PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 166, 501–505 (1981)

Neural Factor in K Homeostasis of Hyperkalemic Ureter-Ligated Dogs (41098)

NATHAN HIATT, LLOYD W. CHAPMAN, AND MAYER B. DAVIDSON

Departments of Surgery and Medicine, and the Medical Research Institute, Cedars-Sinai Medical Center, Los Angeles, California 90048

Abstract. In ureter ligated or nephrectomized dogs continuously infused with 2 mEq KCl/kg/hr, a nonrenal K homeostatic mechanism retards the development of hyperkalemia by transferring much of the K load from extracellular to intracellular fluid. But, the K transfer capacity of ureter-ligated dogs is significantly less than that of equally anuric nephrectomized animals. However, K transfer ability in ureter-ligated dogs can be raised to the nephrectomy level if the kidneys are denervated or if the animals are vagotomized by cutting both cervical vagus trunks; in ureter-ligated preparations with bilateral adrenalectomy, vagotomy is without effect. It has been shown that in anuric dogs activity of β-adrenergic receptors is importantly involved in transfer of a K load to intracellular fluid. Our findings suggest that ureter-ligated kidneys give rise to neural impulses that course in fibers of the cervical vagus trunk and diminish K transfer by suppressing the secretion of epinephrine, a powerful β receptor agonist that is known to increase K transfer markedly in these preparations. Division of the renal nerves or of the vagus trunks in the neck interrupts the inhibiting neural impulses and releases secretion of endogenous hormone, with a corresponding rise of K transfer; unless the source of epinephrine is removed by adrenalectomy.

In anuric dogs infused with 2 mEq KCl/kg/hr a nonrenal K homeostatic mechanism retards the development of hyperkalemia and delays the onset of cardiotoxicity by transferring much of the administered K from extracellular fluid (ECF) to intracellular fluid (ICF). However, K transfer to ICF in ureter-ligated (UL) dogs is significantly less than that in equally anuric nephrectomized (nephx) animals (1).

While studying the influence of cervical vagotomy on the insulin secretory response of UL dogs to KCl infusion, we observed that their tolerance to KCl administration was greater than that of control animals. With continued study we found that K transfer in UL dogs increased to the level of nephx animals if their kidneys were denervated or their cervical vagus trunks cut; and that vagotomy had no affect after adrenalectomy (adrenx).

Materials and Methods. Data were gathered from 37 mongrel dogs of either sex that weighed between 15.1 and 25.8 kg; 16 of these (control dogs, nephx and UL) have been previously reported. All were fasted for 18 hr before an experiment. After anesthesia with Na pentobarbital (30 mg/kg iv) and ventilation with a Harvard respirator, a polyethylene catheter was placed in a forepaw cephalic vein and the animals were infused with 25 ml/hr of 0.15 *M* NaCl. In all dogs the abdomen was then opened through a midline incision. In 14, both kidneys were surgically removed and in 23, both ureters were doubly ligated with silk. Immediately before KCl infusion both cervical vagus trunks were divided in 4 nephx and 12 UL dogs; 5 of the latter 12 were also adrenx. Both kidneys were denervated in 5 UL animals by completely mobilizing the kidney and the upper half of the ureter (the portion above the ligature), stripping the adventitia from all renal arteries, and wrapping the renal pedicle in gauze wet with 2% lidocaine. In each instance, KCl infusion was begun about 20 min after completion of an operative procedure. (Twenty minutes is ~20 half-lives of epinephrine and about one-third the half-life of an adrenal steroid (2, 3); i.e., in the adrenx dogs only the level of epinephrine is close to zero—that of adrenal steroids is still significant.)

The 37 dogs were divided into nephx and UL groups. The former comprised a nephx control and vagotomized group; the latter, one UL control and three experimental

0037-9727/81/040501-05$01.00/0

groups. The protocols and K transfer capacity for each group are tabulated in Table I.

Before an experiment, the saline drip was discontinued and the intravenous polyethylene catheter connected to a Harvard peristaltic pump that delivered 30 ml/hr of a KCl solution of such concentration that each dog received 2 mEq/kg/hr. Before K loading, every dog was connected to a Hewlett-Packard ECG machine. During the course of KCl administration Lead II was monitored at frequent intervals and KCl infusion was continued to the endpoint, i.e., until advanced (prelethal) ECG changes of cardiotoxicity appeared—rapid ventricular tachycardia, ventricular flutter, or a bizarre QRS pattern (4). At the endpoint KCl infusion was immediately discontinued, before blood pressure fell significantly.

Samples of blood from an exposed femoral vein and artery for assay of K, immunoreactive insulin (IRI), hematocrit (Hct), pH, and serum bicarbonate were obtained at the start of KCl infusion, at suitable intervals thereafter, and at the endpoint. Serum K was determined by an Instrumentation Laboratory flame photometer with a lithium internal standard, IRI by the method of Soeldner and Slone (5), and Hct by a routine laboratory method. PCO_2 and pH were measured with a radiometer acid-base analyzer, and used for assaying serum HCO_3-. A Statham strain-gauge transducer measured blood pressure.

The calculation of K transfer to ICF is based on two assumptions; that in anuric dogs, infused K unaccounted for in ECF and RBC is transferred to ICF—and that the sizes of the fluid compartments are relatively unchanged in dogs in which KCl infusion produces negligible changes of Hct and total body water (TBW). Dogs have about 200 ml (1/5 liter) ECF/kg and ~30 ml red blood cells (RBC)/kg (6) with a K concentration that is always very similar to that of serum (Na, not K, is the predominant ion in dog RBC (7, 8). A serum K increase of 1 mEq/liter (unit rise) is equivalent to the addition of 0.23 mEq K/kg (0.2 mEq/kg to ECF and 0.03 mEq/kg to RBC). Δ serum K (prelethal minus preinfusion concentration) × 0.23 = total mEq K/kg added to ECF and RBC at the endpoint.

The ability to transfer K to ICF can be assessed by determining the percentage (P) of infused K transferred to ICF; or by calculating mean transfer efficiency (TE)—transmembrane K transfer per unit rise serum K, i.e., total mEq K/kg transferred to ICF divided by mEq/liter Δ serum K. When K transfer capacity is high TE expresses its changes more clearly than P; the reverse is true when K transfer capacity is low.

Results. Before KCl infusion, mean values in the 37 dogs were: serum K = 4.2 (3.9–4.4) mEq/liter, serum insulin = 8 (4–10) μU/ml, Hct = 39 (37–40) vol%. After KCl infusion, mean Δ serum K = 5.3 (4.7–6.1) mEq/liter, i.e., 1.2 (1.1–1.4) mEq K/kg added to ECF and RBC. (Preinfusion serum K added to mEq/liter Δ serum K of Table II equals the concentration of serum

TABLE I. NEPHX AND UL DOGS INFUSED TO ENDPOINT WITH 2 mEq KCl/kg/hr

Group	Denerv.	Vagot.	Adrenx.	Transfer to ICF
			Nephx	
I (10)[a]	–	–	–	CNL[b]
II (4)	–	+	–	CNL
			UL	
A (6)	–	–	–	CUL[c]
B (5)	+	–	–	CNL
C (7)	–	+	–	CNL
D (5)	–	+	+	CUL

[a] Number of dogs.
[b] Control nephrectomy level.
[c] Control ureter-ligated level.

TABLE II. UL AND NEPHX DOGS INFUSED WITH 2 mEq KCl/kg/hr to ENDPOINT

Group	K infused (mEq/kg)	ΔK (mEq/liter)	K added to ECF, RBC (mEq/kg)	K transfer to ICF (mEq/kg)	P[a]	TE[b]
			Nephx			
I[c]	3.8 ± 0.29[d]	4.7 ± 0.09	1.1 ± 0.08	2.7 ± 0.27	70 ± 2.5	0.60 ± 0.08
II	4.7 ± 0.24	5.7 ± 0.29	1.3 ± 0.07	3.3 ± 0.25	71 ± 2	0.58 ± 0.05
p	NS[e]	<0.02	<0.02	NS	NS	NS
A			UL			
Control	2.5 ± 0.2	5.4 ± 0.15	1.2 ± 0.24	1.2 ± 0.23	49 ± 3.1	0.22 ± 0.02
B						
Vagot.	4.1 ± 0.58	5.4 ± 0.5	1.2 ± 0.11	2.8 ± 0.58	71 ± 4.1	0.58 ± 0.38
p vs Group A	<0.001	NS	NS	<0.001	<.005	<0.001
p vs Group I	NS	NS	NS	NS	NS	NS
C						
Denerv.	4.4 ± 0.50	6.1 ± 0.42	1.4 ± 0.13	3.0 ± 0.44	68 ± 2.5	0.50 ± 0.04
p vs Group A	<0.002	NS	NS	<0.002	<0.01	<0.001
p vs Group I	NS	<0.05	NS	NS	NS	NS
D						
Vagot., Adrenx	2.3 ± 0.7	4.8 ± 0.2	1.1 ± 0.04	1.2 ± 0.08	50 ± 2.0	0.23 ± 0.02
p vs Group A	NS	NS	NS	NS	NS	NS
p vs Group B	<0.005	NS	NS	<0.01	<0.01	<0.01

[a] % infused K transferred to ICF.
[b] K transferred to ICF/ΔK
[c] Nephx control.
[d] Mean and SEM.
[e] $P > 0.05$: Student t test.

K at the end point.) The maximum volume of solution administered to any of the dogs was 75 ml (~4 ml/kg), less than 1% TBW. The maximum Hct change was an increase of 5 vol%. There was no ECG or BP change following vagotomy, with or without adrenx. There was no change of serum K during the 20 min after adrenx, when epinephrine fell to negligible levels in the blood. The operative procedures were seemingly well tolerated; postoperatively, vital signs were within normal limits in all animals.

Group I. Control nephx dogs (Table II). The development of hyperkalemia is retarded by a nonrenal mechanism that transfers a ~70% of infused K from ECF to ICF. K transferred to ICF is more than two and one-half times that added to ECF and RBC, and mean duration of infusion is 112 min. The maximum rise of serum insulin, 52 μU/ml,[1] is attained at the endpoint. Arterial pH before infusion is 7.44 and serum HCO_3^- 24 mEq/liter; at the end point the values are 7.27 and 12 mEq/liter, respectively.

Group II. Nephx dogs with vagotomy (Table II). Mean duration of infusion, K transfer to ICF and K transfer capacity (P and TE) are similar to those values in Group I. The rise of serum insulin and changes of pH and serum HCO_3^- are almost identical.

Group A. Control UL dogs (Table II). Approximately 50% of infused K is transferred to ICF—the same amount added to ECF and RBC. The lesser ability to transfer K to ICF shortens the duration of infusion to ~75 minutes. End point Δ serum IRI is 58 μU/ml. At the start of infusion arterial pH is 7.41, and serum HCO_3^- 25 mEq/liter; at the endpoint the respective values are 7.35 and 17 mEq/liter.

Group B. UL with bilateral renal denervation prior to K loading (Table II). K transfer capacity in this group is highly significantly different from that of UL control dogs and statistically the same as that in

[1] Arithmetic mean.

nephx controls. At the endpoint, after about 130 min of infusion, serum IRI increases by 64 μU/ml. The changes of pH and serum bicarbonate are only slightly different from those in nephx controls.

Group C. UL with bilateral cervical vagotomy (Table II). In this group K transfer capacity is statistically the same as that in nephx control dogs and in UL preparations with bilateral renal denervation. Maximum Δ serum IRI, 75 μU/ml, is attained at the end point after a mean duration of infusion of 122 min. The values of pH and serum HCO_3^- are almost identical with those in Group B.

Group D. UL with bilateral cervical vagotomy and adrenx (Table II). Despite vagotomy, K transfer capacity in the group is statistically the same as in UL controls (Group A). The average time of infusion is 69 min and at the endpoint serum IRI is up by 46 μU/ml. Serum HCO_3^- falls from an average of 25 mEq/liter to 18 mEq/liter, and pH from 7.41 to 7.34 during infusion.

Discussion. Denervation of the kidneys in K loaded UL dogs (Group B) improves the indices of K transfer capacity. P increases by nearly 40% ((68−49)/49 × 100), TE by over 100%, and both become statistically equal to the corresponding values in nephx animals (Group I, A, B, Table II). The neural impulses in the renal nerves that are interrupted by the stripping process seem to traverse fibers that pass through the cervical vagus trunks since dividing them reproduces the effect of renal denervation (Group C, Table II).

In a previous investigation in K loaded anuric dogs we found that β-adrenergic receptors are importantly involved in the K transfer process; that epinephrine, a powerful β agonist, markedly stimulates transmembrane K transfer in UL preparations. Our results suggest that UL initiates neural impulses that course through renal nerves and fibers of the cervical vagus and impair the animals K transfer capacity by inhibiting epinephrine secretions. With release of the inhibition by division of the renal nerves or vagus trunks in the neck, there is hormone secretion, and K transfer capacity is elevated to the nephx level; unless the adrenal—the source of epinephrine—is removed. In the absence of impulses from the kidney, i.e., in nephx dogs, vagotomy has no effect on K transfer capacity (Group II, Table II).

Differences in the insulin response to KCl infusion do not account for the variations of K transfer capacity observed—for in all groups the increases of serum IRI are substantially alike. The differences in arterial pH and serum bicarbonate are the result, not the cause, of the variations of K transfer (9).

Although UL dogs produce no bladder urine, the kidneys continue to secrete urine until pressure above the ligature equals or even exceeds mean arterial pressure (~70 mm Hg) (10). At the end of an infusion experiment, each renal pelvis and ureter above the ligature is grossly distended by ~5 ml urine (7). Since abrupt distention above an obstruction is known to stimulate ureteral pain receptors (10), it is conceivable that in a UL K loaded dog, distention may also stimulate receptors that suppress the secretion of epinephrine. In a previous investigation we observed that early in the K loading process, the K transfer capacity of UL dogs equals that of nephx preparations, and that only after ~45 min of KCl infusion does their transfer ability abruptly decline—while that of nephx dogs K transfer remains unchanged (11). This suggests, among other possibilities, that a certain degree of urinary back pressure must be built up above the ureteral ligatures before there can be stimulation of the appropriate neural receptors.

We continue to find that the nonrenal K homeostatic mechanism of hyperkalemic dogs is highly complicated. The findings in the present experiment suggest that neural stimuli from the kidney may influence K transfer capacity by inhibiting the adrenal medulla and producing an epinephrine deficiency. Epinephrine deficiency may explain the abrupt rise of serum K that can accompany the use of neuromuscular blocking agents in patients with long-standing stress (burns, trauma, etc.). Such drugs (e.g., succinylcholine) produce a persistent depolarization of the cell membrane and a release of K which *usually* does not affect the serum K concentration. However, after 1 to

3 weeks of stress (with adrenal exhaustion?), use of the drug may be accompanied by hyperkalemia that can even be fatal (12). The hyperkalemia may represent diminished K transfer activity that could be restored with epinephrine.

This investigation was supported by the USPHS General Research Support Grant SO1 RR 05468, the Blum Kovler Foundation, and The Surgical Research Project. We gratefully acknowledge the editorial assistance of Ms. Julie Taylor.

1. Hiatt, N., Chapman, L. W., Davidson, M. B., J. Pharmacol. Exp. Ther. **309**, 282 (1979).
2. Ferreira, S. H., and Vane, J. R., Nature (London) **215**, 1237 (1967).
3. Haynes, R. C. Jr., and Larner, J., *in* "The Pharmacological Basis of Therapeutics," 5th Ed. (L. S. Goodman and A. Gilman, eds.), p. 1472. MacMillan New York (1975).
4. Surawicz, B., Prog. Cardiovasc. Dis. **8**, 364 (1966).
5. Soeldner, J., and Slone, D., Diabetes **14**, 771 (1961).
6. Hoff, H. E., Deavers, S., and Huggins, M. A., Proc. Soc. Exp. Biol. Med. **122**, 630 (1966).
7. Hiatt, N., Morgenstern, L., Davidson, M. B., Bonorris, G., and Miller, A., Horm. Metabol. Res. **5**, 84 (1973).
8. Davson, H., Ciba Foundation Colloquia on Ageing. Vol. IV, p. 17. Little Brown, Boston (1958).
9. Roberts, K. E., Magida, M. R., and Pitts, R. E., Amer. J. Physiol. **172**, 47 (1953).
10. Kiil, G., and Kjekshus, J., Proc. 3rd Int. Congr. Nephrol. **2**, 321 (1967).
11. Hiatt, N., Chapman, L. W., Davidson, M. B., Sheinkopf, J. A., and Miller, A., Amer. J. Physiol. **231**, 1660 (1976).
12. Birch, A. B., Jr., Mitchell, G. D., Playford, G. A., and Lang, C. A., JAMA, **210**, 490 (1969).

Received September 1, 1980. P.S.E.B.M. 1981, Vol. 166.