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Renal actions of dihydroergocristine and of phentolamine in anaesthetized cats

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1. Comparison has been made of the effects of dihydroergocristine (DCS) and phentolamine mesylate (phentolamine) on cardiac and respiratory rates, systemic arterial pressure, renal clearances of creatinine (C_{Cr}) and of *p*-aminohippuric acid (C_{PAH}) and on the secretion of Na and K, in cats under chloralose anaesthesia.

2. Phentolamine antagonized vasomotor tone and the pressor effect of circulating noradrenaline to comparable extent. The extent of reduction in urine flow, C_{Cr}, C_{PAH} and Na excretion correlated with the fall in mean arterial pressure. Innervated and denervated kidneys responded similarly. Cardiac and respiratory rates rose slightly as arterial pressure fell.

3. DCS, 10 to 20 μg/kg per min, did not reduce vasomotor tone, markedly reduced the pressor effect of exogenous noradrenaline, caused bradycardia and respiratory slowing but had little or no effect on renal function.

4. DCS, 30 to 40 μg/kg per min, lowered mean arterial pressure by 15–25 mm Hg, decreased C_{PAH} but not C_{Cr}, so raising the filtration fraction and caused a small reduction in urine flow and in Na excretion. Innervated and acutely denervated kidneys responded similarly.

5. DCS, 30 to 40 μg/kg per min, raised mean arterial pressure, decreased C_{PAH}, urine flow and Na excretion but did not alter C_{Cr} in animals pretreated with full α-adrenergic blocking doses of phentolamine.

6. DCS, 30 to 40 μg/kg per min, increased the rate of secretion of sympathetic amines from the adrenal medulla and increased the concentration of renin in renal venous blood.

7. Isolated kidneys perfused at constant pressure from pump-oxygenator circuits and in saline diuresis responded to DCS (15–17 μg/120 ml. blood) by diuresis and natriuresis and by a rise in the rate of secretion of renin. Higher concentrations of DCS (125–250 μg/120 ml.) were without effect on renal function and did not influence renin secretion.

8. The renal effects of full α-adrenergic blocking doses of DCS and of phentolamine were comparable, in the whole animal.

9. The evidence indicates that the release of noradrenaline by DCS 30–40 μg/kg per min from nerve terminals supplying the juxtaglomerular apparatus may have caused the enhancement of renin secretion.

Single intraperitoneal injections of 25, 50 and 100 μg dihydroergocristine (DCS) did not depress mean arterial pressure in unanaesthetized rats (Lockett, Stuart, Wadley, Goss & Siddiqui, 1969), blocked the pressor action of 100 μg (−)-noradrenaline subcutaneously and had only small effect on water diuresis. The clearances of *p*-aminohippuric acid fell to a small but significant extent and potassium (K) excretion diminished. Continuous treatment with DCS, 32 μg per rat three times daily, caused a retention of water and of Na by the third lasting to the fifth day of treatment: this condition reversed by the eighth day. On the fourteenth day of treatment the juxtaglomerular indices (Hartroft & Hartroft, 1953) were found raised, indicating an enhanced rate of secretion of renin (Tobian, 1960), and electrophoretically identifiable growth hormone had accumulated in the adenohypophyses.

The present work is concerned with the influence of DCS on the secretion of renin by cats. Enhancement of the secretion of renin is found to be associated solely with those doses of DCS which antagonize the effects of circulating sympathetic amine but do not markedly diminish vasomotor tone. Finally, a mechanism is exposed whereby the release of renin by DCS may be effected.

Methods

The forty-one cats used in these experiments were anaesthetized by intraperitoneal injection of 9·0 ml./kg 1·0% chloralose (w/v) in 0·9% (w/v) NaCl.

Experiments on renal function in the whole animal

Before every experiment the bladder was exposed through a 5 cm midline suprapubic incision to permit ligation of the urethra and cannulation of the fundus of the bladder through a stab incision made within a purse-string suture which had been stitched through the outer bladder wall. This ligature closed the bladder and secured the cannula in position. The abdominal incision was closed in two layers. Glass tracheal and polythene right femoral arterial and right external jugular cannulae were inserted. From these, records were made of respiration and of right atrial and systemic arterial pressures by means of a thermocouple, Sanborn and Statham transducers, respectively, coupled to a precalibrated Beckman RS dynograph. Electrocardiographs occupied the fourth pen of the dynograph: needle electrodes were implanted in the left posterior and both anterior limbs and were secured in position with adhesive tape. A priming dose, 2 ml./kg, 4·0% (w/v) creatinine and 1·0% (w/v) *p*-amino-hippuric acid (PAH) in 0·9% (w/v) NaCl was injected through a polythene cannula in a forelimb vein. Immediately afterwards a continuous infusion of 1:1 priming fluid and 0·9% NaCl was begun through this cannula and was maintained for an hour before and throughout the experiment at a rate of 0·12 ml./min. A second infusion, 0·9% NaCl, was delivered for 30 min before and throughout the experiment at a preselected rate (0·2 to 0·375 ml./min) through a polythene cannula inserted into the right femoral vein.

Cannulation of the left ureter and denervation of the left kidney

Before four experiments, the left kidney was exposed by the lumbar route; the ureter was cannulated with polythene tubing 1 cm from the pelvis. The renal artery and vein were cleaned of fat; all visible nerves were severed and the rest were destroyed by painting the vessels with 30% (w/v) phenol in 0·9% NaCl. The vessels were swabbed dry and the ureter was divided between ligatures placed

distally to the point of cannulation ; then the ureteric cannula was exteriorized through a small incision made above the right iliac crest and the kidney was returned to its normal position. The lumbar incision was closed.

Collection of renal venous blood

20 cm P.E. 60 tubing, heparin filled and sealed distally, was used to cannulate left gonadal veins 1 cm from their junction with the left renal veins. The sealed distal ends of the cannula were exteriorized through a stab left flank incision before the abdomen was closed in two layers.

Collection of adrenal venous blood

10 cm heparin-filled P.E. 60 tubing, sealed at the distal end, was passed through a small stab incision in the left flank and introduced into the left lumbar vein as it approached the left adrenal. Side branches of the vein were ligated leaving only the connection with the adrenal vein. Right adrenalectomy was performed ; heparin 200 u./kg was administered intravenously before retrograde insertion of the left adrenal venous cannula into the lumbar vein and the subsequent ligature of the entry of the lumbar vein into the inferior vena cava. The collection of left adrenal blood was immediately started ; the abdomen was then closed in two layers.

Treatment of blood samples

All blood samples for assays of renin or of adrenal medullary hormones were collected into ice-cold polythene centrifuge tubes and were immediately centrifuged at 7° C, 4,500 rev/min, for 10 min. The plasma samples were withdrawn at once using polythene syringes and were stored for up to 12 hr in polythene containers at 4° C.

Design of experiments on renal function

Three concentration ranges of DCS were selected for infusion, 10–20, 40–50 and 70–80 μg/kg per min. The lowest dose level was administered for 15 min to eight animals and was followed, 1·5 to 2 hr later, by either the mid or the high dose level. Four animals received only the mid and four only the high dose level. No evidence of dose-interaction emerged. In each experiment five to eight serial collections of urine were made over measured time periods of 5 to 15 min before the saline infusion was replaced by drug in saline. Three to five periods of collection ensued before return was made to saline without drug. Urine collections continued without interruption throughout the experiment. Systemic arterial blood samples (1·5–2·0 ml.) were taken every 20 min early in experiments but at longer intervals (30–40 min) after some hours of experimental observations.

Perfused kidneys

Eight kidneys, taken from cats weighing 0·85 to 1·7 kg, were perfused with blood from other intact animals by a pump-oxygenator system (Lockett, 1968). Blood for renin assays was collected from the overspill (arterial) and from the renal venous

cannula, simultaneously, into ice-cold tubes. Measurements of various parameters of renal function were made as previously.

Biochemical methods

Sodium (Na) and potassium (K) were determined in urine and in protein free plasma filtrates (trichloracetic acid) by flame photometry. Concentrations of creatinine and PAH in plasma were determined as previously (Davey & Lockett, 1960), but two channels of an autoanalyser (Technicon Ltd) were used for the urine samples. Curves relating plasma concentration of creatinine and PAH to time were constructed from the data. Hence clearances were calculated as μg substance appearing in the urine per min divided by μg substance per ml. plasma at the mid-point of each period of urine collection.

Measurement of the concentration of renin in plasma

Plasma samples were prepared for assay of their renin content as described by Skinner (1967), except that pH 3·0 was substituted for pH 3·3 in the first overnight dialysis at 8° C and subsequent hour of dialysis at 32° C. This pH change was found necessary to inactivate cat angiotensinases. The resultant preparations were free of endogenous renin substrate and angiotensinase. Renin substrate was prepared from ox plasma as described by Lever, Robertson & Tree (1964). Undiluted renin containing extracts of plasma was incubated with excess of substrate at pH 7·0 and 37° C. The incubation mixtures were sampled twice at appropriate times (usually at 4 and 20 hr) for immediate assay of pressor activity against aspartyl^1–valyl^3, angiotensin II amide (Hypertensin, Ciba), similarly incubated, on the ganglion blocked rat (Peart, 1955). Injections were kept at 0·2 ml. or less with a 0·05 ml. wash in of 0·9% NaCl. The renin content of plasma was expressed as ng angiotensin synthesized per ml. plasma per interval of time.

Assays of adrenaline plus noradrenaline in adrenal venous plasma

Assays were made by electrocardiograph determination of cardiac acceleration in small ganglion-blocked (pentolinium, 5 mg intravenously, 5 mg intramuscularly, 5 mg subcutaneously) cats under chloralose anaesthesia. Drugs were introduced into the superior vena cava, through a polythene cannula inserted via the right external jugular vein, maximum volume 1 ml., wash in 0·2 ml., every 10 min. The bracket method of assay was used. Limits of error shown are flanking doses of standard, (−)-adrenaline.

Tests for the effectiveness of adrenergic blockade

Left splanchnic nerves were approached retroperitoneally, by muscle splitting, through an 8 cm skin incision which curved from the neck of the last rib, downward along the left lateral border of the erector spinae muscle mass. The greater splanchnic nerve was ligatured as it emerged from the crus of diaphragm and was severed proximal to this ligature. The right ascending cervical sympathetic trunk was dissected from the cervical vagus, was ligated, then severed caudal to the ligature. Rectangular pulses, 200 μsec in duration, were delivered to both these nerves through shielded Palmer electrodes from a Palmer square wave stimulator. Contractions of the right nictitating membrane were recorded by means of a Grass tension transducer coupled to the Beckman R.S. dynograph.

Drugs

Dihydroergocristine was received as a gift from Sandoz Ltd., Basel, Switzerland. Phentolamine mesylate (Ciba), atropine sulphate (British Drug Houses, Ltd), (−)-noradrenaline chloride (Parke Davis & Co. Ltd), (−)-adrenaline bitartrate (L. Light & Co. Ltd), Heparin (Evans Medical Ltd), pentolinium tartrate (May & Baker Ltd), E.D.T.A. (Ajax Chemicals Ltd) and aprotinin (Trasylol, Bayer Products Ltd) were obtained commercially.

Results

The changes in renal function caused by short intravenous infusions of dihydroergocristine (DCS) made into cats under chloralose anaesthesia have correlated throughout with the effects of the drug on systemic arterial pressure. Hence the actions of DCS on these two parameters are presented in tandem.

Infusions of DCS, 10–20 μg/kg per min for 15 to 20 min, produced a bradycardia which was abolished or prevented by atropine (0·2 mg/kg intravenously), and a slight decrease in the respiratory rate. They either did not affect the mean systemic arterial pressure or reduced it by less than 10 mm Hg. Pulse pressure, right atrial pressure and the e.c.g. were unaltered. Renal function sometimes remained unchanged, but sometimes the innervated but usually not the acutely denervated kidney responded by a slight rise in GFR and a slight diuresis accompanied by a slight natriuresis (Fig. 1). Clearances of PAH(C_{PAH}) underwent no significant change.

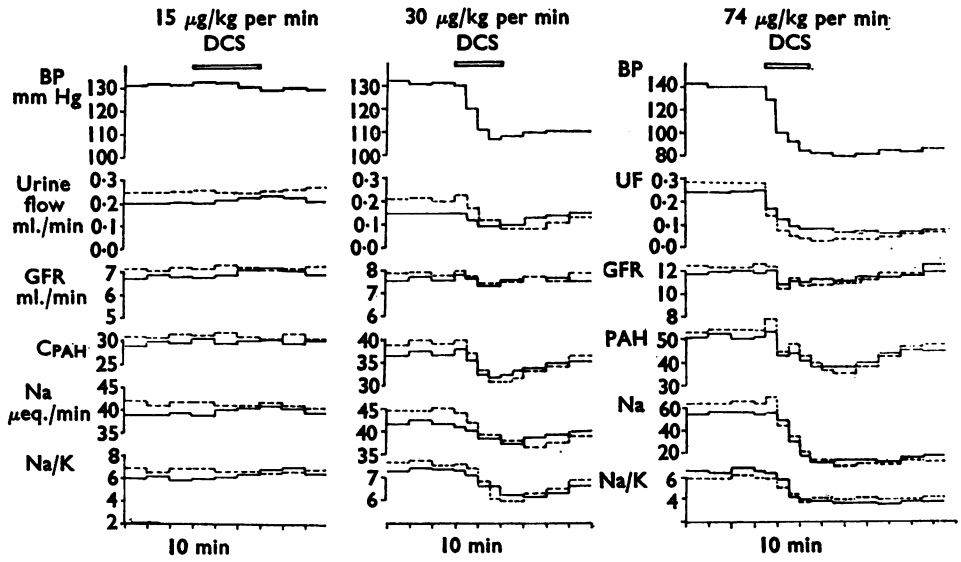

FIG. 1. Actions of dihydroergocristine (DCS) on renal function in two cats under chloralose anaesthesia, weighing 3·8 kg (panels 1 and 2, separated by 112 min) and 4·8 kg (panel 3). Infusion of DCS (open bars) at 15, 30 and 74 μg/kg per min in panels 1, 2 and 3 respectively. Ordinates, from above downward, mean arterial pressure (mm Hg); urine flow, GFR and PAH clearances (ml./min). Na excretion (μeq./min); ratio Na/K in urine. Abscissae. 10 min. Continuous line, innervated: dotted line, denervated kidney.

Infusions of DCS, 40–50 μg/kg per min for 15–20 min, reduced mean systemic arterial pressure by 19±4 mm Hg in five experiments: bradycardia, prevented or abolished by atropine, was well marked. The respiratory rate decreased at the onset of the infusion, but tended to rise to pre-infusion levels as the blood pressure fell. Pulse and right atrial pressures were unaffected. Overall, effects on innervated and denervated kidneys did not differ significantly, but in three experiments the response of the denervated kidney exceeded that of the innervated organ—a mild antidiuresis was accompanied by reduction in the rate of the urinary excretion of Na and in the ratio Na:K in the urine (Fig. 1). The GFR either underwent a marginally significant decrease or remained unchanged. C_{PAH} fell to a small but significant extent in every experiment; hence the filtration fraction presented a small increase.

Infusions of DCS, 70–80 μg/kg per min for 15–20 min, caused progressive reduction in systemic arterial pressure. Pulse pressure increased slightly as the blood pressure fell in five of six experiments. In this one experiment a 20% reduction in pulse pressure developed gradually. The bradycardia and respiratory slowing observed also at the lower dose levels were again marked but, throughout, have outlasted the infusion of DCS for less than 15 min although the actions of this high concentration of the drug on systemic arterial pressure persisted for 2 or more hours. Denervated kidneys responded to these infusions of DCS more markedly than the corresponding innervated organs. Both responded by antidiuresis, Na retention and reduction in the Na:K in the urine. Since a reduction in C_{PAH} exceeded that in GFR, the filtration fraction rose (Fig. 1).

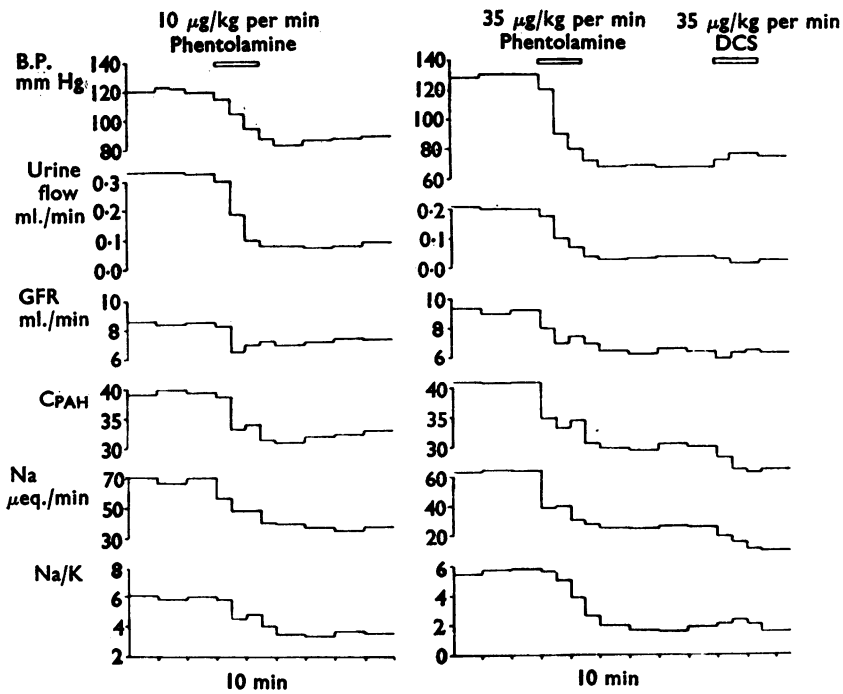

FIG. 2. Effects of phentolamine mesylate on renal function in cats (3·5 and 3·1 kg) under chloralose anaesthesia. Periods of infusion of phentolamine 10 and 35 μg/kg per min and of DCS 25 μg/kg per min are shown as open bars. Ordinates and abscissae as in Fig. 1.

These effects of infusion of DCS were contrasted with those of another α-adrenergic blocking drug, phentolamine mesylate.

Phentolamine, 10 μg/kg per min intravenously, lowered the systemic arterial blood pressure by approximately 40 mm Hg (Fig. 2). Unlike DCS, phentolamine did not cause bradycardia or slowing of respiration: instead, both heart and respiratory rates presented the small expected reflex increase as arterial pressure decreased. Innervated and denervated kidneys responded similarly to phentolamine. The antidiureses caused by this drug exceeded those provoked by DCS at equivalent decrease in mean arterial pressure (cf. Figs. 1 and 2). Antidiureses caused by phentolamine were accompanied by reductions in GFR, C_{PAH}, the urinary excretion of Na and the Na/K of urine. Phentolamine, however, did not influence the filtration fraction, whereas DCS increased it. Sympathetic systemic arteriolar tone was abolished by phentolamine 30 μg/kg per min within 15 min. The resultant large fall in arterial pressure was accompanied by intense antidiuresis and marked decrease in GFR, C_{PAH}, urinary Na and Na:K. The infusion of DCS, 35 μg/kg per min, after abolition of sympathetic vascular tone by phentolamine (Fig. 2), caused a small rise in mean arterial pressure and further slight decrease in urine flow and in the ratio Na:K in the urine. Accompanying reductions in the urinary excretion of Na and C_{PAH} were more marked, but GFR was not significantly changed.

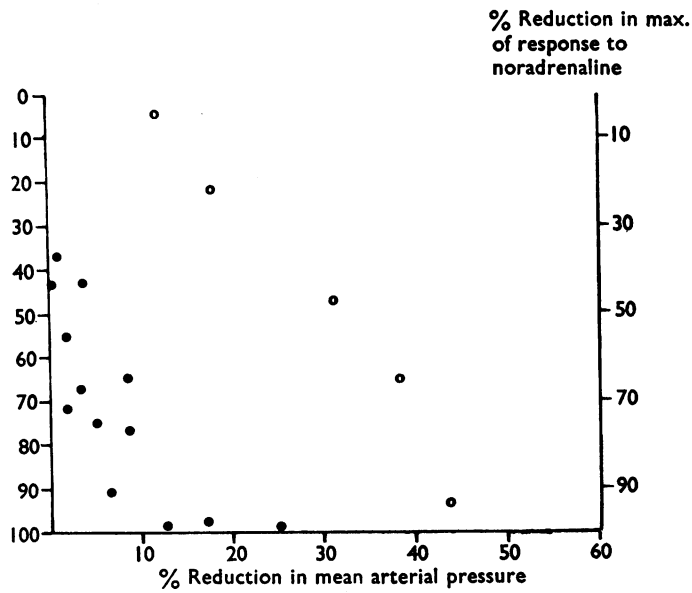

FIG. 3. Proportionate antagonism of vasomotor tone and the vasopressor effects of exogenous noradrenaline is contrasted with the greater antagonism of the pressor actions of exogenous noradrenaline than of vasomotor tone by dihydroergocristine. Ordinates, % reduction of the pressor effect of 2·0 μg (−)-noradrenaline/kg per min. Abscissae, % maximum obtainable reduction in mean arterial pressure. Open circles, DCS: closed circles, phentolamine.

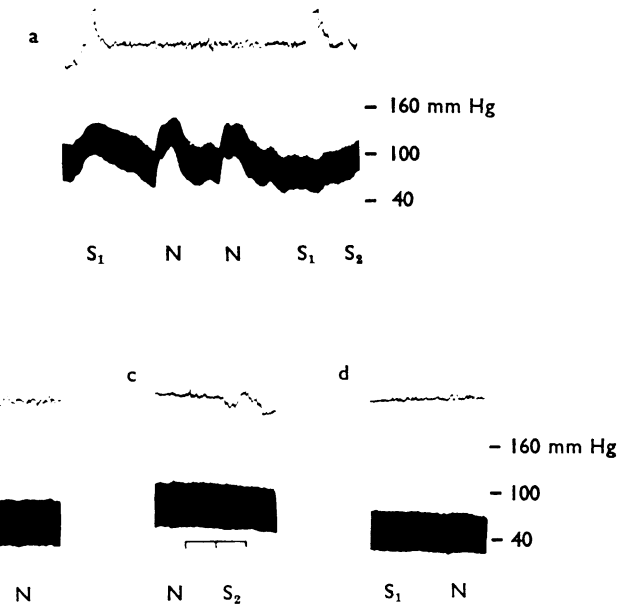

FIG. 4. Responses of the right nictitating membrane (above) and of the systemic arterial pressure (below) of a cat, 2·9 kg, under chloralose anaesthesia to stimulation of the decentralized right ascending cervical sympathetic trunk (S, 10 and S_2, 5/sec) for 30 sec or (N) (−)-noradrenaline, 5 μg, intravenously (a) before and (b) 15 min from the start of DCS 42 μg/kg per min intravenously. This infusion terminated with panel (b). 45 min later DCS, 84 μg/kg per min intravenously, began: panel (c) begins immediately and (d) 16 min after the start of this latter infusion. Time trace, 1 min.

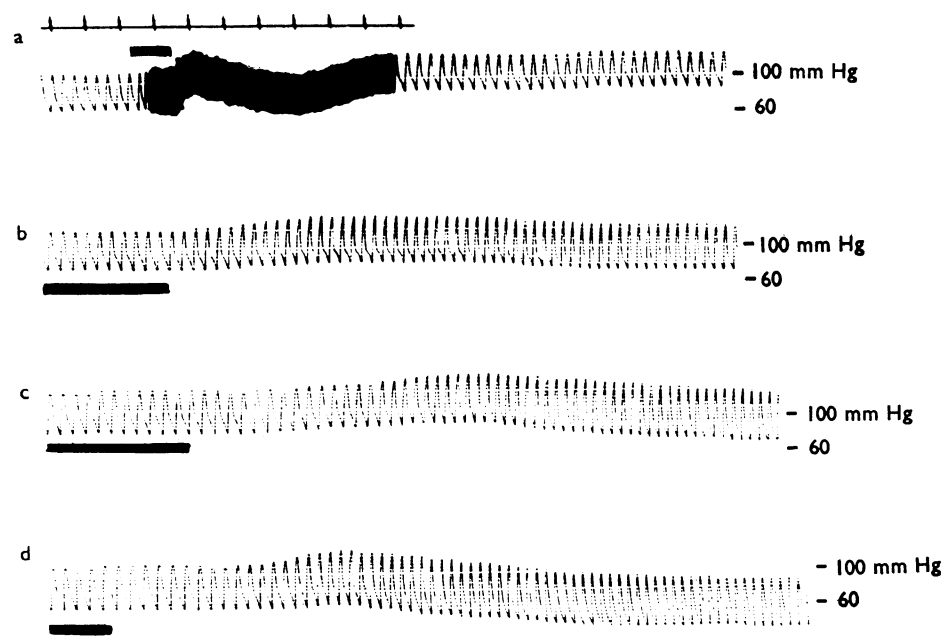

FIG. 5. Records from the right femoral artery of a cat, 2·4 kg, under chloralose anaesthesia showing responses to delivery of impulses 200 μsec, 10/sec, 4 V, for 60 sec to the decentralized left splanchnic nerve. (a) Before and (b) 2 min after the start of a continuous intravenous infusion of DCS, 80 μg/kg per min. (c) Starts 8 min and (d) 22 min from the onset of infusion of DCS. Ordinates, mm Hg. Time marked, min (slow) and sec (fast). Black bars denote stimulation in progress.

Antagonism of the vasopressor actions of exogenous noradrenaline by DCS and phentolamine

It was characteristic of the action of DCS that infusion rates insufficient to cause any significant hypotension produced marked reduction in the pressor effects of exogenous noradrenaline (Fig. 3). By contrast, phentolamine reduced mean systemic arterial pressure and antagonized the pressor effects of exogenous noradrenaline well-nigh proportionately (Fig. 3). Figures 4 and 5 clearly demonstrate the wide difference between the concentration of DCS needed to antagonize the effects of exogenous noradrenaline and to block the consequences of activity in sympathetic nerves. Figure 4 shows that an infusion of 42 μg/kg per min DCS for 15 min abolished the pressor effect of 5 μg (−)-noradrenaline given intravenously, lowered mean systemic arterial pressure by 10 mm Hg, but did not reduce the contraction of the nictitating membrane in response to excitation of the ascending cervical sympathetic trunk. Forty-five minutes after cessation of this infusion the mean arterial pressure had risen to resting levels, but the response to intravenous noradrenaline remained antagonized. DCS was infused, 84 μg/kg per min. Record C (Fig. 4) was obtained immediately after the start of this infusion. Sixteen minutes later mean arterial pressure had fallen to 55 mm Hg and the response of the nictitating membrane to stimulation of the ascending cervical sympathetic trunk had been abolished. Figure 5(a) shows the effect on systemic arterial pressure of stimulation of the left splanchnic nerve for 1 min at 10/sec, before and 2 min (b) after the start of an infusion of DCS, 80 μg/kg per min. The initial pressor response to splanchnic stimulation which results from constriction of the splanchnic bed was absent, but the tachycardia which results from the release of adrenaline was well

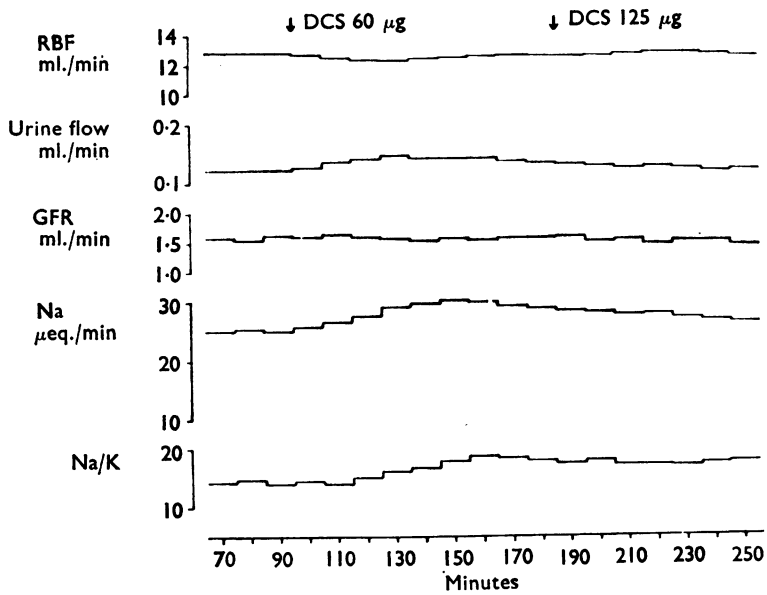

FIG. 6. Effects of dihydroergocristine (DCS) on a kidney, 6·8 g, perfused at 121 mm Hg and 38° C, with normal blood. DCS was added to the reservoir at arrows, 60 and 125 μg respectively. Circuit volume, 120 ml. Ordinates from above downward, renal blood flow, urine flow and GFR, all ml./min ; Na excretion μeq./min and Na/K of urine. Abscissae, minutes.

marked 8 min (c) after the start of the infusion. Fourteen minutes later (d), splanchnic stimulation elicited a marked tachycardia and the start of the infusion. After another 14 min, mean systemic arterial pressure had decreased by nearly 30 mm. Hg. Splanchnic stimulation again provoked a delayed tachycardia and, now, a well marked fall in arterial pressure, typical of adrenaline reversal.

Actions of dihydroergocristine and phentolamine mesylate on isolated kidneys perfused at constant temperature and pressure from pump-oxygenator circuits

Phentolamine mesylate (0·1–2·0 μg/ml. blood) was without effect on RBF, GFR, urine flow and the excretion of Na and K. DCS (0·3 to 0·5 μg/ml. blood) caused a small reduction in RBF, no change in GFR and a mild diuresis and natriuresis in each of four experiments. The diuretic natriuretic effect of these lower concentrations of DCS developed slowly, reached maximum in 30–40 min and then gradually declined. DCS (0·3–0·5 μg/ml.) was, however, without effect on these parameters in kidneys pretreated with phentolamine mesylate (0·4 μg/ml. blood) and itself effectively blocked the acute vascular responses of isolated kidneys to intra-arterial injection of 0·5 μg noradrenaline. By contrast, higher concentrations of DCS (1·25 to 2·50 μg/ml. blood) twice caused a slight initial decrease in RBF and GFR which lasted for less than 5 min. In four other experiments, however, these concentrations of DCS were without action on the blood and urine flows and the excretion of Na and K by the isolated kidney (Fig. 6).

Release of catecholamine from the adrenal medulla by dihydroergocristine

Infusions of DCS 30–40 μg/kg per min, intravenously, enhanced the secretion of catecholamine into adrenal venous blood. This action of DCS was not prevented

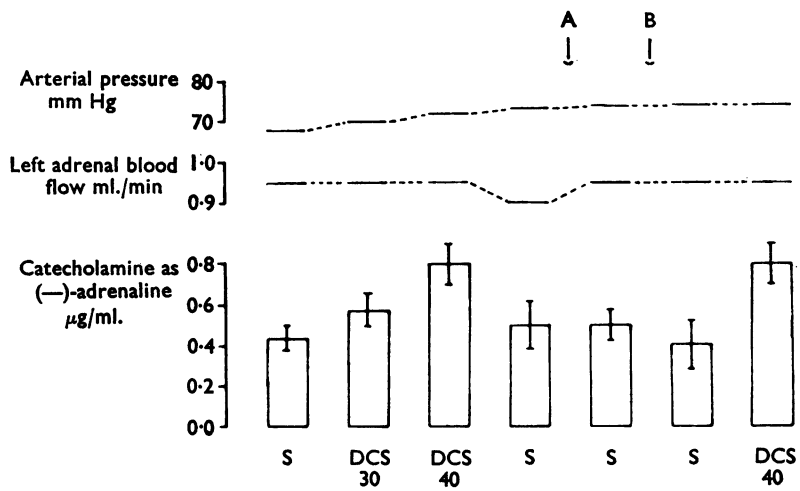

FIG. 7. Release of sympathetic amines from the left adrenal gland by dihydroergocristine. Data from an experiment on a cat, 3·3 kg, under chloralose anaesthesia. Ordinates, from above downward, mean arterial pressure, mm Hg; left adrenal blood flow, ml./min; sympathetic amine in plasma of adrenal venous blood as μg (−)-adrenaline/ml. Abscissae, infusion, intravenously, 0·375 ml./min: 0·9% NaCl (S); DCS, 30 and 40 μg/kg per min. A and B denote intravenous injections of pentolinium tartrate (10 mg) and phentolamine mesylate (5 mg) respectively. Right adrenal removed before the experiment.

by blockade of the autonomic ganglia with pentolinium tartrate or full α-adrenergic blocking doses of phentolamine mesylate (Fig. 7).

Influence of dihydroergocristine on the secretion of renin by the kidney

In the intact cat, when vasomotor tone had been abolished by infusion of DCS, 80 μg/kg per min, the arteriovenous difference across the kidney in plasma renin concentration did not differ significantly from the values obtained before administration of DCS. By contrast, concentrations of DCS which blocked the vasopressor action of circulating catecholamine but which did not markedly reduce vasomotor tone (Fig. 1) increased the arteriovenous difference across the kidney in plasma renin concentration and increased the rate of the renal secretion of renin (Fig. 8).

A similar phenomenon was found in isolated kidneys perfused at constant pressure. The lower (0·3 to 0·5 μg/ml.) concentrations of DCS which caused mild diuresis and natriuresis (Fig. 6) and a small decrease in RBF increased the renal arteriovenous difference in the plasma concentration of renin (Fig. 9). This release of renin by DCS was prevented by phentolamine, 1 mg/120 ml. blood. The higher concentrations of DCS which were without influence on the measured parameters of renal function (Fig. 8) did not influence the secretion of renin by the isolated kidney.

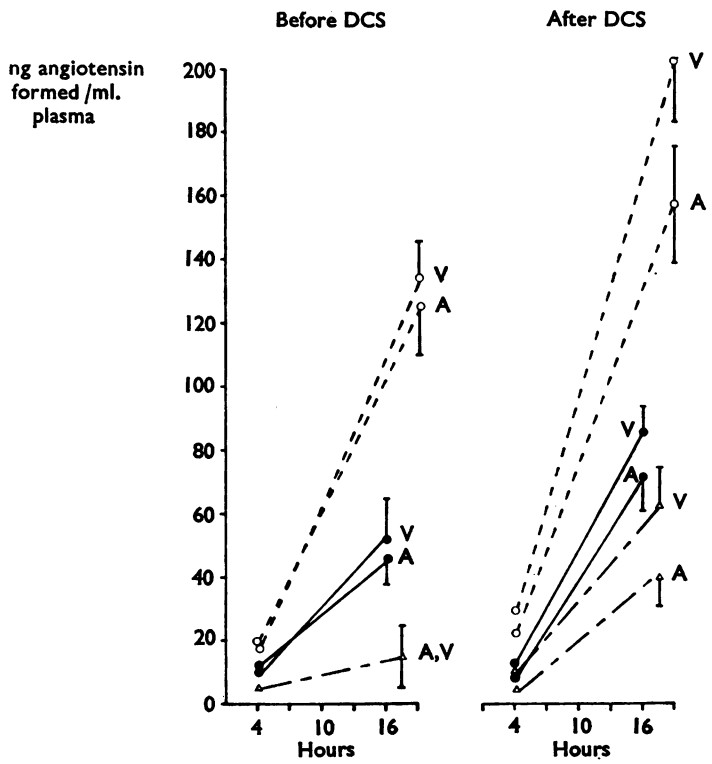

FIG. 8. Effect of dihydroergocristine 30–40 μg/kg per min for 10–15 min on the secretion of renin by cats (3·1, 3·3 and 3·8 kg) under chloralose anaesthesia. Ordinates, ng angiotensin formed per ml. plasma. A, Arterial and V, renal venous. Abscissae, incubation time in hours.

Discussion

The α-adrenoceptor blocking actions of dihydroergocristine and of phentolamine differ. Whereas the same concentration of phentolamine reduces vasomotor tone and the pressor effect of circulating noradrenaline well-nigh proportionately, concentrations of DCS one-quarter of those necessary to block the effects of stimulating sympathetic nerves effectively inhibit the pressor action of injected amine. Concentrations of DCS too low to block the effects of sympathetic nerve stimulation accelerate the release of renin from the kidneys and release sympathetic amine from the adrenal medulla. The increase in the plasma concentration of sympathetic amine resulting from this adrenal release cannot, however, cause a rise in mean arterial pressure, for these same concentrations of DCS antagonize the vasopressor effects of DCS on the adrenal medulla. DCS-induced renin secretion is probably mediated by DCS-induced release of noradrenaline from the terminations of the adrenergic fibres which innervate the juxtaglomerular apparatus (Barajas, 1964 ; Wägermark, Ungerstedt & Ljungquist, 1968). The release of renin by noradrenaline is well known (Walther, Kingsbury, Stouder, Schneider & Rostorfer, 1965 ; Vander, 1965). Moreover, the acceleration of renin secretion by DCS is prevented by full α-adrenoceptor blocking doses either of phentolamine or of DCS.

Hence, the rise in filtration fraction, antidiuresis and Na retention, caused by infusions of DCS, 30–40 μg/kg per min, unaccompanied by any marked fall in

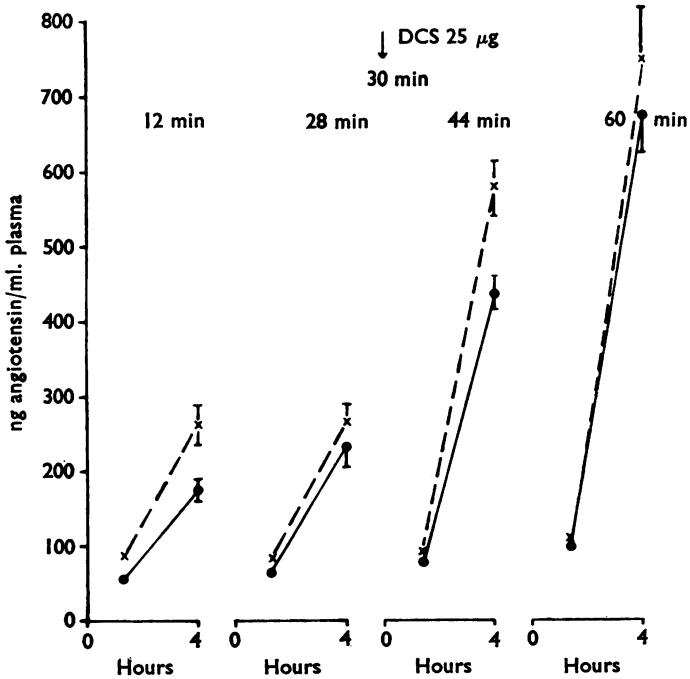

FIG. 9. Effect of dihydroergocristine on the secretion of renin by an isolated kidney, 6·1 g, perfused at 112 mm Hg and 38° C. Ordinates, ng angiotensin formed per ml., arterial (●——●) and renal venous (×——×). Abscissae, incubation time in hours. Inset minutes: time of collection of plasma samples. The arrow signifies the addition of 25 μg DCS to the blood in the reservoir, circuit volume 120 ml.

systemic arterial pressure are attributable to the release of renin and the consequent rise in the plasma concentration of angiotensin arising from interaction of this renin with its α-globulin substrate (Peart, 1965). Antidiuresis, Na retention and a rise in the filtration fraction are characteristic of the action of small doses of angiotensin in the whole animal (Bock & Kreke, 1958 ; Finnerty, De Carlo Massaro, Chupkovitch & Tuckman, 1961). Similarly the diuresis, natriuresis and rise in filtration fraction exhibited by perfused kidneys in saline diuresis when exposed to DCS (15–60 μg/120 ml. blood) is attributable to the release of renin by DCS, for these effects are characteristic of the action of angiotensin on perfused cat kidneys when in saline diuresis (Lockett, 1967).

The small pressor response occasioned by DCS after abolition of vasomotor tone by phentolamine may be attributed to the weak smooth muscle stimulant properties of the dihydroergot alkaloids. It is probable that the release of noradrenaline at the terminations of the vasomotor nerve fibres and the release of renin from the kidneys contribute to the more marked pressor effect of DCS demonstrable in the ganglion-blocked animal (Rothlin & Cerletti, 1949).

The bradycardia characteristic of ergot alkaloids of the peptide group is well known and is considered mainly of central origin: it is manifest only on the innervated heart and is abolished by atropine or vagotomy (Rothlin, 1950).

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