Deoxycorticosterone hypertension in the pig


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Summary

1. Deoxycorticosterone acetate (DOCA) implantation (100 mg/kg) caused mean arterial pressure to rise in 5–10 days from control pressures of 100–115 mmHg to stable hypertensive values of 140–160 mmHg in approximately 1 month. In six of seven pigs elevations of mean arterial pressure were entirely the result of increased total peripheral resistance.

2. Single implants maintained serum DOCA at approximately ten times normal concentration for up to 90 days.

3. Moderate but variable decreases in serum aldosterone followed implantation.

4. Hypokalaemia, polydipsia and suppressed plasma renin activity were evident by the fifth post-implantation day and persisted thereafter. No consistent change occurred in serum sodium.

5. Noradrenaline or angiotensin caused increases in total peripheral resistance at lower threshold infusion rates in hypertensive pigs compared with control animals.

6. In isolated, perfused hind-limb preparations, hypertensive vascular beds were characterized by both functional (increased vascular smooth muscle sensitivity) and structural (elevated resistance of maximally dilated vascular bed) changes. 'Protection' from increased arterial wall stresses in hypertensive pigs prevented structural, but not functional, alterations.

Key words: aldosterone, angiotensin, cardiac output, deoxycorticosterone, hypertension, hypokalaemia, noradrenaline, renin, vascular resistance.

Introduction

This study was undertaken to develop a model of mineralocorticoid hypertension in an animal larger than the rat. The use of the pig facilitated studies of the mechanisms causing elevated arterial pressure after implantation of DOCA. Uninephrectomized pigs, implanted with DOCA, readily became hypertensive; this occurred without added salt in their food or drinking water. The model provides a basis for studies of comparative pathophysiology.

Methods

Chester-White or Yorkshire feeder pigs weighing 20–30 kg were studied. They were housed in 4 ft x 4 ft metabolic pens and given one meal (5% body weight) of Purina Pig Chow per day with water ad libitum.

Pigs were subjected to three surgical procedures. In the first, under ketamine and pentobarbitone anaesthesia, the heart and great vessels were exposed through a left thoracotomy in the third intercostal space. An electromagnetic flowprobe (Zepeda Instruments, Seattle, Washington, U.S.A.) was placed around the ascending aorta. A Herd & Barger (1964) Tygon catheter was inserted into the aorta just distal to the flowprobe. Catheter and flowprobe leads passed out through the fourth intercostal space, and were secured to a subcutaneous binding loop (copper wire in Tygon tubing). Pigs were placed on postoperative antibiotics for 7–10 days. Heavy canvas jackets protected the exteriorized devices, and allowed easy exposure for use in daily flow and pressure monitorings.

$^{(1)}$ Abbreviations: DOCA, deoxycorticosterone acetate; TPR, total peripheral resistance; PRA, plasma renin activity.
One to 2 weeks after the initial operation, with similar anaesthesia, a midline laparotomy was performed. A Herd–Barger catheter, inserted into the abdominal inferior vena cava, was advanced into the thoracic cava for central venous pressure measurements. Catheters were brought out through the abdominal wall and anchored on the previously placed binding post. Unilateral (right) nephrectomy was performed. One external iliac artery was ligated proximally. This represented the so-called ‘protected hind limb’.

Pigs were subjected to a third procedure when they had completely recovered from the abdominal operation, and after base-line measurements had been acquired over approximately a 2 weeks period. Under thiamylyl (Surital) anaesthesia, a 1–2 cm skin incision was made in the left flank and strips of DOCA/silicone rubber were inserted subcutaneously. Implants were prepared by mixing DOCA (Sigma Chemical Co.) with silicone rubber (Dow Corning) in a ratio of 1:1.5. Before insertion, the strips were gas-sterilized with ethylene oxide. The total dose of DOCA was 100 mg/kg.

Cardiac output, arterial and central venous pressures were monitored daily. Total peripheral resistance was calculated from these measurements. Plasma aldosterone was measured by a modification (unpublished) of the radioimmunoassay method of Mayes, Furoyama, Kem & Nugent (1970); plasma renin activity by a radioimmunoassay method for angiotensin I (Cohen, Grim, Conn, Blough, Guyer, Kem & Lucas, 1971); DOCA was assayed by a modification of a radioimmunoassay method for plasma 11-DOCA (Manlimos, Margoulis & Abraham, 1975). Serum sodium and potassium concentrations were determined by flame photometry. Salt and water balance was computed on the basis of daily urine collection and measured food and water intake. The only sodium available to the animals was that contained in the Purina Pig Chow (3–5 mmol day⁻¹ kg⁻¹).

Whole-animal vascular reactivity studies were performed by intravenous noradrenaline and angiotensin infusions in conscious animals. Dosages varied from subthreshold amounts to those producing a 50–70 mmHg increase in arterial pressure. Aortic and central venous pressures, as well as cardiac output, were recorded and TPR was calculated. Hind-limb perfusion studies were conducted as terminal experiments. Animals were anaesthetized with pentobarbitone, heparinized, and a large catheter was placed proximally within the infrarenal aorta. This catheter was connected with two constant-flow peristaltic perfusion pumps that delivered blood to each hind limb. Vascular reactivities in the ‘protected’ and ‘unprotected’ hind limbs were determined in response to noradrenaline injected intra-arterially into the perfused vascular bed. Structural resistances of each hind-limb vascular bed were determined after intra-arterial injections of papaverine–HCl caused maximal vasodilatation.

Results
Of seven pigs implanted with DOCA, all exhibited increases in mean arterial pressure that began in 5–10 days. Pressures rose from control values (100–115 mmHg) to 140–160 mmHg by the fourth week, and remained elevated until the experiments were terminated 40–90 days post-implantation. Three control pigs showed no change in pressure over a comparable time-period. Six pigs demonstrated a rise in TPR as early as the third day after implantation. Cardiac output did not rise above control values in these animals. One of the seven pigs demonstrated an initial elevation of cardiac output, followed by an increase of TPR, and then a subsequent fall of cardiac output.

Serum DOCA rose to as high as 3800 ng/100 ml within 8 h of implantation (control DOCA concentrations were 30–60 ng/100 ml). The high DOCA concentrations gradually decreased to 300–800 ng/100 ml by the end of the study period. Suppressed PRA, to activities below the limits of the assay (about 0.02 ng h⁻¹ ml⁻¹), occurred in all animals 4–7 days after implantation (control PRA was 3.2 ± 0.85 (SEM) ng h⁻¹ ml⁻¹). Plasma aldosterone, although suppressed in four of seven animals, rose to near control values (11.8 ± 2.9 ng/100 ml) 17–57 days post-implantation. Two pigs exhibited no decrease in aldosterone.

Although all DOCA-implanted animals increased their fluid intake from 2 to 4 l/day to as much as 20 l/day after implantation, parallel increases in urinary output occurred, and there was no evidence of fluid retention in three animals so studied. Similarly, no convincing evidence of sodium retention, or increased potassium loss in the urine, existed despite dramatic hypokalaemia (2–3 mmol/l) that commenced 3–4 days after DOCA implantation. No consistent change in serum sodium was found.

Preliminary data from whole-animal infusion
studies demonstrated greater systemic sensitivity to noradrenaline and to angiotensin in hypertensive compared with control pigs. This difference occurred early in the development of hypertension before maximal blood pressure elevations were noted. Hind-limb perfusion experiments in hypertensive animals demonstrated significantly greater resistances than normotensive control pigs, both before and after maximal vasodilatation with papaverine. Noradrenaline infusion in the hypertensive pigs demonstrated significantly greater maximum pressor responses compared with control pigs, shifts in the dose–response curves to the left and lower thresholds for noradrenaline stimulation. Vascular resistance before and after papaverine vasodilatation was significantly greater in ‘unprotected’ hind limbs exposed to hypertension, than that found in the ‘protected’ hind limbs of hypertensive animals. Both the ‘protected’ and ‘unprotected’ hind limbs demonstrated greater sensitivity to noradrenaline stimulation than did the hind limbs of normotensive control animals. The ‘protected’ vascular beds, however, demonstrated smaller maximal pressor responses compared with those occurring in the ‘unprotected’ vascular beds.

Discussion

Uninephrectomized pigs develop hypertension rapidly and consistently after implantation of DOCA without supplemental salt administration. Hypertension is maintained without further DOCA implantation for as long as 90 days. Increased mean arterial pressure results from rapid increases in TPR. This lends credence to the hypothesis that high serum concentrations of DOCA may increase vascular reactivity by some direct action on vascular smooth muscle. It is concluded from the whole-animal and hind-limb studies of vascular reactivity that structural changes appear to be secondary to increased wall stress, but functional changes in vascular smooth muscle are not.

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References


