

EFFECTS OF DESOXYCORTICOSTERONE AND SALT ON AN EXPERIMENTAL NEPHROTIC SYNDROME DUE TO LIGATION OF A RENAL VEIN

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A nephrotic syndrome has been elicited in a small proportion of rats that underwent subtotal ligation of the renal vein and contralateral nephrectomy.¹ A similar state has also been observed in rabbits, in which it was regularly intensified by an excess of salt given in the drinking water.^{2,3} Our studies show that this effect of salt is likewise demonstrable in rats, and that by giving desoxycorticosterone acetate with salt to intensify further the effect, the pattern of renal injury is only complicated by a superimposed nephrosclerosis.

Methods

The *effects of salt* were studied in three groups of rats. Group I, used as control, comprised 10 uninephrectomized animals; group II and group III comprised respectively 19 and 21 rats that underwent unilateral renal venous constriction and 12 days later contralateral nephrectomy. Drinking fluid consisted of 1 per cent sodium chloride solution, in groups I and II; in group III, tap water was first given starting at the time of renal venous constriction, followed by 1 per cent saline solution on the twenty-fifth day, and 1.25 per cent saline solution on the thirty-eighth day. The experiment was terminated on the fifty-second day.

The *effects of desoxycorticosterone acetate*† (hereinafter termed DCA) were studied in four groups of 10 animals each at the daily dose levels of 1 mg. of DCA (groups I and II) and of 0.2 mg. of DCA (groups III and IV); injections of DCA in aqueous suspension were given subcutaneously. Animals of groups I and III were uninephrectomized on the seventh day of treatment and were used as respective controls for those of groups II and IV which underwent unilateral renal venous constriction on the first day and contralateral nephrectomy seven days later. The experiments were terminated on the thirtieth day.

Sprague Dawley rats weighing from 90 to 110 gm. were used. Partial constriction of the renal vein was accomplished by tying a silk ligature around it and a stylet (diameter 0.55 mm.) that subsequently was withdrawn. Urinary flow, proteinuria, and arterial pressures were measured twice weekly. At the end of the experiment, total serum protein, blood urea nitrogen, and serum cholesterol values were determined, the animals were killed and the organs were removed for histologic studies.

Supported in part by a grant from the Kidney Disease Foundation (Northern Ohio) to Dr. A. C. Corcoran, formerly Member of the Staff of The Cleveland Clinic Foundation.

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†Generously supplied by Dr. R. Gaunt, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

Results

Effects of salt. Administration of 1 per cent sodium chloride solution in the control group I (uninephrectomy) caused diuresis in the average amount of 50 ml. daily (range 32 ml. to 83 ml.), while proteinuria remained about 30 mg. per day, which is normal in the rat.

In group II (renal venous constriction plus contralateral nephrectomy) administration of 1 per cent saline solution initially resulted in the same fluid and protein outputs as in group I. Then, about the seventh day postnephrectomy, while urinary flow remained unchanged, daily proteinuria increased in the range of 100 mg. to 500 mg. The mean serum cholesterol concentration was 121 mg. as compared with 85 mg. per 100 ml. in the control animals, and blood urea nitrogen content was elevated to 29 mg. as compared with the control value of 20 mg. per 100 ml.; the total serum protein content was 6.8 gm. per 100 ml., which is normal.

In group III (renal venous constriction plus contralateral nephrectomy) tap water given during the first 25 days resulted in normal urinary flow and proteinuria (*Fig. 1*). Substitution with 1 per cent saline solution increased proteinuria to concentrations of about 150 mg.; replacement with 1.25 per cent salt solution on the thirty-eighth day increased proteinuria to concentrations in the range of 500 mg. to 900 mg., and diuresis to 100 ml. daily. Beginning at about the fifth day of administration of hypertonic saline solution (1.25 per cent), body weights began to fluctuate widely as a result of phasic fluid retention and excretion; blood pressures at that time were greater than 200 mm. of Hg (*Fig. 1*). In two of four survivors, the total serum protein content was less than 6 gm. per 100 ml.; serum cholesterol content was more than 200 mg. and blood urea nitrogen was more than 50 mg. per 100 ml.

In groups II and III operative mortality due to excess renal venous constriction and uremia was about 50 per cent, with development of a nephrotic state in about 25 per cent of the survivors; this represents an incidence of about 10 per cent in the salt-treated groups. The renal lesions in these animals resembled those described previously.¹ With 1 per cent sodium chloride they were limited to glomerular basement membranes; these were irregularly frayed and focally impregnated with material in droplet or diffuse form giving a positive reaction with the periodic acid-fuchsin stain. With 1.25 per cent sodium chloride, lesions involved both glomeruli and tubules. Glomeruli showed the above membranous changes, accompanied by simplification of tufts, focal proliferative changes and exudate in subcapsular spaces. Tubular basement membranes were thickened and the lumens contained casts.

Effects of desoxycorticosterone and salt. In the control group I (uninephrectomy plus 1 mg. of DCA), proteinuria remained normal until the tenth day when it increased and reached a maximum of 300 mg. between the fifteenth and twentieth days. In the experimental group II (renal-vein ligation plus uninephrectomy plus

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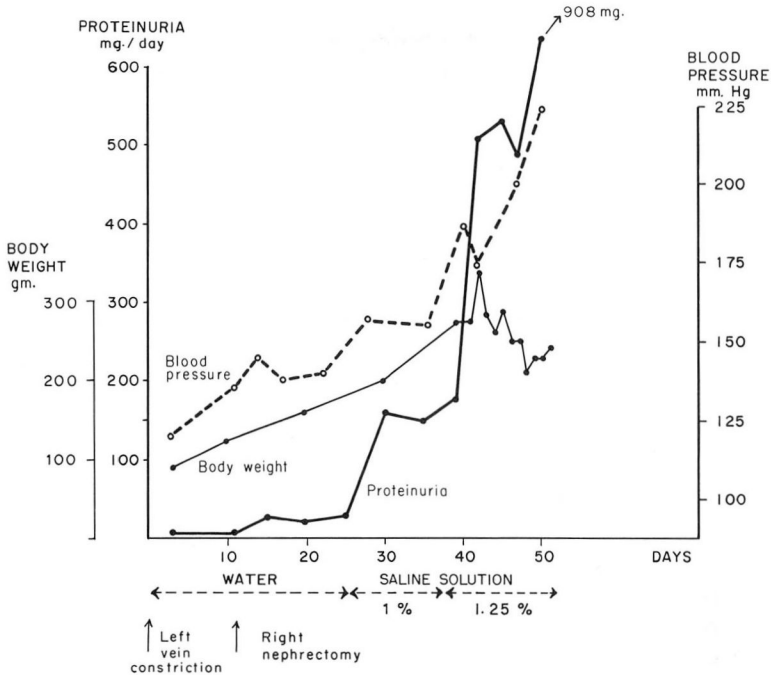


Fig. 1. Graph showing the effects of drinking water of 1 per cent and of 1.25 per cent saline solution in a rat with renal venous constriction and contralateral nephrectomy.

1 mg. of DCA) proteinuria increased rapidly about the tenth day to reach a maximum of about 600 mg. During the period of intense proteinuria, these rats showed crises of phasic fluid retention and excretion: one animal's weight increased from 182 gm. to 219 gm. during 24 hours, and decreased to 152 gm. during the next 24 hours. The experiment was terminated on the thirtieth day. Mean blood pressures, serum cholesterol values and protein concentrations were alike in both groups. At necropsy, the kidneys were large and pale with irregular surfaces. Splanchnic arteritis was present in two of the the five survivors in group II. In both groups kidneys showed histologic nephrosclerotic changes that were more severe in group II. In the latter group these were superimposed upon and masked any possible membranous changes so that differences between the groups were barely noticeable.

The effects of DCA at the dose level of 0.2 mg. (groups III and IV) were qualitatively similar to those just described in groups I and II.

Discussion

Excess sodium chloride given in drinking water intensified the nephrosis induced by renal venous constriction in rats, as it did in rabbits.^{2,3} The intensifi-

cation is associated with augmented proteinuria and phasic fluid retention, and is greater with 1.25 than with 1 per cent saline solution used as drinking fluid. The situation is reminiscent of that evoked by prolonged administration of salt,⁴ and the syndrome elicited by the administration of renin.^{5,6} Difficulty in producing it in rats is apparent from our data. Other investigators⁷ have attributed their failure to the small size of the renal pedicle.

The experiments in which DCA was given to increase salt retention do not show noteworthy further intensification of the nephrotic process. This is because they were complicated by hypertension and its associated lesions, so that the pattern of renal injury was too complex for comparative analysis. This rapidly hypertensive effect even of small doses of DCA, again demonstrates the enhanced pressor effects of this agent when given in the presence of a sufficient, but not of itself hypertensive degree of renal injury. Such effects have been described as occurring in rats treated with antikidney serum,⁸ or subjected to perinephritis⁹ or to figure-of-eight renal ligation.¹⁰

Summary

Administration of salt (1 per cent sodium chloride solution as drinking fluid) to rats with partial renal venous constriction produced a nephrotic state, including glomerular basement membrane changes; substitution with hypertonic (1.25 per cent) saline solution, intensified the syndrome. However, the procedure remains technically tedious and results in an incidence of about 10 per cent of nephrotic animals. Any further intensification of the nephrotic syndrome by desoxycorticosterone acetate was obscured by the nephrosclerotic effect of the steroid.

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