Carbohydrate Diet Prolongs Survival of Rats with Acute Uremia after Bilateral Nephrectomy

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$3.8 \pm 0.8(4)$ $4.8 \pm 0.4(4)$ $8.4 \pm 0.7(12)$ $8.2 \pm 0.6(32)$

$2.9 \pm 0.8(8)$ $3.9 \pm 0.8(12)$ $5.5 \pm 1.2(16)$ $6.4 \pm 0.8(28)$

Average number of days after the second nephrectomy $\pm$ standard deviation (number of rats in parentheses). Special diets started when the first nephrectomy was done (7 days before second nephrectomy). Antibiotics in drinking water started 3 days before the second nephrectomy.

Dear Sir,

Removal of both kidneys is used to elucidate renal functions, whether excretory, metabolic or endocrine. Bilateral nephrectomy also provides a model for the study of uremic toxicity [1], dialysis [2] and pharmacokinetics without the influence of renal excretion. However, the brief survival of anephric rats, usually 2 or 3 days, limits its usefulness [3-15]. In this communication we report prolongation of survival to 6-9 days.

The survival of bilaterally nephrectomized rats has been prolonged by dietary means in the past. Pretreatment with potassium-deficient diets retarded the development of lethal hyperkalemia [5, 11, 13]. Also, low-protein and/or high-carbohydrate diets reduced the elevation of blood ammonia seen in uremia by reducing the source of exogenous and endogenous nitrogenous precursors. We have carried the dietary approach to its limit by feeding a protein-free, potassium-free, exclusively carbohydrate diet, namely, pure sucrose. Not only was this diet more effective for prolonging survival, but sucrose cubes are readily available, cheaper than specialized commercial diets, highly palatable and useable in conventional pellet feeders.

Female Sprague-Dawley rats, 100-200 g in weight, or male Lewis rats, weighing 200-300 g, were anesthetized with ketamine hydrochloride 50 mg/kg and acepromazine maleate 5 mg/kg intramuscularly. The right kidney was removed through incisions in the midline dorsal skin and the right costovertebral angle muscle. At the same time, the Purina Formulab 5008 Chow was replaced by a potassium-deficient diet (purified rodent diet AIN-93G, modified by omission of

Rodent chow Potassium-deficient diet Sucrose Sucrose + oil

potassium salts from the mineral mix [16], potassium content 29 mg/kg, from Dyets Inc., Bethlehem, Pa., USA, No. 113510), by sucrose cubes (Domino Dots, Domino Sugar Corp., New York, N.Y., USA) or oil-treated cubes as specified in table 1. Seven days later, the left kidney was removed. No change was made in the diet, and tap water was freely available at

all times. The right nephrectomy was done in advance to reduce the surgical stress at the time uremia is induced by the second nephrectomy. The interval between nephrectomies also allowed the right adrenal to recover from any surgical injury that might have occurred [17]. During this interval, chow-fed rats increased their body weight by 6-15% while rats on the potassium-deficient diet lost about 10% and rats fed sucrose lost 20% of initial body weight. The nephrectomized rats fed a normal diet survived only 2-4 days (table 1). The potassium-deficient diet increased survival to 3-5 days. Rats fed sucrose fared better, surviving 4-7 days (average 5.5 days). Supplements of corn oil were reported to be helpful to chronically uremic rats [18], so we investigated the effect of oil in our model. Soaking the sugar cubes for 1 to 3 days in corn oil added approximately 7% of lipid to the diet as determined by weights before and after soaking. This had only a minimal additional effect (not statistically significant), but some 7- and even 8-day survivals occurred. Soaking the cubes in cod liver oil or injecting a mixture of water and lipid-soluble vitamins subcutaneously daily (0.1 ml of MVI Multivitamins) did not prolong the life of sucrose-fed rats.

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Another approach to prolonging life in anephric rats is the use of antibiotics to reduce the conversion of relatively nontoxic urea to highly toxic ammonia by bacterial urease in the bowel. Therefore, we studied the survival of rats whose drinking water contained 120 mg neomycin and 50 mg di-hydrostreptomycin in each 100 ml, starting 3 days before the second nephrectomy [11]. Survival was markedly improved by the sucrose diet combined with antibiotics compared to ordinary chow or the potassium-deficient diet with or without antibiotics or compared to the sucrose diet without antibiotics (table 1; highly significant by Wilcoxon two-sample rank test, $p < 0.001$).

The longer survival of nephrectomized rats on sucrose can probably be ascribed to the absence of dietary potassium and nitrogenous sources of ammonia and other uremic toxins [4, 5, 7, 9-12]. However, the rats fed sucrose lost a great deal of weight so that loss of endogenous as well as exogenous potassium and nitrogenous molecules may have contributed to the prolongation of survival. The sucrose diet prolonged survival better than the more expensive low-potassium diet. The increased survival of sucrose-fed rats may increase the usefulness of bilateral nephrectomy in pharmacokinetic studies, and such studies would have immediate applicability to problems of drug disposition in uremic patients.

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