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# Kaluresis and Cardiac Sensitivity to Hyperkalaemia in Intact and Adrenalectomized Rabbits[1] (38728)

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Intact dogs loaded with K by infusion of 2 meq KCl/kg/hr excrete about 20% of the administered K in the urine and develop prelethal electrocardiographic (ECG) changes of hyperkalemic cardiotoxicity at a serum K level of ~10.2 meq/liter (1). In dogs, K loaded 4 hr after adrenalectomy, urinary K loss is moderately decreased (approximately 12% of infused K is still found in the urine (2)), but cardiac sensitivity to K is strikingly increased, with prelethal ECG changes of hyperkalemia appearing at a mean serum K level of 7.6 meq/liter (3). In order to determine whether these changes took place in animals other than dogs, a similar investigation was undertaken in rabbits infused with 2 meq KCl/kg/hr. We found kaluresis and cardiac resistance to hyperkalemia significantly greater than in dogs, and that the effect of adrenalectomy was exactly opposite—urinary K loss was profoundly diminished by the operation, while cardiac resistance to hyperkalemia remained essentially unaffected.

*Methods.* Pertinent experiments were carried out in 14 New Zealand rabbits that weighed between 1.8 and 3.4 kg. Each animal was fasted for ~ 15 hr, anesthetized with a very slow infusion of 25 mg/kg of sodium pentobarbital iv and then connected with a Hewlett-Packard ECG machine. The bladder was emptied with a small feeding tube, a specimen taken for K determination, and the tube left in place for the collection of urine. A femoral artery and vein were cannulated with polyethylene tubing; the former for collection of nonhemolyzed blood specimens, the latter for infusion of fluid with a Harvard peristaltic pump. The animals were divided into three groups; one experimental and two controls.

1. *Group A.* Six control rabbits infused, at the rate of 7 ml/hr, with a KCl solution whose concentration was such that each received 2 meq KCl/kg/hr.

2. *Group B.* Six experimental rabbits infused with 20 ml 0.15 *M* NaCl/hr and bilaterally adrenalectomized, transabdominally, in 45–60 min. After 4 hr the rate of NaCl administration was halved and the animals infused through the other femoral vein with 2 meq KCl/kg/hr as in Group A.

3. *Group C.* Two sham-adrenalectomized control rabbits treated exactly as those in Group B except that after mobilization of the adrenals the venous pedicles to the inferior vena cava were not divided, and the glands not actually removed.

During KCl administration, Lead II of the ECG was monitored at frequent intervals and infusion discontinued when bizarre QRS complexes appeared; these signaled the imminent onset of fatal ventricular fibrillation or asystole. Specimens of arterial blood for the analysis of serum K were obtained soon after anesthesia, before infusion of KCl was begun and when it was discontinued; in adrenalectomized rabbits the blood hematocrit (Hct) was determined. The volumes of urine excreted in the 4 hr after an operative procedure and during the periods of infusion were measured separately and the K levels determined. K was assayed with an Instrumentation Laboratories Flame-Photometer using lithium as an internal standard. In our laboratory the rabbit diet (Purina Rabbit Chow) contains approximately 1.2% K.

*Results.* In the 14 apparently healthy rabbits of this experiment, normal serum K was 3.08 ± 0.19[3] meq/liter and the pre-

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[3] SEM

operative urine K, 107.6 ± 16.0[3] meq/liter in the random samples collected when each bladder was emptied after anesthesia.

*Group A.* Control rabbits infused with 2 meq KCl/kg/hr. In these, the K concentrations of both serum and urine increased during the period of infusion. Prelethal, bizarre QRS complexes appeared on the ECG and infusion was discontinued after approximately 7 hr; the mean serum K was then 14.9 meq/liter, an increase in the preinfusion level (Δ serum K) of 11.8 meq/liter (Table I). The urine, with a K concentration increased to over four times the mean preoperative level, contained more than 55% of the administered K, in a volume approximately equal to the volume of KCl infused. (There were no studies of urine K after infusions were stopped since all of the rabbits quickly succumbed to ventricular fibrillation or asystole) (Table I). In five of the six rabbits the ECG was essentially normal during most of the nearly 7-hr infusion period—with changes of hyperkalemia developing only during the last 90 min or less. The changes in PR interval, T wave, and ST segment were typical of hyperkalemia, but no arrhythmias were observed other than a terminal ventricular fibrillation that was invariably heralded by an abrupt widening and distortion of the QRS (Fig. 1A).

*Group B.* Adrenalectomized rabbits infused with 2 meq KCl/kg/hr. Four hours after adrenalectomy the rabbits had each received 80 ml 0.15 *M* NaCl and seemed normal—ECGs unchanged, Hcts within normal limits, and serum K only moderately elevated to 4.22 ± 0.38[3] meq/liter. Urinary volume was a small proportion (~12%) of the volume of saline solution infused; urine K concentration varied widely, but its mean value was somewhat greater than that measured before operation (142 ± 30 meq/liter). During KCl infusion serum K rose rapidly, attaining a mean prelethal level similar to that of the control animals of Group A in about 15% of the time, i.e., in just over an hour (Table I). Urine K concentration, on the other hand, did not rise, and this, added to a marked fall of urine volume, made for a sharp drop in urinary K loss (Table I). Typical ECG changes of hyperkalemia (other than ventricular arrhythmias) appeared quickly, developed rapidly, and invariably ended with bizarre QRS followed by ventricular fibrillation or asystole in 5–10 min (Fig. 1B).

*Group C.* Sham adrenalectomized rabbits

TABLE I. RESULTS OF INFUSION 2 MEQ KCL INTO RABBITS WITH AND WITHOUT ADRENALS

| | Total K[a] infused (meq/kg) | Prelethal serum K (meq/liter) | Vol KCl infused (ml) | Urine volume (ml) | Urine K (meq/liter) | Urine K loss (meq/kg) | Rate urine K loss (meq/kg/hr) |
|---|---|---|---|---|---|---|---|
| Control | | | | | | | |
| (Group A) | 13.75 ±0.75[b] | 14.9 ±0.42 | 48 ±4.8 | 46.1 ±4.7 | 440 ±17.6 | 7.6 ±0.59 | 1.1 ±0.5 |
| Adrenalectomy[c] | | | | | | | |
| (Group B) | 2.13 ±0.18 | 14.1 ±0.56 | 7.5 ±0.6 | 1.5 ±0.35 | 148 ±28.8 | 0.14 ±0.2 | 0.13 ±0.02 |
| *P* | | | | | | | |
| (Groups A and B) | <0.005 | NS | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 |
| Sham adrenalectomy | | | | | | | |
| (Group C) | 14.0 ±0.1[d] | Not attained[e] | 50 ±1.0 | 37 ±6.0 | 460 ±20.5 | 6.7 ±0.3 | 0.95 ±0.05 |

[a] Duration infusion (min): Control = 419 ± 24.7; adrenalectomy = 64.2 ± 5.5; sham adrenalectomy = 420 ± 0.

[b] Mean and SEM.

[c] Hct = −4.3 ± 1.7.

[d] Mean and extremes.

[e] Final serum K = 8.4 meq/liter (8.2–8.6 meq/liter).

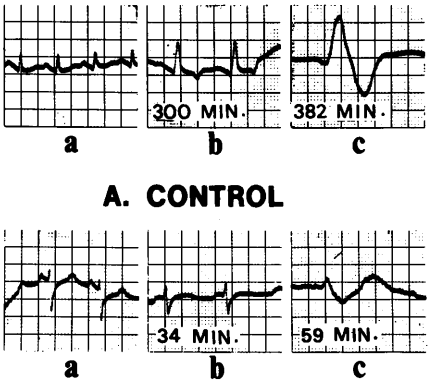


FIG. 1. Typical ECG changes in control and adrenalectomized rabbits infused with 2 meq KCl/kg/hr: a, preinfusion; b, earliest constant evidence of hyperkalemia, c, prelethal. Standard = 20 mm; rate = 50 mm/sec.

infused with 2 meq KCl/kg/hr. Four hours after the sham operation each of the rabbits had received 80 ml of 0.15 *M* NaCl and seemed normal, with ECGs unchanged, and no elevations of serum K. Urine volume was still a fairly small proportion (~25%) of the volume of 0.15 *M* NaCl infused, and its mean K concentration was comparable to that of adrenalectomized animals before KCl infusion (160.0 ± 26.0[4] meq/liter). During KCl infusion serum K rose slowly, reaching a mean level of 8.4 meq/liter after 7 hr, when experiments were discontinued. Urine K concentration, on the other hand, as in Group A, rose to three times that of of KCl-infused adrenalectomized animals (Group B), and contained almost one-half of the administered K, in a volume approximately 75% of the volume of KCl infused (Table I). There were no ECG changes.

*Discussion.* Cardiac muscle fibers are so sensitive to an increase in the concentration of serum (extracellular fluid—ECF) K that animals must have some mechanism for promptly clearing K from ECF, when excess ion is rapidly infused, i.e., after crushing of muscle or hemolysis of RBC. In rabbits the mechanism seems mainly to involve a considerable ability to excrete K in the urine and an increased resistance of myocardial fibers to elevated concentrations of serum K; nearly 3/5 of administered K is excreted and prelethal ECG changes do not appear until mean serum K is 14.9 meq/liter—an average rise (ΔK) of 11.8 meq/liter above the preinfusion level. In K-loaded intact dogs, urine K is only about 1/5 of infused K, mean prelethal serum K approximately 10.2 meq/liter ($P < 0.005$) and ΔK around 5.6 meq/liter (1).

The considerable ability of rabbits to excrete administered K is matched and even exceeded by other herbivores (sheep (4), cows (5)), and seems related to their high K intake; the dogs kept on a high K diet, develop a similar proficiency in excretion of infused K (6). K infusion and high K diets both stimulate the secretion of aldosterone (7), a powerful kaluretic (8). Herbivores, animals that live on high K grasses, probably can secrete large quantities of hormone, and produce brisk kaluresis in response to KCl infusion. In rabbits, kaluresis of excess K seems aldosterone dependent, for there is almost no urinary K loss if K ion is infused after adrenalectomy. In dogs, other mechanisms are involved since urinary K loss drops by no more than ~40% in K loaded adrenalectomized animals (2).

The oliguria associated with infusion of 0.15 *M* NaCl after adrenalectomy seems largely due to the surgical procedure and anesthesia, since the sham operations yield essentially the same results (Results: Groups B and C). However, the near anuria produced by infusion of KCl into adrenalectomized animals is due to the absence of the gland. It does not reflect hemoconcentration (Table I) and is not present in sham-operated animals (Table I, Group C). The two rabbits of Group C are too few for statistical study, but they clearly respond like control animals (Group A) and indicate that in rabbits, adrenalectomy not only suppresses the excretion of K but also that of water. The reason for the antidiuresis is at present not clear. It is, of course, possible that the oliguria stems from the hypotension that overtakes untreated, adrenalectomized animals (9), and blood pressure studies would provide the answer. However, the exact coincidence of marked oliguria and the beginning of KCl infusion suggests

[4] Mean and extremes

that the excess K is involved in activating (or deactivating) a mechanism involved in renal water loss.

In control rabbits the ECG is normal for all but 90 min (or less) of the nearly 7-hr infusion period. Four hours after adrenalectomy, when the concentrations of circulating steroids is negligible (9), the ECG changes that accompany K loading are typical and the same as in control animals, but they are markedly accelerated. Abnormalities appear in 30 min, progress rapidly, and terminate in ventricular fibrillation or asystole within a little over an hour, at a mean serum K level (14.1 meq/liter) that is not significantiy different from that of intact animals. The acceleration of hyperkalemic cardiotoxicity stems mainly from the failure to excrete infused K and the consequent rapid rise of serum K. In dogs, adrenalectomy also accelerates the heart's response to the toxic effects of increased serum K, but here it is largely due to marked increase in cardiac sensitivity to hyperkalemia, with prelethal ECG changes appearing at 7.6 meq K/liter a level considerably below the 10.2 meq/liter of intact animals (1, 3).

The reason for the species difference in the cardiac response to K loading after adrenalectomy may be due to differences in the effect of adrenal steroids on the permeability of cardiac cell membranes. The resting membrane potential (RMP) of a cardiac cell is a function of the ratio between the extracellular and intracellular concentrations of K, and the lowering of RMP brought about by hyperkalemia is one of the factors in the production of ventricular fibrillation (11). It seems that in rabbits, adrenal steroids simply do not affect the permeability of the myocardial fiber to K; in dogs, their absence may permit K to leave the cardiac cell and drop RMP to the fibrillation level when ECF K is only moderately elevated. In adrenalectomized rats, a 25% fall in myocardial cell RMP that is coupled with diminished intracellular fluid K concentration, has been observed (11). Adrenalectomy also removes a mass of tissue that produces epinephrine and norepinephrine. No replacement experiments have been done in rabbits—but in dogs, replacing epinephrine does not seem to affect cardiac sensitivity to hyperkalemia (3).

*Summary.* Rabbits K loaded by infusion of 2 meq KCl/kg/hr excrete over 55% of the administered K in the urine and do not develop prelethal ECG changes until mean serum K attains to 14.9 meq/liter, i.e., 11.8 meq/liter above the average preinfusion level. Four hours after bilateral adrenalectomy there is a profound diminution of urinary K loss in K loaded rabbits—less than 7% of the infused K is excreted. There is, however, no significant change in cardiac sensitivity to hyperkalemia.

K loaded dogs lose only about 20% of infused K in the urine and develop prelethal ECG changes at ~10.2 meq/liter, i.e., 5.6 meq/liter above the mean of the preinfusion levels. After adrenalectomy, urinary K loss is only moderately diminished (12% of infused K is still found in the urine), but cardiac sensitivity to K is markedly increased: prelethal ECG changes appear at a serum K level of ~7.6 meq/liter—about 2.9 meq/liter above the preinfusion value.

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