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Differential Effects of DOCA on Renal and Gastrointestinal Handling of Sodium and Potassium in Pigs (41735)

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Abstract. Young, male pigs eating standard pig chow, *ad libitum*, received approximately 170 mEq Na and 290 mEq K per day. Electrolyte intake, urinary and fecal electrolyte output, and plasma electrolyte levels were determined daily in 12 deoxycorticosterone acetate (DOCA)-treated pigs and in 6 control pigs. Daily Na and K balances (dietary intake − urinary + fecal output) were calculated. DOCA caused a reduction in urinary Na output from 1.53 mEq/kg/day to 0.57 mEq/kg/day during the first 48 hr following implantation. Escape from the renal sodium retaining effect of DOCA was complete within 3 days, with urinary Na output returning to pre-DOCA levels. Fecal Na output decreased from 0.65 mEq/kg/day during the preimplant period to 0.13 mEq/kg/day during the postimplant period. No escape from GI Na retention occurred by Day 15. Plasma Na rose to significantly higher levels by Day 15. Sodium balance was significantly elevated in DOCA-treated pigs for that first 48 hr postimplant. Urinary K output decreased from 3.50 mEq/kg/day to 1.74 mEq/kg/day during the first 2 days, but returned toward preimplant levels by Day 4. Fecal K output was increased for the first week, and thereafter returned to preimplant levels. Plasma K fell from 3.9 to 2.9 mEq/liter by Day 15. Potassium balance fell slightly in both experimental and control animals. No significant differences in potassium balance were present between the two groups. The control pigs showed no significant changes in plasma electrolyte concentration or in electrolyte balance. It is concluded that DOCA has differential effects on renal and gastrointestinal handling of electrolytes and that DOCA may induce an intracellular shift of potassium in pigs.

The phenomenon of transient renal sodium retention with subsequent escape induced by deoxycorticosterone acetate (DOCA) administration has been well documented in humans, dogs, rats, rabbits, and pigs (1–8). Renal handling of potassium following DOCA administration, however, is not as uniform among these species. Excess urinary loss of potassium has been reported in humans, dogs and rats (1–6). This urinary potassium excess has been cited as the cause of the hypokalemia also observed in these species during the DOCA-treatment period. On the other hand, although hypokalemia also occurs in rabbits and pigs, these animals have a reduction in urinary potassium excretion following DOCA administration. Accordingly, it has been suggested that this hypokalemia without kaliuresis demonstrates an intracellular shift of potassium (7, 8). It has also been suggested that the hypokalemia may have been produced by an excess fecal potassium loss. Dawborn and Ross (7) have indeed observed an increase in fecal potassium loss in rabbits administered aldosterone. However, despite this excess gastrointestinal potassium loss, the rabbits maintained a positive potassium balance due to a greater reduction in urinary potassium output (7).

This study was conducted to compare the renal and gastrointestinal effects of DOCA on sodium and potassium balance in the pig, an animal which does not have a kaliuresis in response to DOCA administration.

Methods. Eighteen male feeder pigs (Yorkshire) with a mean body weight of 33.7 ± 1.5 kg were studied. All pigs were housed in metabolic cages throughout the study. The pigs were fed Purina pig Grownena (112 mEq Na/kg and 191 mEq K/kg) and tap water (Na and K content negligible), both *ad libitum*. No excess salt was added to the diets. Pigs grew at an average rate of 0.5 kg/day. The pigs were chronically instrumented with hemodynamic monitoring devices (9–11). Strips of silicone rubber (Dow Corning) impregnated with DOCA (Sigma) were implanted subcutaneously in the left flank of 12 experimental pigs

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under thiamylal anesthesia (Surital, Parke-Davis). The total dose of DOCA was 100 mg/kg body weight. Previous studies with this regimen produced serum DOC levels which remained well above normal throughout the treatment period (8). Six control pigs received DOCA-free implants, again under thiamylal anesthesia.

Measurements of total food intake and total urinary and fecal output were made every 24 hr (at approximately 9:00 AM). The collection period began 5 days before implant and ended 15 days after implant. Homogeneous urine samples were collected and frozen until assayed. The entire fecal output for each 24-hr period was collected and homogenized with distilled water. Approximately 1-g aliquots of the homogenate were ashed overnight at 500°C, digested with 10–15 ml of 1.0 *N* nitric acid, diluted to 100 ml with deionized water, then diluted 1:1 with lithium nitrate, 30 mEq/liter. Plasma samples for electrolyte determination were collected in tubes pretreated with lithium heparin daily from 5 days before through 5 days after implant and every fifth day thereafter. The plasma samples were stored at 4°C until assayed. Sodium and potassium in plasma, urine, and feces were measured on a National Instrument Laboratories flame photometer (IL 443) with an internal lithium standard of 15.0 mEq lithium/liter. Daily electrolyte intakes and outputs corrected for body weight (mEq/kg body weight/day) were recorded as were daily balances (dietary intake − urinary + fecal output).

Statistical comparisons between groups were performed using a Student's *t* test. Within group comparisons utilized the paired *t* test. Comparisons within and between groups over more than 2 days were made using profile analysis. Plasma sodium concentrations in the pre- and postimplant periods were compared using a pairwise *t* test with Bonferroni multiple comparisons procedure.

Results. All animals receiving DOCA had a rise in mean arterial pressure 24 hr after implantation. Pressure rose from a mean of 94.3 ± 1.7 mm Hg before implant to 101.1 ± 2.2 mm Hg 24 hr after implant ($P < 0.05$). Pressure continued to rise gradually for the next 10 days, reaching a level of 117.5 ± 2.6 mm Hg. No significant change was seen in arterial pressure in control animals.

Sodium intake and urinary and fecal sodium output were stable during the period before DOCA implantation in the experimental pigs (Fig. 1). During the first 2 days following implantation, daily urinary sodium output decreased from 1.53 ± 0.16 to 0.57 ± 0.15 mEq/kg body weight ($P < 0.001$), and fecal sodium fell from 0.65 ± 0.07 to 0.19 ± 0.03 mEq/kg body weight ($P < 0.001$). The reduction in sodium output was greater than the fall in intake which also occurred following implantation, resulting in a transient increase in positive sodium balance from 2.60 ± 0.21 mEq/kg/day preimplant to 3.07 ± 0.21 mEq/kg/day. This increase was significant ($P < 0.05$). By Day 3, urinary sodium returned to pre-DOCA values, and remained stable throughout the study. The decrease in fecal sodium persisted for the entire 15 days of study. Mean fecal sodium output was 0.13 ± 0.02 mEq/kg/day during the 3rd to 15th day of the period compared to 0.65 ± 0.07 mEq/kg/day during the preimplantation period ($P < 0.001$). Sodium balance on Days 3–15 was not different from that seen during the basal period.

Control animals had no consistent change in urine or fecal sodium output following im-

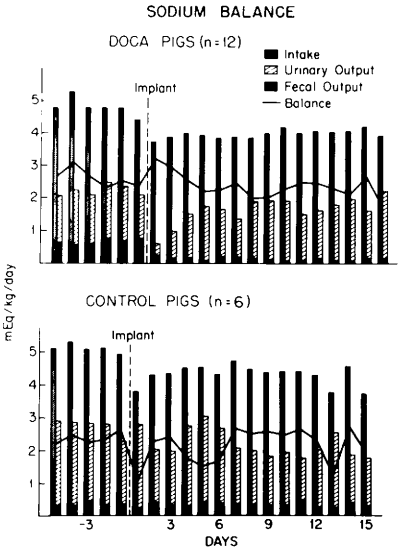

FIG. 1. Sodium balance in DOCA hypertensive and control pigs. Following DOCA implantation there was a transient decrease in urinary sodium and a sustained decrease in fecal sodium excretion.

plantation of the silicone rubber. Sodium balance showed no consistent changes.

Potassium intake and urinary and fecal output were also stable during the pre-DOCA period in experimental animals (Fig. 2). For the first 2 days following DOCA implantation, urinary potassium fell from 3.50 ± 0.26 to 1.74 ± 0.21 mEq/kg/day ($P < 0.001$). Although increasing by Day 4, urinary potassium remained below preimplant levels for the remainder of the study (N.S.). Kaliuresis was not observed in the experimental animals at any time. Fecal potassium output increased from a mean of 1.28 ± 0.12 mEq/kg/day during the preimplant period to 1.85 ± 0.22 mEq/kg/day for Days 2–7 following DOCA ($P < 0.001$). Thereafter, however, fecal potassium was 1.16 ± 0.17 mEq/kg/day, not significantly different from basal values. Control animals had no consistent change in urinary or fecal potassium throughout the study.

The mean positive potassium balance in experimental pigs was 3.40 ± 0.38 mEq/kg/day during the preimplant period. This decreased to a mean value of 2.97 ± 0.21 mEq/kg/day over the entire post-DOCA period, a decrease of 0.43 mEq/kg/day (N.S.). Potassium balances of the control animals were also lower following implantation; preimplant potassium balance was 3.84 ± 0.29 mEq/kg/day, whereas postimplant balance was 2.98 ± 0.19 mEq/kg/day, a fall of 0.86 mEq/kg/day ($P < 0.001$).

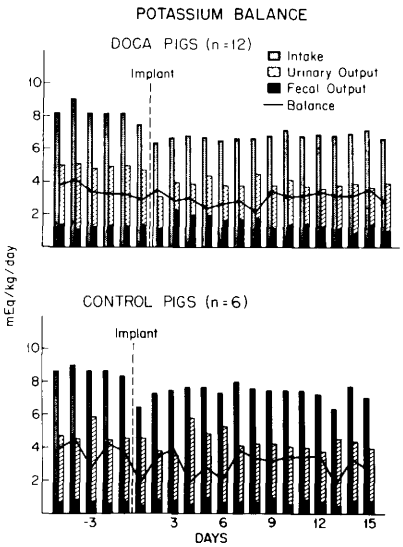

FIG. 2. Potassium balance in DOCA hypertensive and control pigs. DOCA implantation resulted in a decrease in urinary potassium. Fecal potassium was increased for 6 days following implantation of DOCA but then returned to basal levels.

Sequential changes in plasma sodium and potassium are depicted in Fig. 3. No significant change in plasma sodium was observed during the first 5 days after DOCA implantation. Mean plasma sodium during the entire postimplant period, however, was significantly increased compared to the preimplant period ($P < 0.05$). No such difference was observed in the control animals. Plasma potassium fell steadily in the DOCA-treated pigs beginning the day after DOCA implantation, decreasing from 3.9 ± 0.1 mEq/l to 2.9 ± 0.2 mEq/l by Day 15. No change in plasma potassium was seen in the control animals. The fall in plasma potassium was significant in the DOCA-treated pigs by Day 3 when compared to preimplant levels ($P < 0.001$). Plasma potassium in DOCA pigs 3 days after implant was also significantly lower than in control pigs on Day 3 ($P < 0.05$).

Discussion. Deoxycorticosterone acetate caused consistent and characteristic changes in urinary and fecal sodium output in pigs. Unlike the transient decrease in urinary sodium excretion, the fall in fecal sodium excretion persisted throughout the DOCA-treatment period. The persistent gastrointestinal sodium retention likens the pig gut to sweat and salivary glands in man and other animals, which also do not escape from the effects of mineralocoricoids (12, 13).

The different responses to DOCA by the gut and kidney suggest that two different mechanisms of sodium handling operated in these two organs. The persistence of sodium retention in the gut after escape from renal sodium retention is complete indicates that (i) a general DOCA antagonist is not responsible for the escape phenomenon (14), and (ii) if a humoral factor is indeed responsible for escape (15), receptor sites for the factor are not present in the gastrointestinal tract.

The maintenance of constant plasma sodium levels in the period during which dramatic changes in urine and fecal sodium output are occurring (Days 1 to 5) is different than findings reported by Terris and Sim-

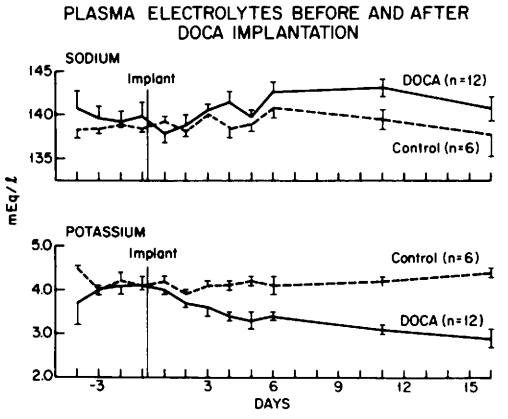

FIG. 3. Plasma sodium and potassium following DOCA implantation. Sodium was significantly increased in experimental animals after DOCA implantation. Potassium fell steadily following implantation.

monds, who cited an increase in plasma sodium 2 to 3 days after DOCA intervention in the Yucatan miniature boar (16). The eventual development of hypernatremia in DOCA implanted animals is contrary to our previous experience, in which no significant changes in serum Na were seen (8). The most likely explanation of this new finding is an improvement in the method of measuring plasma sodium.

The effects of DOCA on the handling of potassium by the kidney and gastrointestinal tract are species specific. DOCA administered to humans, dogs, and rats generally causes an increase in both urinary and fecal potassium (1–6). In contrast, pigs in the present study show a decrease in urinary potassium and only a small (although statistically significant) increase in fecal potassium. Since potassium balance for both DOCA and control pigs decreases slightly over time, and since only DOCA-treated pigs became hypokalemic during that same time interval, excess potassium loss cannot explain the 1.0 mEq/liter fall in plasma K in the experimental pigs.

The most likely explanation for this fall in plasma potassium is a shift of potassium into the intracellular space. Dilution of serum potassium by DOCA-induced fluid retention may contribute to the fall, but previous studies have shown DOCA-induced fluid retention in pigs to be approximately 5% of total body water (8). Dilution of this magnitude would not be likely to lower plasma potassium by more than 0.1 to 0.2 mEq/liter.

The cause of an intracellular shift of potassium in DOCA-treated pigs is not obvious. We believe that it is unlikely that a direct effect of DOCA causes this intracellular shift. In DOCA treated animals given a low-sodium diet (20 mEq/day) for 17 days, serum potassium returned to normal despite elevated serum DOC levels throughout the study (17). If a direct DOCA effect upon cells were mediating an intracellular shift of potassium, hypokalemia would be expected to persist under these conditions.

A more likely cause of the intracellular shift of potassium is mineralocorticoid-induced alkalosis. DOC induces distal tubular hydrogen ion secretion, and mineralocorticoid excess states are uniformly associated with systemic metabolic alkalosis (18). As hydrogen ion concentration falls, increased potassium–hydrogen exchange occurs across the cell membrane, buffering the extracellular fluid.

As can be seen in Fig. 2, there is a progressive decrease in potassium balance in control pigs. Although we cannot explain this decrease, it seems possible that as the animals grow older, the rate of growth diminishes when expressed as percentage change in body weight. If this is true, the positive balance of most nutrients would be expected to diminish when calculated per kilogram of body weight. Sodium balance does not diminish in control pigs, apparently reflecting the different mechanisms of renal handling of these two ions.

These studies demonstrate the effects of DOCA administration upon fecal sodium and potassium excretion. A persistent decrease in fecal sodium excretion was seen throughout the study. Although fecal potassium was increased for the first week after implantation, no significant change in total (urine plus fecal) potassium excretion occurred. Hypokalemia in DOCA hypertensive pigs appears to be caused by an intracellular shift of this ion.

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