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β Receptor Mediated Transfer in Potassium Loaded Nephrectomized Dogs (41208)

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Abstract. In nephrectomized dogs continuously infused with 2 mEq KCl/kg/hr, the development of hyperkalemia and cardiotoxicity is retarded by a homeostatic mechanism that transfers some 70% of the K load to intracellular fluid. Activity of the mechanism involves a β adrenergic receptor agonist since K transfer capacity is approximately halved by treatment with a blocking dosage of propranolol. The agonist is not endogenous epinephrine—adrenalectomy produces no change of K transfer ability; evidently an extraadrenomedullary agonist activates the β receptors involved in transport of a K load to intracellular fluid. Limiting blood flow to the brain by ligation of the cephalic arteries (an operation that elicits no immediate circulatory or cardiac impairment in dogs) also produces a significant fall of K transfer capacity; it is prevented by stimulating β receptors with epinephrine, i.e., combined with propranolol the hormone has no effect. The findings suggest that an extra adrenomedullary agonist of β receptors involved in K transfer is activated only if blood flow to the brain is unimpaired, since impairment, by ligation of cephalic arteries, results in a reduction of K transfer that is prevented by treatment with pharmacological dosages of epinephrine. Circulation in the cephalic arteries determines both blood flow and access of the K load to the brain. Thus it is possible that in nephrectomized dogs passage of K through the brain regulates activation of the β receptor agonist involved in K transfer.

Infusion of nephrectomized (nephx) dogs with 2 mEq KCl/kg/hr activates a nonrenal K homeostatic mechanism that retards the development of hyperkalemia (and cardiotoxicity) by mediating the transfer of some 70% of the administered K to intracellular fluid (ICF) (1). A β adrenergic receptor agonist seems to be importantly involved in the process, for K transfer is reduced over half by administration of blocking dosages of propranolol (1). K transfer is also reduced if intracranial blood flow is decreased by ligation of the cephalic arteries (2). Reduction of cephalic blood flow also diminishes access of the K load to the brain. In a previous communication we hypothesized that passage of K through the brain influenced the ability to transfer a K load from extracellular fluid (ECF) to ICF (2). This investigation was an attempt to strengthen the validity of the hypothesis by determining the role of epinephrine alone or with propranolol in the K transfer mechanism of preparations with ligation of the cephalic arteries; and of endogenous hormone in unligated dogs.

We found that K transfer capacity of nephx dogs was unaffected by adrenalectomy (adrenx). In preparations with ligation of the arteries to the brain K transfer capacity was improved by treatment with epinephrine alone—together with propranolol it was without effect. The possible significance of these findings is discussed.

Methods. Data were gathered from 27 dogs of either sex weighing between 15.5 and 23.8 kg and apparently in good health. All were fasted for 18 hr before an experiment, anesthetized with sodium pentobarbital (30 mg/kg iv), and ventilated with a Harvard respirator. Depending on the experiment, one or two forepaw cephalic and one external jugular veins were kept open by infusion of approximately 25 ml/hr of 0.15 *M* NaCl. The animals were divided into five groups whose protocols and K transfer capacities are detailed in Table I. In each dog both kidneys were surgically removed and in six, both adrenal glands were also removed. In 11 dogs both common carotids (CC) and both vertebral arteries (VA) were ligated close to the junc-

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TABLE I. NEPHX DOGS INFUSED TO END POINT WITH 2 mEq KCl/kg/hr

Group	Adrenx	Ligated VA and CC	Epi.	Prop.	K transfer capacity
I (10)[a]	−	−	−	−	C[b]
II (6)	+	−	−	−	C
III (4)	−	+	−	−	↓
IV (4)	−	+	+	−	C
V (3)	−	+	+	+	↓

[a] Number of dogs.
[b] Control level.

tion with the subclavians before the start of an experiment. The animals were infused, through separate veins, with KCl alone, together with epinephrine or together with epinephrine and propranolol. All were loaded with K by discontinuing one of the NaCl infusions and connecting the animals to a Harvard peristaltic pump that delivered 30 ml/hr of a KCl solution of such concentration that each received 2 mEq/kg/hr. Seven dogs, with ligation of the arteries to the brain, were also infused with 20 μg/kg/hr of epinephrine (Adrenaline, Parke–Davis) in 30 ml water, and in three of these β receptors were blocked 15 min before KCl infusion by a priming iv injection of 0.3 mg/kg propranolol followed by infusion of 0.3 mg/kg/hr in 30 ml 0.15 *M* NaCl. KCl and epinephrine administration was begun about 45 min after anesthesia, 30 min after nephrectomy, and 15 min after adrenalectomy. During infusion femoral artery blood pressure (BP) was measured with a Statham strain gauge transducer and Lead II of the electrocardiogram (ECG) monitored with a Hewlett–Packard machine. When advanced ECG changes of hyperkalemic cardiotoxicity appeared, i.e., ventricular bradycardia of less than 20 beats/minute, ventricular flutter or a bizarre QRS pattern (3), KCl administration was immediately discontinued (end point) before a significant change of the mean blood pressure impaired circulation.

Venous blood samples were obtained from common femoral veins immediately after anesthesia, before KCl infusion was begun, at 30-min intervals as it proceeded, and when it was discontinued at the end point. Serum K was determined with an Instrumentation Laboratory flame photometer that used lithium as an internal standard, hematocrit (Hct) by a routine laboratory method, and the concentration of serum insulin (IRI) by radioimmune assay (4). Transmembrane K transfer was determined in the way previously described (2); by subtracting the K increment of extracellular fluid (ECF) and red blood cells (RBC) (0.23 × Δ serum K (end point minus preinfusion mEq/liter)) from the known quantity of K infused. In dogs, Na, not K, is the main intracellular ion in RBC, and RBC K concentration is only slightly higher than that of ECF at all levels of serum K (5).

Although end-point ΔK is quite constant within each experimental group, it varies between groups with, as yet unexplained, changes in cardiac electrophysiology that are related to the operative procedures and substances infused; and not to unusual deposition of K in the heart (personal observation). Cardiac sensitivity to K is an important factor in determining the duration of infusion, since it helps fix the quantity of KCl infused and thus the actual number of mEq K/kg deposited in ICF. Transfer capacity may be vigorous, but if cardiac sensitivity to K is sufficiently increased, prelethal ECG changes of hyperkalemic cardiotoxicity appear after infusion of a relatively small amount of KCl and the transfer of but few mEq K/kg to ICF. Therefore, the actual quantity of K transferred to ICF is no reliable measure of K transfer capacity. An animal's ability to transfer K to ICF can be measured by determining mean transfer efficiency (TE)—transmembrane K transfer per rise of serum K by 1 mEq/liter (unit rise), i.e., total mEq K/kg transferred to ICF divided by mEq/liter Δ serum K. K transfer ability can also be measured by determining the

percentage (P) of infused K that is transferred to ICF. Student *t* test was used for statistical analysis.

Results. Hct never differed by more than 6 vol% from the preinfusion level and the maximum addition of fluid was ~6 ml/kg, or about 1% total body water (TBW). Before KCl infusion the condition of the operated dogs (including those with ligation of both CC and both VA) seemed to be excellent; ECG and vital signs were within normal limits in each. In those with ligation of the arteries to the brain, mean BP rose by ~15% (to about 115 Torr) and stayed at that level throughout the course of infusion. Preinfusion serum immunoreactive insulin (IRI) was 5–14 μU/ml. Serum K ranged between 4.0 and 4.8 mEq/liter before infusion and from 7.6 to 10.0 mEq/liter at the end point; mean ΔK at the end point was 4.2 mEq/liter (3.5 to 4.9) and represented the average addition of ~1 mEq to ECF and RBC (0.81 to 1.1). The values calculated for P and for TE at any of the 30-min intervals after the start of infusion were essentially the same as those determined at the end point.

Group I. Control infused with KCl (Table II). Infusion of almost 4 mEq/kg was needed to raise serum K to a level that produced the appropriate ECG changes of hyperkalemic cardiotoxicity. Some 70% of the infused K was transferred to ICF and average transfer efficiency was 0.6 mEq K/kg/unit rise serum K. Serum insulin rose by 52 ± 4.1 μU/ml (mean and SEM).

Group II. Adrenx dogs infused with KCl (Table II). K transfer ability (as measured by P and TE) was not statistically different from that in controls. However, a distinct increase of cardiac sensitivity to ECF K decreased the duration of infusion, the quantity of KCl infused and the number of mEq K/kg transferred to ICF. IRI rose by only 19 ± 5 μU/ml.

Group III. Infused with KCl after ligation of the cephalic arteries (Table II). Compared to controls (Group I) there was a striking fall of K transfer capacity; P was down by two-fifths (70% − 42%/70%) and

TABLE II. NEPHX DOGS INFUSED WITH 2 mEq KCl/kg TO END POINT

Group	K infused mEq/kg	Δ Serum K[a] (mEq/L)	ECF,RBC[b] ΔK (mEq/kg)	K trans. to ICF[c] (mEq/kg)	*P* % trans.	TE[d]
I Control	3.8 ± 0.2[e]	4.6 ± 0.32	1.1 ± 0.08	2.7 ± 0.27	70 ± 2.5	0.60 ± 0.08
II Adrenx	2.7 ± 0.25	3.5 ± 0.2	0.81 ± 0.05	1.9 ± 0.26	68 ± 4	0.58 ± 0.08
P vs Group I	—	—	—	—	NS[f]	NS
III Ligat. VA,CC	1.8 ± 0.10	4.6 ± 0.9	1.1 ± 0.01	0.71 ± 0.25	42 ± 3	0.17 ± 0.02
P vs Group I	—	—	—	—	<0.001	<0.005
IV Ligat. VA,CC Epi.	3.7 ± 0.1	4.9 ± 0.9	1.1 ± 0.04	2.6 ± 0.1	70 ± 1.0	0.53 ± 0.04
P vs Group III	—	—	—	—	<0.001	<0.001
P vs Group I	—	—	—	—	NS	NS
V Ligat. VA,CC Epi., Prop.	1.8 ± 0.04	3.9 ± 0.06	0.89 ± 0.01	0.87 ± 0.04	48 ± 0.7	0.22 ± 0.01
P vs Group III	—	—	—	—	NS	NS
P vs Group IV	—	—	—	—	<0.001	<0.001

[a] End point minus preinfusion level in mEq/liter.
[b] *a* times 0.23 = mEq K/kg in ECF and RBC.
[c] K infused minus *b*.
[d] K transferred divided by ΔK: mEq K/kg transferred per unit rise serum K.
[e] Mean ± SEM.
[f] $P > 0.05$: Student *t* test.

TE reduced by nearly three-fourths. Serum IRI level was similar to that in control dogs (Group I).

Group IV. Infused with KCl and epinephrine after ligation of the cephalic arteries (Table II). In these preparations the measures of K transfer capacity (P and TE) were restored to the control level (Group I); serum IRI rose by 64 ± 7 μU/ml.

Group V. Infused with KCl, epinephrine and propranolol after ligation of the cephalic arteries. K transfer capacity fell to a level similar to that in dogs with ligation of the cephalic arteries (Group III). Serum IRI rose by 43 ± 8 μU/ml.

Discussion. In K loaded nephx dogs, treatment with propranolol more than halves K transfer capacity; a β adrenergic receptor agonist seems to be an important component of the K homeostatic mechanism that retards the development of hyperkalemia by transporting a K load from ECF to ICF (1). The agonist is not endogenous epinephrine, for K transfer capacity is unchanged by adrenalectomy (Group II, Table II), an operation that reduces blood epinephrine to a negligible level in less than 10 min (8).

In dogs with ligation of the arteries to the brain there are no immediate cardiac or circulatory changes (2) despite a reduction of cephalic blood flow that is subsequently manifest in changes of behavior (6, 7). In K loaded nephx dogs there is a fall of K transfer capacity following cephalic artery ligation, that is similar to that which follows propranolol blockade of β receptors (Group III, Table II). The fall is prevented by stimulating β receptors with epinephrine, i.e., the hormone has no effect in preparations simultaneously treated with propranolol (Groups IV, V, Table II). This suggests that epinephrine replaces a β receptor agonist whose activity is reduced when cephalic circulation is decreased. (Epinephrine does not affect K transfer capacity in nephx dogs with patent arteries to the brain (2).)

Ligation of the cephalic arteries reduces blood flow and the passage of K, through the brain. It appears that passage of K through the brain is importantly involved in K transfer capacity; an increase, produced by administering the K load by way of a VA instead of a peripheral vein, is associated with marked enhancement of K transfer ability (9). The improved K transfer ability seems to be due to a humoral substance that arises from neither the adrenal, the pancreas or pituitary (submitted for publication).

In a previous communication we hypothesized that passage of K through the brain of a nephx dog activates a K transfer mechanism (2). The results of our present investigation are compatible with that hypothesis since they suggest that passage of K through the brain controls activation of an extra adrenomedullary agonist of β adrenergic receptors involved in transfer of a K load to ICF. The reduction of K transfer capacity associated with cephalic arteries ligation (reduced blood flow and reduced passage of K through the brain) can be prevented by stimulating β receptors with adequate dosages of exogenous epinephrine.

The β receptor agonist that mediates transfer of a K load to ICF in nephx dogs, may be a humoral substance elaborated outside the adrenal medulla. On the other hand, β receptor activity may be due to the effect of K (or K with diminished blood flow) on brain centers that control the sympathetic nervous system.

In the course of our investigation we found that in each of the groups investigated serum IRI rose, but the rise was unrelated to the observed changes in K transfer capacity. For example, in the adrenx group (Group II) the rise was significantly less than in the other groups—yet K transfer capacity was at the control level. In the other groups K transfer capacity varied, although in each, the rise in serum IRI was essentially the same.

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