh, Hm or 5-HT. They antagonise C 10 and NHT on the frog rectus, but do not antagonise contractions caused by ACh, but 1-hydrazino-*iso*quinoline HCl potentiated the response to ACh.

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DISCUSSION

The paper was presented by MR. S. M. KIRPEKAR.

DR. G. E. FOSTER (Dartford) asked about the toxicity of the compounds.

DR. G. BROWNLEE (London). What was the significance of the pressor component of adrenaline at AA in Figure 3? Did the authors prove it to be a cardiac effect? It was clearly different from the effect seen with noradrenaline. Was isoprenaline also used? If there were a peripheral site of action, then there seemed to be an effect in addition to the one being demonstrated. Since there was evidence that the pressor effects were being modified, the word "modified" and not "antagonise" might have been preferred.

MR. E. M. BAVIN (Ware). Were the effects tried in other hypotensive animals such as dogs and rats.

DR. B. K. MARTIN (Slough). The maximum concentration employed by the authors was roughly one thousand times that of the minimum concentration, but to consider the mode of action, it was necessary to operate in a much narrower concentration range.

MR. T. D. WHITTET (London). The compounds had not proved satisfactory by themselves, but when used with ganglion-blocking agents the total effect was increased.

MR. H. D. RAPSON (Dorking) said that the response curves looked like sigmoid curves. Was there any relationship between the significance

of the sigmoid curve and mode of action of pharmacologically active material?

The AUTHORS in reply said it had been shown that about 200 mg./70 kg. was not very toxic; and for dihydrallazine this could be increased to 500 mg./70 kg. LD50's in mice for hydrallazine were about 80 mg./kg. and for dihydrallazine about 200 mg./kg. Isoprenaline had not been used. The remaining pressor response was due to a cardiac effect and the evidence pointed to a direct action on the walls of the blood vessels rather than to some action in the brain or spinal cord. In Figure 5 it would be noticed that there was a fairly considerable fall in blood pressure over a period—in that case of thirty minutes. The word "antagonise" was used in the conventional sense. Other animals had not been used and in the experiments concentrations were maintained which were roughly equivalent to those found clinically in the blood. When hydrallazines were used with ganglion-blocking agents they were more effective. It was hazardous to deduce mathematical data from the response curves.