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Influence of Cerebral Blood Flow on Transmembrane K Transfer in Hyperkalemic Dogs (40784)

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In both nephrectomized (nephx) and intact dogs given 2 meq KCl/kg/hr iv, a nonrenal K homeostatic mechanism retards the development of hyperkalemic cardiotoxicity by transferring 70–75% of the infused net K (NK)[1] from extracellular fluid (ECF) to intracellular fluid (ICF) (1, 2). The proportion of NK transferred to ICF rises to 85–90% when the site of K loading is moved from a peripheral vein (PV) to a vertebral artery (VA) ((3), personal observation). The latter finding suggests that increased passage of K through the brain enhances nonrenal K transfer activity (3). Copious quantities of K given by vein, e.g., administration of 2 meq KCl/kg/hr, could very well produce some increase of K passage through the brain and in this way influence nonrenal K transfer.

If this is true in dogs K loaded iv, it follows that reducing the quantity of blood reaching the brain by ligation of cerebral arteries should reduce transmembrane K transfer, by diminishing the amount of K passing through the brain. Dogs tolerate not only ligation of both VA (their major blood supply to the brain) (4), but also simultaneous ligation of both VA and common carotids (CC) (5), with no apparent cardiovascular changes of significance following the arterial occlusion and no change of serum K for up to 3 hr, i.e., K in the brain is not mobilized by vascular closure (personal observation).

In this investigation arteries to the brain were ligated in nephx and intact dogs just prior to iv injection of 2 meq KCl/kg/hr. Ligation of both VA in nephx dogs produced a considerable fall of transmembrane K transfer; the fall was markedly increased in animals with simultaneous ligation of both VA and CC. In intact dogs ligation of the VA and CC also diminished the ability to transfer K to ICF significantly, although less markedly than in nephx animals.

Methods. Data were gathered from 30 mongrel dogs of either sex that were fasted for 18 hr before an experiment. Following anesthesia with Na-pentobarbital (30 mg/kg iv), each was infused with a 0.15 *M* NaCl drip (~100 ml/hr) and connected with a Harvard respirator. In 18 dogs both kidneys were surgically removed. In four of the nephx dogs both VA were ligated a few moments before KCl infusion, and in four both VA and CC were occluded just prior to KCl administration. In six intact dogs ligation of both VA and CC immediately preceded K loading. The protocols in the five groups of dogs that were investigated are given in Table I.

Before an experiment the saline drip was discontinued and replaced with a Harvard peristaltic pump that infused 30 ml/hr of a KCl solution of such concentration that each dog received 2 meq/kg/hr iv. KCl infusion was begun ~30 min after nephx and immediately after arterial ligation. In non-nephx dogs KCl infusion was begun 30 min after anesthesia, immediately following ligation of the VA and CC.

Well before K loading, each dog was connected to a Hewlett–Packard ECG machine. In those animals with ligation of cerebral arteries, Lead II of the ECG was monitored before and after occlusion of each vessel. During the course of KCl administration Lead II was monitored at fre-

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[1] Net K in nephx dogs is equal to infused K; in intact dogs, it equals infused K minus urinary K loss.

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TABLE I. K-LOADED DOGS WITH AND WITHOUT LIGATION OF CEREBRAL ARTERIES

Group	Nephx	Ligated VA	Ligated CC
I Control (10)[a]	+	–	–
II (4)	+	+	–
III (4)	+	+	+
IV Control (6)	–	–	–
V (6)	–	+	+

[a] Number of dogs.

quent intervals and infusion continued to the endpoint, i.e., until advance (prelethal) ECG changes of hyperkalemic cardiotoxicity appeared—ventricular bradycardia of <20 beats/min, ventricular flutter, or bizarre QRS pattern (6). At the endpoint KCl infusion was immediately discontinued, before BP fell significantly.

Femoral vessels were the source of blood samples that were obtained at the start of KCl infusion, at 30-min intervals thereafter, and at the endpoint; venous blood for counting of β particles and for assay of serum K, Hct, and serum immunoreactive insulin (IRI), arterial blood for determination of pH and $p\mathrm{CO}_2$. K was determined with an Instrumentation Laboratory flame photometer that used lithium as an internal standard, IRI by the method of Soeldner and Slone (7), and Hct by a routine laboratory test. ECF volume during the course of KCl infusion was determined in one dog of each group 30 min after the injection of $^{35}\mathrm{SO}_4$ (8) by counting β particles with a Tri-Carb liquid scintillation counter (Model 3385); pH and $p\mathrm{CO}_2$ were measured with a Radiometer acid–base analyzer, and serum bicarbonate was calculated from these values. BP was measured with a Statham strain gauge transducer.

NK (see footnote 1 and note the different meanings in intact and nephx dogs) represents the K added to ECF and RBC and the K transferred to ICF. K transfer to ICF is calculated by substracting the K increment of ECF and red blood cells (RBC) from the known amount of NK infused. The calculation is based on the assumptions that NK 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 changes of Hct and total body water (TBW) are insignificant. (We know that K loss into the lumen of the GI tract is negligible (9).) Dogs have about 200 ml (1/5 liter) ECF/kg and ~30 ml (about 1/30 liter) RBC/kg (10) with a K concentration that is always very similar to that of serum (Na, not K, is the predominant ion in dog RBC (9)). A serum K increase of 1 meq/liter (unit rise) is equivalent to the addition of 0.23 meq/kg (0.2 meq/kg K to ECF and 0.03 meq/kg K to RBC) or ΔK (endpoint minus preinfusion level in meq/liter) $\times$ 0.23 = total meq K/kg added to ECF and RBC; this value substracted from NK is meq K/kg transferred to ICF. An animal's ability to transfer K to ICF can be measured by determining *P*—the percentage of NK that is transferred to ICF. It can also be measured 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. The relation between the two is TE = $0.23\ P/100 - P$. When K transfer capacity is high, TE is a more expressive (though no more valid) index of a change in K transfer ability than is *P;* the opposite is true when K transfer capacity is low.

Results. The maximum volume of solution administered to any of the dogs was less than 5 ml/kg, considerably below 1% TBW; in most dogs about half that volume was infused. The maximum Hct change was an increase of 5 vol%. In all cases operative procedures were well tolerated. Ligation of the VA and CC produced no apparent evidence of cardiovascular collapse; the ECG did not change and systolic BP showed a persistent *rise* of about 15 mm Hg. In all preparations BP was steady during the course of KCl infusion, but there was a brief drop of mean BP, by about 10 mm Hg, at the endpoint.

Before KCl infusion mean serum K was 4.1 meq/liter (3.8–4.6) and mean serum IRI 9 μU/ml (4–13). At the endpoint mean serum K (preinfusion K + ΔK) varied insignificantly in the several groups because ΔK did not vary significantly (Table II). The

TABLE II. NEPHX AND INTACT DOGS LOADED IV WITH 2 meq KCl/kg/hr TO ENDPOINT, BEFORE AND AFTER LIGATION OF CEREBRAL ARTERIES

Group	K infused (meq/kg)	Net K[a] (meq/kg)	K added to[b] ECF and RBC, meq/kg (ΔK meq/liter)	K transfer[c] to ICF (meq/kg)	*P* (% NK transfer to ICF)	TE[d]
I (10)[e] Nephx control	3.75 ± 0.29[f]	3.75 ± 0.29	1.07 ± 0.08 (4.65)	2.68 ± 0.27	70 ± 2.5	0.60 ± 0.08
II Nephx with ligat. VA (4)	2.81 ± 0.07	2.81 ± 0.07	1.22 ± 0.10 (5.30)	1.61 ± 0.10	57 ± 2	0.31 ± 0.03
P Group I vs II	< 0.05	< 0.05	NS[g]	< 0.01	<0.01	<0.05
III Nephx with ligat. VA and CC (4)	1.84 ± 0.10	1.84 ± 0.08	1.05 ± 0.01 (4.56)	0.76 ± 0.12	42 ± 3	0.17 ± 0.02
P (Group I vs III) (Group II vs III)	< 0.005 < 0.05	< 0.005 < 0.05	NS NS	< 0.005 < 0.05	< 0.001 < 0.01	< 0.005 < 0.01
IV Intact control (6)	6.3 ± 0.48[h]	5.1 ± 0.5	1.2 ± 0.10 (5.22)	3.8 ± 0.5	74 ± 1	0.75 ± 0.04
V Intact and ligat. VA and CC (6)	4.9 ± 0.4[i]	3.28 ± 0.11	1.26 ± 0.07 (5.48)	2.16 ± 0.15	62 ± 2	0.40 ± 0.04
P (Group IV vs V)	< 0.05	< 0.005	NS	< 0.01	< 0.05	< 0.05

[a] NK = K infused minus urinary K loss.
[b] Serum ΔK (endpoint minus preinfusion meq/liter) ×0.23.
[c] NK minus K added to ECF and RBC.
[d] K transfer to ICF/serum ΔK.
[e] Number of dogs.
[f] Mean ± SEM.
[g] $P > 0.05$: Student *t* test.
[h] Urine K loss = 1.2 ± 0.3 meq/kg.
[i] Urine K loss = 1.49 ± 0.3 meq/kg.

average volume of ECF, determined in five dogs, was 209 ± 9 (mean ± SEM) ml/kg, less than 5% greater than the volume used in calculation of K transfer to ICF. There was no correction for urinary $^{35}SO_4$ loss in intact dogs.

Group I: Control nephx dogs (Table II). Despite the absence of kaluresis the development of hyperkalemia is slow. The rise of serum K is retarded by activity of a powerful nonrenal mechanism that transfers more than 70% of infused K from ECF (where it is highly cardiotoxic) to ICF (where it is relatively harmless). pH (mean = 7.29) and serum bicarbonate (average = 14 meq/liter) are at their lowest levels, and serum IRI (52 ± 4.1 μU/ml) at its highest, at the endpoint.

Group II: Nephx VA ligation (Table II). In Group II there is a significant reduction in the proportion of infused K transferred to ICF; *P* falls by 20%. The fall is not due to impaired IRI secretory response to KCl infusion, for the insulin response is essentially the same as that of control nephx animals (a maximum 58 ± 14 μU/ml at the end of KCl infusion). Endpoint changes in pH (mean = 7.37) and serum bicarbonate (average = 19 meq/liter) are less marked than in control dogs (% fall $P = (P$ Group I $- P$ Group II$/P$ Group I$) \times 100)$.

Group III: Nephx with ligation of both

VA and CC (*Table II*). In Group III there is a striking fall in the ability to transfer infused K to ICF. Compared to nephx controls *P* falls by over 40% and TE by nearly 75%. At the endpoint mean arterial blood pH is 7.39, serum bicarbonate 22 meq/liter, and serum IRI 87 ± 21 μU/ml.

Group IV: Control intact dogs (*Table II*). In Group IV a nonrenal mechanism transfers nearly 75% of NK to ICF. At the endpoint, changes of pH, serum bicarbonate, and serum IRI are very similar to those in control nephx dogs; mean pH = 7.24, average serum bicarbonate = 11 meq/liter, and serum IRI = 59 ± 12μU/ml.

Group V: Intact dogs with ligation of both VA and CC (*Table II*). In Group V *P* is reduced by over 15% and TE almost halved. At the endpoint, mean pH is 7.35, average serum bicarbonate 19 meq/liter, and IRI 98 ± 29 μU/ml.

Discussion. In a previous investigation in intact, ureter-ligated (UL) and UL-pancx dogs, we found that administration of KCl via a VA activated a K transfer mechanism that was much more active than that stimulated by iv KCl. We concluded that a chemoreceptor in the brain was sensitive to the rate at which the concentration of serum K in cerebral arterial blood rises; when the rate is rapid (as in VA KCl administration), the "K sensor" activates a highly efficient K transfer mechanism (3). However, it is difficult to imagine situations that would exclusively flood the blood in a VA with K.

However, the results in our present experiments suggest that the brain is involved in K homeostasis when a K load enters the venous circulation—a more conceivable situation (see below). Diminution of blood flow to the brain reduces a dog's ability to transfer an iv K load to ICF, and in nephx dogs the reduction of K transfer capacity is less with VA occlusion than with both VA and CC ligation (Table II). The reduction is unrelated to the level of serum IRI or changes in ECF volume; the changes of pH and serum bicarbonate in the various groups may be the results, rather than the causes, of differences in K transfer (11). In short, our findings suggest that a mechanism that responds to passage of K through the brain may be involved in the transmembrane K transfer mechanism of dogs K loaded by vein.

No studies of cerebral blood flow were done, but VA ligation and simultaneous ligation of the VA and CC must certainly reduce cerebral blood flow—the former less than the latter. In the latter, one-third of the dogs die following ligation (time of demise not given) and those that survive appear to return to normal in up to 18 days (5). Despite transient (up to 18 day) effects, all of our dogs seemed to withstand short-term occlusion of both VA and CC well. Apparently enough blood enters the brain to prevent shock and hypotension and to maintain essentially normal ECG activity and that of vital cardiovascular centers; possibly by anastamoses between the muscular rami of the VA and branches of the subclavian arteries (5), and possibly via the spinal branches of the vertebral arteries (4).

In dogs that are given 2 meq KCl/kg/hr intravenously, it is possible that the brain does not respond to the passage of K through it. The reduction of K transfer capacity following VA and CC ligation may be due to activation or suppression of neural stimuli, i.e., diminution of blood flow to the brain may give rise to nervous impulses that activate an anti-K transfer mechanism in hyperkalemic dogs just as bilateral ureter ligation does ((12), submitted for publication). However, that does not diminish the importance of an adequate blood flow to the brain in mediating the transfer of an iv K load to ICF; reduced cerebral blood flow means reduced transmembrane K transfer (Table II).

The mechanism that decreases K transfer capacity in animals with reduced cerebral circulation is, as yet, entirely unclear. It does not involve changes in insulin secretion. Catecholamines were not measured, but we know that in nephx dogs removal of the adrenals has no significant effect on K transfer (personal observation). By supplying K to the brains of dogs with ligated VA and CC we sought to "prove" that impaired access of K to that organ was responsible for the diminished K transfer capacity. However, administration of K through a VA (distal to the ligature) is quickly fatal—often in less than 15 min—and the final levels of serum K are so variable that the results are meaningless. K specifically is fatal—2 meq NaCl/kg/hr can be administered above a ligated VA for hours with no apparent ill effect.

We believe that sudden bouts of potentially cardiotoxic hyperkalemia are not rare—that they may accompany the release of K-rich ICF after destruction of tissue by trauma or surgery—especially certain types of cardiac surgery in patients treated with propranolol (13).

We now know that K homeostasis in hyperkalemic dogs is a complicated matter and that animals have several nonrenal mechanisms that can rapidly remove K from ECF. The importance of these mechanisms differs in different preparations. In the present investigation we find that reducing the blood flow to the brain reduces K transfer capacity of nephx dogs considerably more than that of intact dogs. (This observation may prove to be important in K homeostasis of the numerous anephric patients now encountered.) On the other hand, in intact dogs the effect on K transfer of adrenalectomy, or of untreated postpancreatectomy diabetes, is much more profound than that in similarly prepared nephx dogs (1, 14, submitted for publication).

K loading may have some limitations in studying K homeostasis in health and disease. It seems, however, for the present, a legitimate method for the study of the emergency mechanisms involved in coping with potentially cardiotoxic bouts of hyperkalemia.

Summary. In nephrectomized and intact dogs given a continuous intravenous (iv) injection of 2 meq KCl/kg/hr the development of hyperkalemia is markedly retarded by a mechanism that transfers most of the infused K across cell membranes to intracellular fluid. Activity of this nonrenal K homeostatic mechanism is enhanced when the site of K administration is moved from a peripheral vein to a vertebral artery; it seems that increased passage of K through the brain improves K transfer activity. In this investigation passage of K through the brain was *decreased* by closure of cerebral blood vessels. Groups of nephrectomized dogs were K loaded by vein after ligation of both vertebral arteries, or of both vertebral and both common carotids; and a group of intact dogs was similarly infused after simultaneous ligation of both vertebrals and common carotids (for several hours after occlusion such arterial ligations are well tolerated). In each group the ability to transfer K to ICF was significantly reduced. The results suggest that iv K loading may influence K transfer activity by increasing passage of K through the brain.

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