Br. J. Pharmac. (1971), **42**, 179–192.

Responses of mean arterial pressure to pressor agents and diuretics in renal hypertensive and salt hypertensive rats

T. E. NICHOLAS*

Department of Pharmacology, The University of Western Australia, Nedlands, W.A. 6009, Australia

Summary

1. The responses of the mean arterial pressure to (−)-noradrenaline, tyramine, angiotensin II-val^5-amide, vasopressin and rat renin have been contrasted in renal hypertensive and in salt plus desoxycorticosterone hypertensive rats. The responses were measured in rats both unanaesthetized and rats anaesthetized with pentobarbitone.

2. Responses of unanaesthetized, ganglion blocked renal hypertensive rats to noradrenaline, tyramine and vasopressin markedly exceeded, and to angiotensin II and renin were markedly smaller than, those of unanaesthetized ganglion blocked salt + DOC hypertensive animals. Responses to angiotensin and to renin were apparently enhanced in the latter animals.

3. Hydrochlorothiazide and frusemide markedly reduced mean arterial pressure in salt + DOC hypertensive rats before and after ganglionic blockade.

4. Neither diuretic caused significant reduction in the mean arterial pressures of unanaesthetized, renal hypertensive rats in the absence of ganglionic blockade: frusemide did so in anaesthetized and unanaesthetized rats after ganglionic blockade.

5. Whereas the diuretics did not affect the responses of the renal hypertensive rats to pressor agents, frusemide and to a lesser extent hydrochlorothiazide tended to depress the responses to pressor agents in salt induced hypertension.

6. Hydrochlorothiazide did not influence mean arterial pressure in unanaesthetized rats with neurogenic hypertension.

Introduction

The elevated arterial peripheral resistance found in hypertension could result from a change in the vascular responsiveness to vasoactive substances. Most evidence suggests that isolated vascular muscle preparations from animals with hypertension induced by the removal of both kidneys (McQueen, 1956), constriction of one renal artery (McQueen, 1956, 1957 ; Gordon & Nogueira, 1962 ; McGregor & Smirk, 1970), constriction of the aorta above the renal arteries (Nolla-Panades, 1963), prolonged treatment with desoxycorticosterone (DOC) (Sturtevant, 1956) and genetic

* Present address: Cardiovascular Research Institute, University of California Medical Center, San Francisco, California 94122, USA.

inbreeding (Phelan, Eryetishir & Smirk, 1962) exhibit enhanced responses to a variety of pressor agents. Likewise, Doyle, Frazer & Marshall (1959) found that the responses of the human forearm to noradrenaline, angiotensin and 5-hydroxytryptamine (5-HT) were greater in the hypertensive than in the normotensive patient. The systemic responses to adrenaline, tyramine and posterior pituitary extract were greater in rabbits with hypertension due to renal artery constriction than in normotensive controls (Verney & Vogt, 1938; Brown & Maegraith, 1941). Renal encapsulation in the same species resulted in a hypertension associated with an enhanced response to noradrenaline (Conway, 1955). Similarly, rats with hypertension due to renal artery constriction showed enhanced responses to adrenaline and noradrenaline, but a normal response to tyramine (Olsen, Schroeder & Menhard, 1950). In contrast, dogs with hypertension due to renal encapsulation (Page & McCubbin, 1951) and rats with adrenal regeneration hypertension (Gardner & Honoré, 1964) responded normally to a variety of pressor agents.

Little attention appears to have been paid to the influence of the type of hypertension on the changes invoked in vascular reactivity, although Phelan (1966) has compared the responses of rats with inherited spontaneous hypertension and those with constricted renal artery hypertension to noradrenaline, angiotensin and vasopressin. He found that the renal hypertensive rats were more responsive only to vasopressin. In humans, Kaplan & Silah (1964) found that whereas essential hypertensives were more sensitive to angiotensin than were normotensives, malignant and renovascular hypertensive patients tended to have depressed responses. The cardiovascular actions of the benzothiadiazine diuretics may also be determined by the type of hypertension present: these drugs depressed arterial pressure in salt hypertensive rats (Daniel, 1962), but were ineffective in hypertension induced by constriction of a renal artery (Tobian & Coffee, 1964).

The experiments described here compare the changes in cardiovascular responses to diuretics and to various pressor agents during the development of three experimentally induced hypertensions: those induced by administration of salt plus DOC, by constriction of a renal artery and by section of both aortic and both carotid sinus nerves.

Methods

Male Wistar rats, 180–240 g, were used in all experiments. They were housed in open wire-topped cages in a single air conditioned room at 24° ± 1° C, ate a pellet diet (Wesfarmers Ltd., Australia) containing 0·2 to 0·5% NaCl and drank tap water freely: all exceptions to this routine are stated.

Preparative surgery

Anaesthesia was induced by an intraperitoneal injection of 40 mg/kg sodium methohexitone (Eli Lilly & Co. Ltd.).

Indwelling cannulae

Polyethylene cannulae were inserted into the caudal artery and a lateral caudal vein and were firmly taped into position before the tail was enclosed in a glass tube anchored at its distal end to an aperture in the cage through which the cannulae passed (Agrelo & Dawson, 1968). On recovery, the rat moved about the cage

anchored by the tip of the tail. A mid-dorsal incision was used for the induction of renal hypertension. The animal was laid on one side, a single kidney was exposed through the flank and a silver ribbon clip was applied to the renal artery by the method of Schaffenburg (1959). The body wall and skin incisions were then sutured separately. A clip clearance of 0·20 mm produced a satisfactory proportion of healthy hypertensive animals.

Neurogenic hypertension

After pretreating rats with atropine sulphate (0·5 mg s.c. per rat), both aortic depressor and both sinus nerves were sectioned through a midline cervical incision as described by Krieger (1964).

Salt hypertension

The colony of rats used had been for many generations fed a pellet diet containing 1·0–1·5% NaCl, and this had resulted in a mild hypertension. Two generations before the reported experiments with pure salt hypertensives, the NaCl content was decreased to normal range and this was accompanied by a fall in mean arterial blood pressure of about 15 mmHg (1 mmHg≡1·333 mbar). Mild hypertension once again resulted if 0·7% NaCl was substituted for drinking water for a period of 50 days. Although no controlled experiments were run, it appeared that the longer the colony had been fed pellets of normal NaCl content, the progressively harder it became to induce salt hypertension. Eventually it became necessary to substitute 1·0% NaCl for drinking water and to subcutaneously inject 1·5 mg desoxycorticosterone per rat 4 times per week for 4 weeks in order to induce mild hypertension.

Preparation of renin

A single sample of crude renin was prepared from rat kidneys by the method of Katz, Cockett & Moore (1966).

Records of mean arterial pressure

These were made from indwelling polyethylene cannulae in the caudal artery of unanaesthetized rats (see above) or in the carotid artery of rats anaesthetized with sodium pentobarbitone (40 mg/kg). Pressure was measured by means of a force displacement transducer coupled to a pen recorder. All drugs were injected via cannulae inserted either into a lateral caudal vein of unanaesthetized rats or into an external jugular vein of rats under pentobarbitone anaesthesia.

Administration of diuretics

Dose-effect and time-effect curves were available in the laboratory for the renal effects of hydrochlorothiazide, frusemide and amiloride. The doses chosen produced similar marked diuretic and natriuretic effects during the period selected for measurement of their action on the responses of rats to pressor agents. Hydrochlorothiazide (Ciba Ltd.) (2 mg/rat), frusemide (Hoechst Ltd.) (40 mg/rat) and amiloride (Merck, Sharpe & Dohme Ltd.) (2·5 mg/rat) were administered orally 3, 2 and 1 h, respectively, before the experiments. When administered in this fashion, hydrochlorothiazide and frusemide depress both the pressor response to intravenous noradrena-

line and the resting mean arterial blood pressure in mildly salt hypertensive rats (Lockett & Nicholas, 1968).

Design of experiments

One hundred and forty-four rats were used. Of these, forty-seven were converted to renal hypertensives, fourteen to DOC + salt hypertensives, fifteen to pure salt hypertensives ; the moderator nerves were cut in six. The remaining sixty-two animals served as controls which were sham operated whenever appropriate. The rats to be used for each experiment were divided into groups of comparable weight: a pretreatment was randomly assigned to each group. Since each experiment necessarily extended over several weeks, pretreatments were staggered to permit equal numbers of animals from each group to be examined each day. Control animals invariably received mock treatments.

Pressor agents

The pressor drugs selected for use were (−)-noradrenaline (Levophed, Ciba Laboratories), tyramine hydrochloride (B.D.H. Ltd.), vasopressin (Pitressin, Parke Davis & Co. Ltd.), angiotensin II-val^5-amide (Hypertensin, Ciba Laboratories) and crude renin (see above). A single dose of each pressor agent was selected for use in the absence of ganglionic blockade and another for use after ganglionic blockade, such as to produce submaximal effects lying on the linear parts of the log dose-effect curves. Experiments began when a series of near constant responses to the fixed dose of noradrenaline had been demonstrated. Each dose was administered twice (vasopressin and renin excepted) in the sequence: noradrenaline, tyramine, angiotensin, tyramine, angiotensin, noradrenaline, vasopressin, renin.

Additional drugs used were pentolinium tartrate (Ansolysen, May & Baker Ltd.), heparin (Evans Medical Ltd.), atropine sulphate (B.D.H. Ltd.), neomycin sulphate (Andrews Laboratories Pty Ltd.) and aprotinin (Trasylol, Bayer, Germany).

Results

Effect of standardized intravenous doses of pressor agents on the mean arterial pressures of hypertensive rats

Renal hypertension

The resting mean arterial pressure found in twenty-nine rats 10 days after constriction of a single renal artery exceeded 170 mmHg in nineteen animals (group a), fell between 140 and 170 mmHg in four animals (group b) and did not exceed 140 mmHg in six animals (group c) (Fig. 1). Mean arterial pressure in group c did not differ significantly from that found in sixteen sham operated animals. Blockade of autonomic ganglia by subcutaneous administration of pentolinium tartrate reduced the resting mean arterial pressure markedly but to levels still significantly greater in groups a and b than in sham operated animals ($P<0{\cdot}001$). Group a rats sustained a significantly greater fall in resting mean arterial pressure (mean $\pm$ S.E.: $73{\cdot}3 \pm 7{\cdot}5$ mmHg) than did the group b rats (mean $\pm$ S.E.: $40{\cdot}2 \pm 2{\cdot}9$ mmHg) following ganglionic blockade. There remained, however, a significant difference between the mean values for each group.

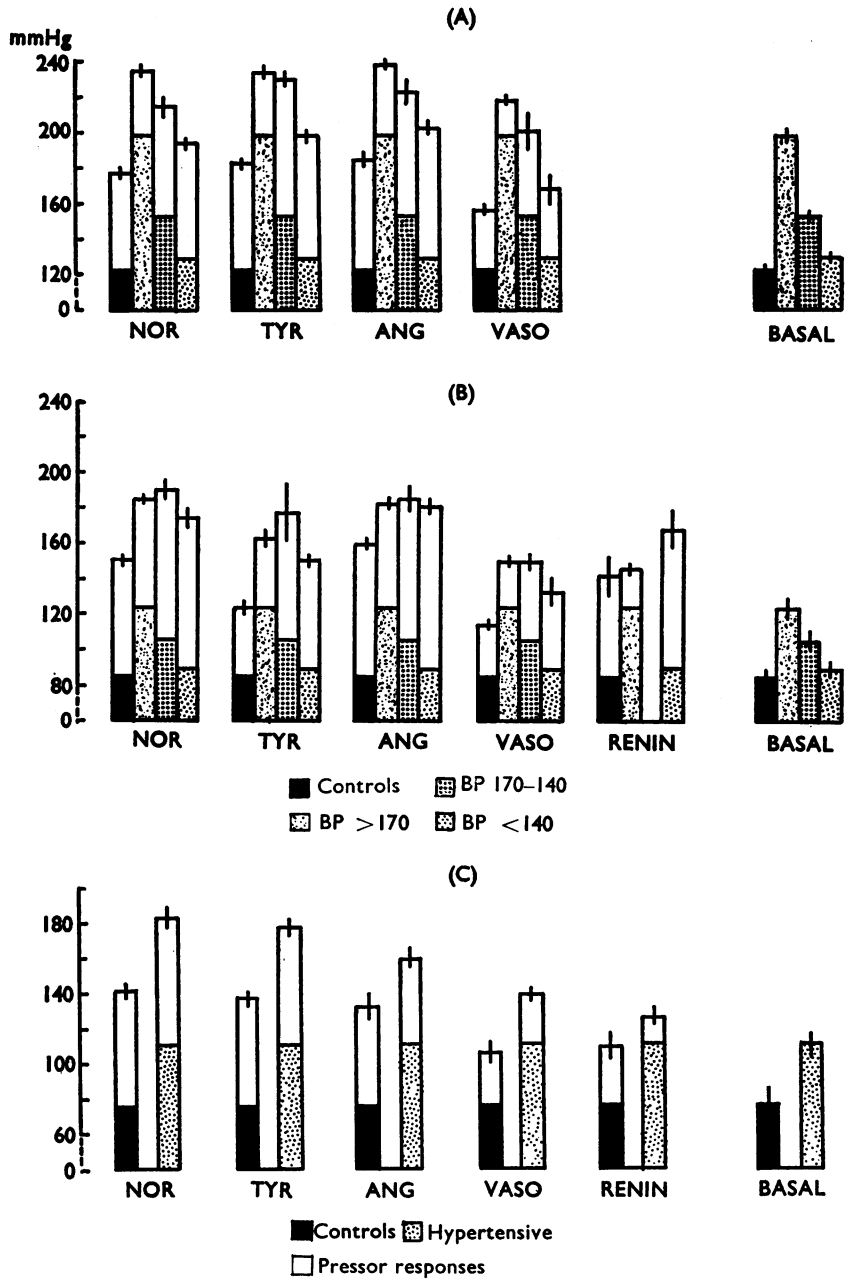

FIG. 1. Resting mean arterial pressures and responses of mean arterial pressure to pressor agents in normal (sixteen) and renal hypertensive (twenty-nine) rats. The three groups of renal hypertensive rats were: (a) nineteen, basal BP exceeding 170 mmHg; (b) four, basal BP 140–170 mmHg; (c) six, basal BP less than 140 mmHg. The doses of the pressor agents used before and after ganglionic blockade by pentolinium tartrate (50 mg/kg) were: (−)-noradrenaline, NOR (500 and 125 ng); tyramine, TYR (50 and 10 μg); angiotensin II-val^5-amide, ANG (125 and 25 ng); vasopressin, VASO (2·0 and 0·5 mU); renin, RENIN (0·1 ml/rat). The heights of the columns show values of mean arterial pressure before (shaded), and after (open), intravenous injection of pressor agent; the standard errors of the means are shown. (A), Unanaesthetized rats before induction of ganglionic blockade; (B), unanaesthetized rats after induction of ganglionic blockade. (C), Anaesthetized (i.p. pentobarbitone-Na, 40 mg/kg) and ganglion blocked. Ordinates, mean arterial pressure (mmHg).

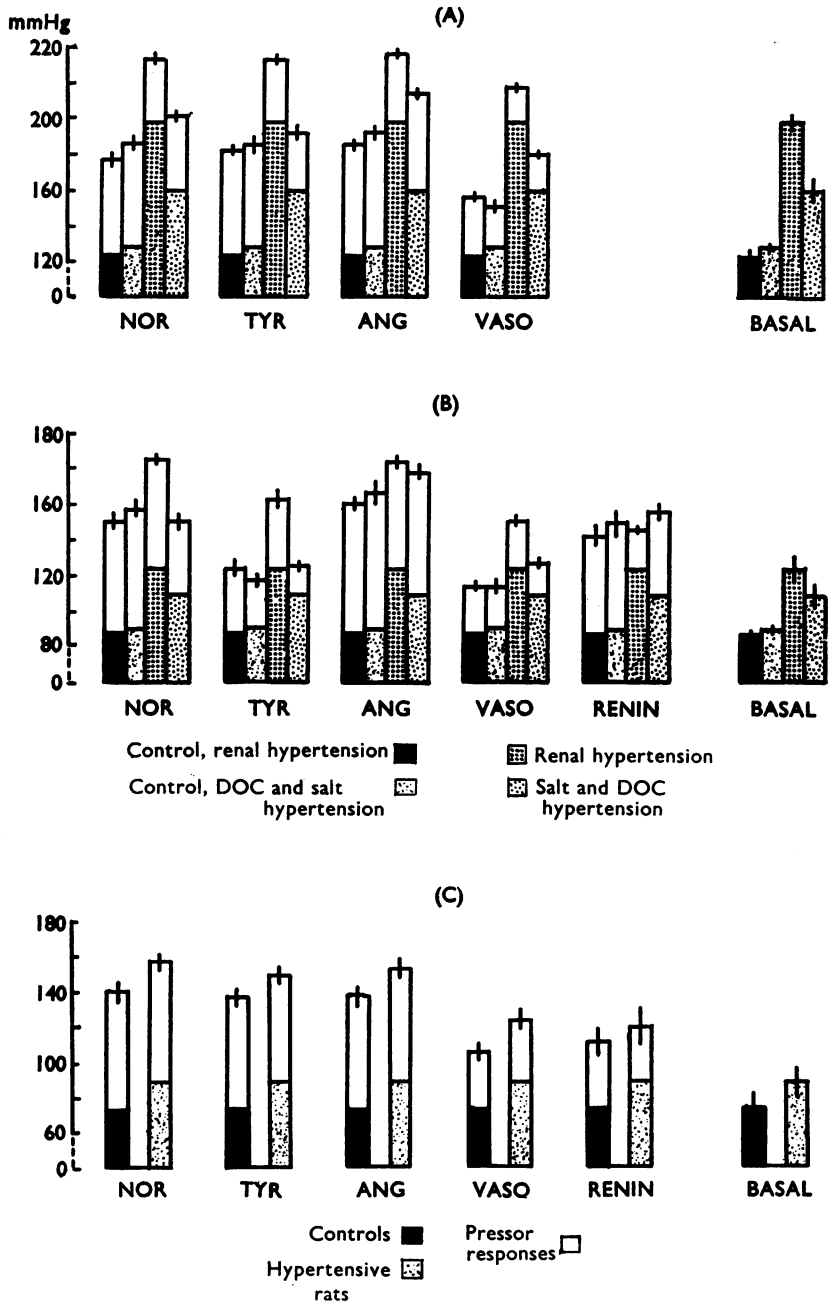

FIG. 2 (A & B). Comparison of the responses of the mean arterial pressure in renal hypertensive (nineteen) and sham operated (sixteen) rats with salt+DOC hypertensive (nine) and control (eight) rats. (A), Unanaesthetized rats before ganglionic blockade; (B), unanaesthetized rats after ganglionic blockade. Shaded columns represent the mean arterial pressure before, and open columns the mean pressure after, the intravenous injection of pressor agents (doses as in Fig. 1) under various conditions. (C), Resting mean arterial pressures and responses of the mean arterial pressure in rats with moderator nerves sectioned (five) and in sham operated (six) rats. Rats anaesthetized with pentobarbitone-Na and ganglion blocked. Shaded columns represent the mean arterial pressure before, and the open columns after, the intravenous injection of pressor agents (doses as in Fig. 1) under various conditions.

Without exception the responses of group a rats were significantly less than those of the sham operated group before ganglionic blockade ($P<0{\cdot}001$) (Fig. 1). Following ganglionic blockade, these differences tended to disappear with the exception of the depressed response to angiotensin. The response to renin was also depressed in the ganglion blocked group a animals. A similar pattern was observed with group b rats. It would appear that any increase in response of group a and b rats may be obscured by the high mean arterial pressures of these two groups when compared with controls. It is interesting that group c rats, which did not differ significantly from the sham operated animals with respect to blood pressure, showed significantly greater responses to all pressor agents except vasopressin, in the case of the unblocked rats, and renin in the blocked animals. No significant differences occurred in pressor responses of anaesthetized renal hypertensives and sham operated rats following ganglionic blockade, although the responses to angiotensin and renin tended to be smaller in the hypertensives (Fig. 1). The resting mean arterial pressures did, however, remain significantly different ($P<0{\cdot}05$). (Renal hypertensive rats, mean $\pm$ S.E.: $111{\cdot}3 \pm 5{\cdot}7$ mmHg; sham operated rats, mean $\pm$ S.E.: $76{\cdot}2 \pm 10{\cdot}1$ mmHg.)

Salt + DOC hypertension

Treatment with salt plus DOC for 4 weeks raised the mean arterial pressure of nine rats to levels comparable with those found in the middle range of the renal hypertensive animals (group b). As with the renal hypertensive animals, ganglionic blockade reduced the resting mean arterial pressure of these salt + DOC hypertensive rats to values still significantly in excess of those found for normal rats after ganglionic blockade (Fig. 2, A & B). Although the fall in pressure following ganglionic blockade tended to be greater in the hypertensive rats (mean $\pm$ S.E.: $51{\cdot}1 \pm 6{\cdot}4$ mmHg), this was not significantly greater than that of the controls (mean $\pm$ S.E.: $38{\cdot}9 \pm 3{\cdot}3$ mmHg) at the 0·05 level. The hypertensive rats responded to a lesser extent to pressor agents than did the controls. This was particularly evident in the case of the responses to noradrenaline and tyramine, both before and after ganglionic blockade. In contrast to the renal hypertensive rats, following blockade the response of the salt + DOC hypertensive rats to noradrenaline diminished in comparison with the controls.

Comparison of renal and salt + DOC hypertensive rats

The responses of renal hypertensive rats can be directly compared with those of the salt + DOC hypertensive rats, because no significant differences occurred between the responses of the control rats for both groups (with the exception of that to vasopressin in the unblocked rats). Such a comparison has been made in Fig. 2, A & B. Although the resting arterial pressure of the renal hypertensive animals was significantly greater than that of the salt + DOC hypertensive animals before ganglionic blockade, the pressor responses to noradrenaline, tyramine and vasopressin did not differ from one group to the other. The response of the salt + DOC hypertensive group was, however, significantly greater to angiotensin than that of the renal hypertensive animals. Following ganglionic blockade, the responses of the salt + DOC hypertensive rats to angiotensin and renin greatly exceeded, and to noradrenaline, tyramine and vasopressin were markedly smaller than, those in renal

hypertensive animals. The difference in resting mean arterial pressure between these same hypertensive groups fell from 39·6 mmHg to 16·2 mmHg following ganglionic block and was no longer significant.

Neurogenic hypertension

The mean arterial pressures of unanaesthetized rats 1–2 weeks after section of all four moderator nerves were very unstable and oscillated over as much as 160 mmHg. Part of the fluctuation was attributable to the considerable hypertensive responses shown by these animals to any external sound, and part also coincided very clearly with spontaneous movement. Measurement of pressor responses to drugs was therefore only possible after ganglionic block under anaesthesia. The mean arterial

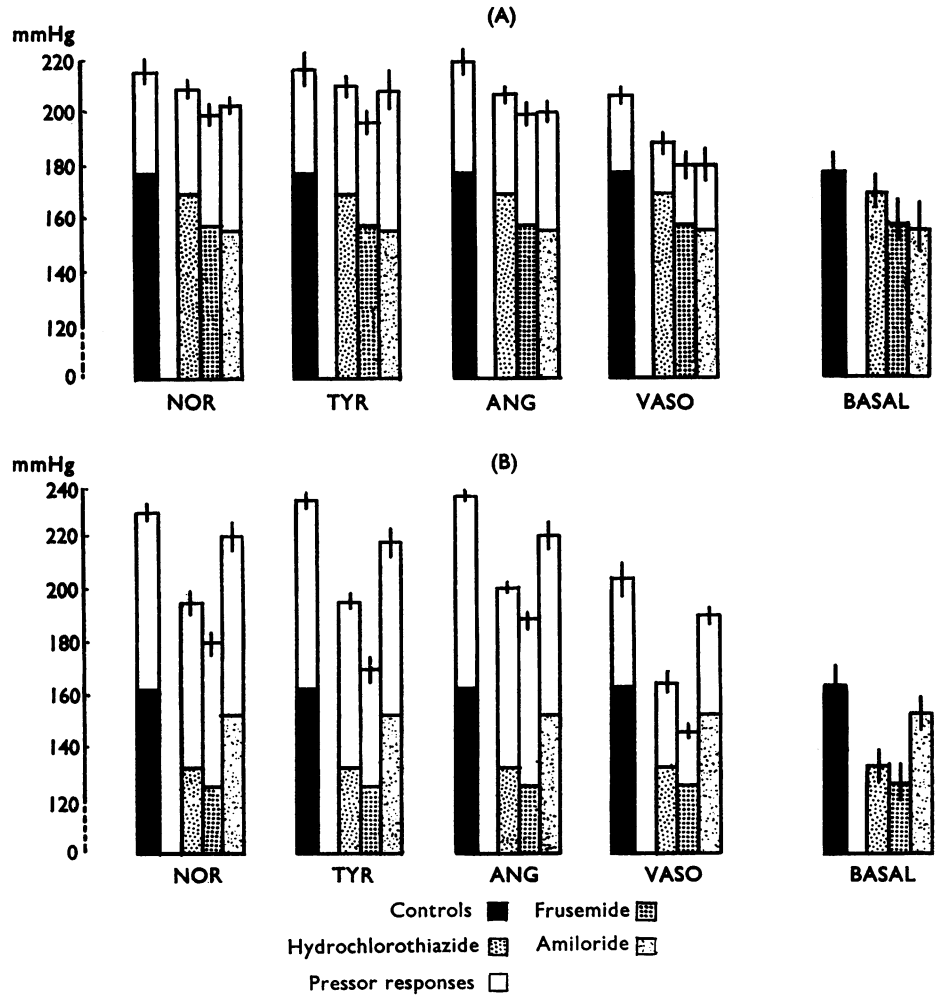

FIG. 3. Effect of diuretics on the responses of the mean arterial pressures to pressor agents (doses in Fig. 1) in renal hypertensive (nineteen) rats (A) and salt+DOC hypertensive (nine) rats (B). Unanaesthetized and without ganglion blockade. Shaded columns represent the mean arterial pressures before, and the open columns the mean pressures after, the intravenous injection of pressor agents under various conditions. Hydrochlorothiazide (2 mg/rat); frusemide (40 mg/rat); amiloride (2·5 mg/rat) were administered orally 3, 2, and 1 h respectively, before experiments.

pressure of the neurogenic hypertensive rats, which exceeded that of control rats by 55 mmHg, only exceeded the pressure of these rats by 17 mmHg following ganglion blockade in both groups. No significant difference then existed between the mean arterial pressures of these two groups. The pressure increments caused by fixed doses of noradrenaline, tyramine, angiotensin, vasopressin and renin also did not differ from those found in the control animals (Fig. 2C).

Effect of diuretics on the responses of the mean arterial pressures of hypertensive rats to pressor agents

Renal hypertension

Unanaesthetized, renal hypertensive rats were resistant to the hypotensive actions of hydrochlorothiazide, frusemide and amiloride before (Fig. 3) and after (Fig. 4) ganglionic blockade. Frusemide alone significantly lowered the resting mean arterial pressure in the anaesthetized, ganglion blocked animals ($P<0{\cdot}01$) (Fig. 5).

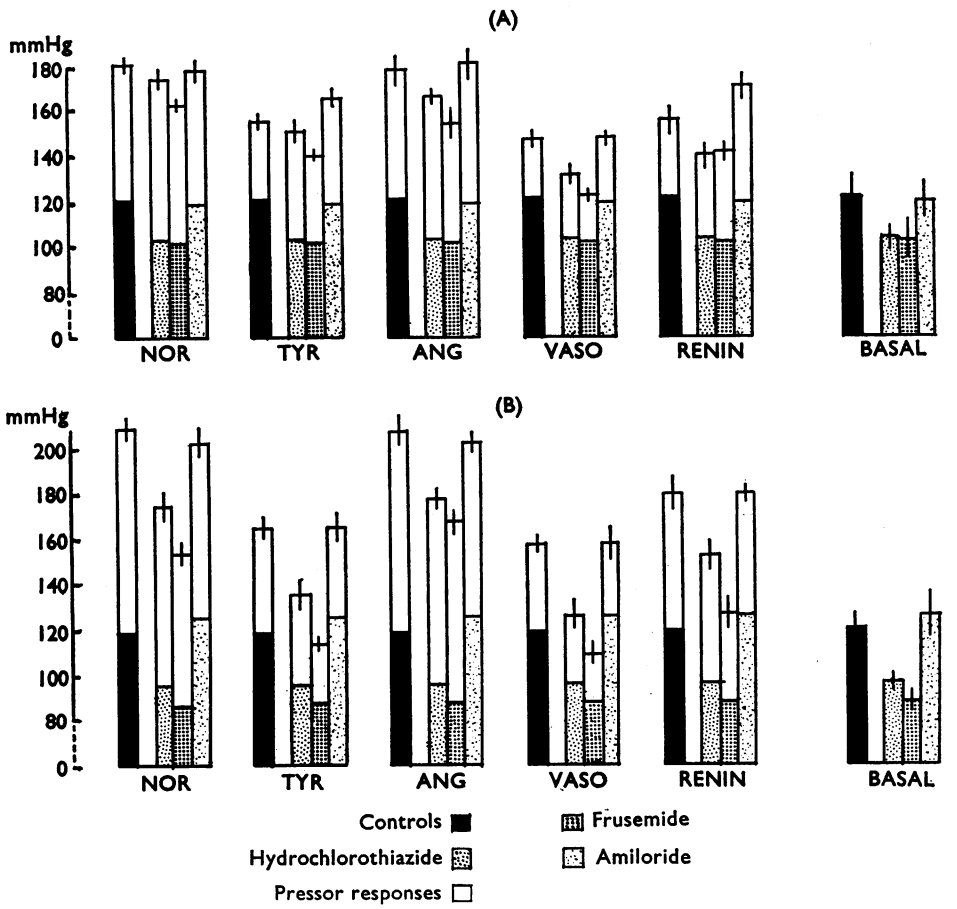

FIG. 4. Effect of diuretics on the responses of the mean arterial pressures to pressor agents (doses as in Fig. 1) in renal hypertensive (nineteen) rats (A) and salt+DOC hypertensive (nine) rats (B) after ganglionic blockade. Unanaesthetized. Shaded columns represent the mean arterial pressures before, and the open columns the mean pressures after, the intravenous injection of pressor agents under various conditions. Doses of diuretics as in Fig. 3.

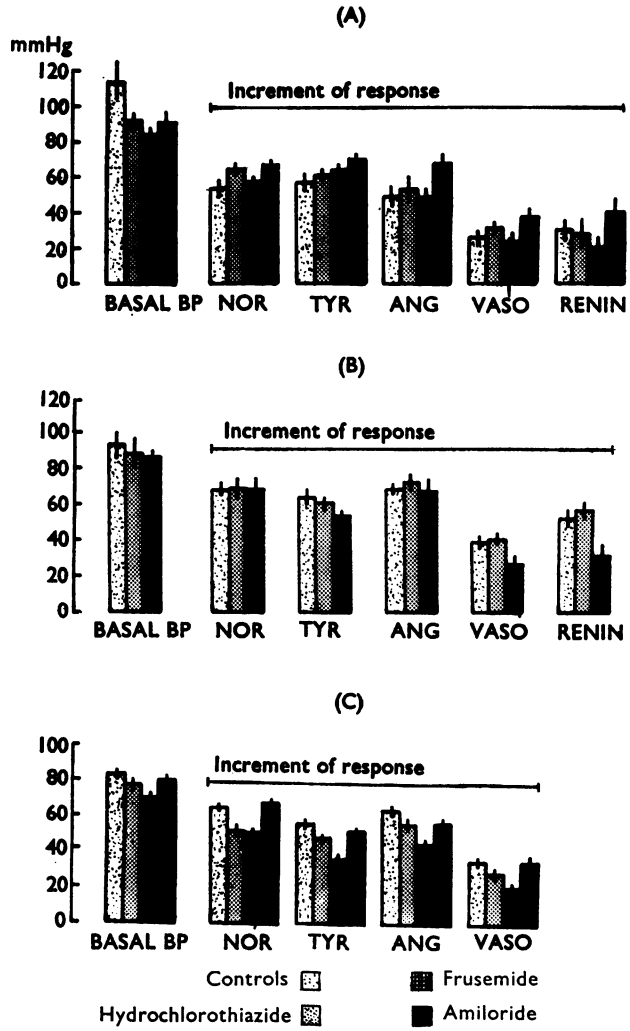

FIG. 5. Effect of diuretics on the increments of the mean arterial pressure caused by pressor drugs (doses as in Fig. 1) in anaesthetized ganglion blocked rats. (A), Renal hypertensive (nineteen) rats; (B), rats made hypertensive with DOC and salt (eight); (C), rats exposed to 0·7% NaCl in the drinking water for 50 days (six). Doses of diuretics as in Fig. 3.

TABLE 1. *Effect of diuretics on the resting mean arterial pressure of anaesthetized salt and salt + DOC rats before and after ganglionic blockade*

	No. of animals	Ganglion blocked	No block
Salt hypertension			
Hydrochlorothiazide	6	77·58±2·5	162·00±2·7
Frusemide	6	69·83±1·9	156·82±2·6
Amiloride	6	79·75±2·3	186·33±3·2
Controls	6	83·33±2·1	186·89±3·4
Salt+DOC hypertension			
Hydrochlorothiazide	5	87·80±8·8	147·60±8·9
Frusemide	6	86·03±4·2	137·83±8·9
Controls	7	93·54±6·9	168·86±5·6

All results expressed as mean pressure±S.E. in mmHg.

None of the diuretics had any effect on the responses of the renal hypertensive rats to pressor agents (Figs. 4 and 5).

Salt hypertension

By contrast the same oral dose of hydrochlorothiazide and frusemide, ineffective in renal hypertensive rats, lowered the resting mean arterial pressure very significantly in salt+DOC hypertensive animals both in the presence ($P<0{\cdot}01$) and absence ($P<0{\cdot}01$) of blockade of autonomic ganglia (Figs. 3 and 4). The hypotensive actions of the two diuretics were, however, less marked in these rats after anaesthesia, both before and after ganglionic blockade (Table 1). Amiloride was without hypotensive effect. Hydrochlorothiazide and frusemide significantly depressed the mean resting arterial pressure of anaesthetized, pure-salt hypertensive rats both before, and to a lesser extent after, ganglionic blockade (Table 1 and Fig. 5). Frusemide significantly reduced the response of the mean arterial pressure to noradrenaline, tyramine, vasopressin and angiotensin in the pure salt hypertensive rats when anaesthetized and ganglion blocked (Fig. 5); to noradrenaline, tyramine, renin and vasopressin in ganglion blocked unanaesthetized salt+DOC hypertensive rats (Fig. 4); and to tyramine, angiotensin and vasopressin in the unanaesthetized salt+DOC hypertensive rats in the absence of ganglionic blockade (Fig. 3). Although hydrochlorothiazide tended to depress the responses of the salt+DOC hypertensive, unanaesthetized rats to all pressor agents both before and after ganglionic blockade, this did not become significant at the 0·05 level (Figs. 3 and 4).

Whereas hydrochlorothiazide significantly depressed all pressor effects in ganglion blocked anaesthetized, pure salt hypertensive rats, this diuretic had no influence on responses to pressor drugs in anaesthetized, ganglion blocked animals which were suffering from hypertension induced by salt+DOC (Fig. 5). There was no statistical difference in the responses of the control groups of these two types of hypertensive rats to any of the pressor drugs.

Neurogenic hypertension

The large spontaneous fluctuations in mean arterial pressure shown by rats 1–2 weeks after section of all four moderator nerves were unaffected by the slow intravenous injection of 2 mg hydrochlorothiazide per rat into a lateral caudal vein, throughout an observation period which varied from 5 to 6 h in five experiments.

Discussion

The most interesting feature arising from this work is the contrast between the pressor responses of rats with renal hypertension and those with salt plus DOC hypertension.

Unanaesthetized rats with renal hypertension show an increase in response of the mean arterial pressure to noradrenaline, tyramine and vasopressin, relative to their responses to angiotensin and renin. Because of the disparity between the resting mean arterial pressures of the control and the hypertensive groups, this result could be due either to an increase in the response to noradrenaline, tyramine and vasopressin or to a decrease in response to angiotensin and renin. If it is due to the former this would be in accordance with the observations of Brown & Maegraith (1941), who showed that the responses of the mean arterial pressure to

adrenaline, tyramine and posterior pituitary extract in rabbits with constricted renal arteries exceeded those in control animals. One source of this hypersensitivity has been traced to the vascular bed, for McQueen (1956) has demonstrated increased responses to noradrenaline in hindquarter preparations from rats in which one renal artery had been constricted.

Kaplan & Silah (1964) have suggested that the response to infused angiotensin in man is inversely related to the plasma concentration of endogenous angiotensin. It is therefore possible that increased responses to noradrenaline, tyramine and vasopressin and depressed responses to angiotensin and renin would reflect an increase in the plasma concentration of angiotensin. My results are, however, at variance with those of McCubbin & Page (1963) and McCubbin, DeMoura, Page & Olmsted (1965) who found that whereas renal artery constriction or an infusion of angiotensin in dogs enhanced the pressor response to tyramine, there was no change in magnitude of the responses to noradrenaline and angiotensin. This discrepancy could be due to a species difference or to the fact that these workers had performed a unilateral nephrectomy. The role of the contralateral kidney in renal hypertension has not yet been explained. It is interesting that the normotensive rats with occluded renal arteries (group c animals) showed a non-specific enhancement of response to all pressor agents used. Post-mortem examinations in these animals revealed that the kidney with occluded artery was extremely calcified and probably non-functional, although it is impossible to know at what time after clipping occlusion of the renal artery occurred. It remains to be explained why these rats were not hypertensive despite their enhanced responses to pressor agents. The observation suggests that such an increase in reactivity is not sufficient to maintain a hypertension.

In contrast to the renal hypertensive rats, salt plus DOC hypertensive rats showed depressed responses to noradrenaline, tyramine and vasopressin relative to their responses to angiotensin and renin. The changes in plasma sodium concentration, due to administration of 1% saline and DOC for 4 weeks, should be of the order of those found by Heistad, Abboud & Eckstein (1967). These workers demonstrated a direct relationship between the sodium concentration and the response of the human forearm to angiotensin. In a previous study Sturtevant (1956) found that rats maintained on 0·6% saline and injected with DOC developed metacorticoid hypertension and showed enhanced responses to adrenaline, noradrenaline, 5-HT, vasopressin and renin. The period of maintenance was approximately 4 times that of this study and allowed ample time for considerable arterial degeneration and cardiac hypertrophy to occur. Their apparent non-specific increase in reactivity may, then, be due to secondary factors.

Although the interval between the start of induction of hypertension and measurement of drug action was relatively short in my experiments (10 days for the renal and 4 weeks for the salt+DOC hypertensive rats), it is probable that effects secondary to the elevated pressure had developed. Such secondary effects may account for the higher mean arterial pressure of the hypertensive rats than that of the control animals following ganglionic blockade and do not discount the possibility of the autonomic nervous system playing a dominant role in the aetiology of the conditions.

The hypertension induced by section of the moderator nerves was found to be maintained solely by an elevated sympathetic and parasympathetic nervous activity

as judged by the return of the mean arterial pressure to normal following ganglionic blockade.

Renal hypertensive and salt plus DOC hypertensive rats also differed in their response to diuretics. The hypotensive actions of hydrochlorothiazide and frusemide were absent and weak, respectively, in renal hypertensive rats, but were marked in salt plus DOC hypertensive animals. Amiloride was without antihypertensive effect. The same pattern was found in the responses of the different hypertensive rats to pressor agents after treatment with the diuretics.

It is difficult to explain why frusemide and hydrochlorothiazide should have depressed the pressor responses to a greater extent in the pure salt than in the salt plus DOC hypertensive rats, but this may relate to excessive amounts of DOC being present. Kalsner (1969) has shown that DOC itself will potentiate the response of the isolated rabbit aortic strip to adrenaline and noradrenaline by inhibiting catechol-ortho-methyltransferase.

Different forms of experimental hypertension may thus be characterized by their responses to various pressor agents and also to diuretics. Although differentiation between the effects of hydrochlorothiazide and frusemide could not be made from these experiments, it is interesting that amiloride had no effect when administered in equivalent natriuretic doses.

It is a pleasure to thank Professor M. F. Lockett for her encouragement and interest throughout this work and for assistance in its presentation.

REFERENCES

AGRELO, C. & DAWSON, W. (1968). The continuous recording of arterial blood pressure in the conscious unrestrained rat. *J. Pharm. Pharmac.*, **20**, 959–960.

BROWN, G. M. & MAEGRAITH, B. G. (1941). Characteristics of the circulation of hypertensive rabbits. *J. Physiol., Lond.*, **99**, 304–311.

CONWAY, J. (1955). The behaviour of the blood pressure in normal and hypertensive rabbits in response to l-noradrenaline and to ganglion block by hexa- or pentamethonium. *J. Physiol., Lond.*, **127**, 69–80.

DANIEL, E. E. (1962). On the mechanism of antihypertensive action of hydrochlorothiazide in rats. *Circulation Res.*, **11**, 941–954.

DOYLE, A. E., FRAZER, J. R. E. & MARSHALL, R. J. (1959). Reactivity of forearm vessels to vasoconstrictor substances in hypertensive and normotensive subjects. *Clin. Sci.*, **18**, 441–454.

GARDNER, D. L. & HONORE, L. H. (1964). Vascular response to catecholamines and to acetylcholine in adrenal-regeneration hypertension. *Archs int. Pharmacodyn.*, **150**, 504–515.

GORDON, D. B. & NOGUEIRA, A. (1962). Increased vascular reactivity in experimental hypertension. *Circulation Res.*, **10**, 269–273.

HEISTAD, D. D., ABBOUD, F. M. & ECKSTEIN, J. W. (1967). Serum sodium concentration and vascular responsiveness in man. *Clin. Res.*, **15**, 407.

KALSNER, S. (1969). Steroid potentiation of response to sympathomimetic amines in aortic strips. *Br. J. Pharmac.*, **36**, 582–593.

KAPLAN, N. M. & SILAH, J. G. (1964). The effect of angiotensin II on the blood pressure in humans with hypertensive disease. *J. clin. Invest.*, **43**, 659–669.

KATZ, Y. J., COCKETT, A. T. K. & MOORE, R. S. (1966). A simplified method for the extraction and bioassay of renin. *Investigative Urology*, **4**, 64–68.

KRIEGER, E. M. (1964). Neurogenic hypertension in the rat. *Circulation Res.*, **15**, 511–521.

LOCKETT, M. F. & NICHOLAS, T. E. (1968). The effects of hydrochlorothiazide and frusemide on noradrenaline sensitivity and blood pressure of salt-loaded rats before and after nephrectomy. *Br. J. Pharmac. Chemother.*, **33**, 136–144.

MCCUBBIN, J. W., DEMOURA, R. S., PAGE, I. H. & OLMSTED, F. (1965). Arterial hypertension elicited by suppressor amounts of angiotensin. *Science, N.Y.*, **149**, 1394–1395.

MCCUBBIN, J. W. & PAGE, I. H. (1963). Neurogenic component of chronic renal hypertension. *Science, N.Y.*, **139**, 210–215.

MCGREGOR, D. D. & SMIRK, F. H. (1970). Vascular responses to 5-hydroxytryptamine in genetic and renal hypertensive rats. *Am. J. Physiol.*, **219**, 687–690.

MCQUEEN, E. G. (1956). Vascular reactivity in experimental renal and renoprival hypertension. *Clin. Sci.*, **15**, 523–532.

McQUEEN, E. G. (1957). Cited from LAVERTY, R., McGREGOR, D. D. & McQUEEN, E. G. (1968). Vascular reactivity in experimental hypertension. *N.Z. med. J.*, **67**, 303–309.

NOLLA-PANADES, J. (1963). Hypertension and increased hindlimb vascular reactivity in experimental coarctation of the aorta. *Circulation Res.*, **12**, 3–9.

OLSEN, N. S., SCHROEDER, H. A. & MENHARD, E. M. (1950). Effect of certain amines on the blood pressure of normotensive and hypertensive rats. *Proc. Soc. exp. Biol. N.Y.*, **74**, 581–583.

PAGE, I. H. & McCUBBIN, J. W. (1951). The pattern of vascular reactivity in experimental hypertension of varied origin. *Circulation*, **4**, 70–86.

PHELAN, E. L. (1966). Cardiovascular reactivity in rats with spontaneous inherited hypertension and constricted renal artery hypertension. *Am. Heart J.*, **71**, 50–57.

PHELAN, E. L., EYRETISHIR, I. & SMIRK, F. H. (1962). Observations on the responses of rats with spontaneous hypertension and control rats to pressor drugs and to hexamethonium. *Circulation Res.*, **10**, 817–824.

SCHAFFENBURG, C. A. (1959). Device to control constriction of the main renal artery for production of hypertension in small animals. *Proc. Soc. exp. Biol. N.Y.*, **101**, 676–677.

STURTEVANT, F. M. (1956). Studies on vascular reactivity in normotensive and metacorticoid hypertensive rats. *Am. Heart J.*, **52**, 410–418.

TOBIAN, L. & COFFEE, K. (1964). Effect of thiazide drugs on renovascular hypertension in contrast to their effect on essential hypertension. *Proc. Soc. exp. Biol. N.Y.*, **115**, 196–198.

VERNEY, E. B. & VOGT, M. (1938). Experimental investigation into hypertension of renal origin with some observations on conclusive "uremia". *Q. Jl exp. Physiol.*, **28**, 253–303.

(*Received September* 1, 1970)