Epinephrine and potassium homeostasis

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Epinephrine and potassium homeostasis. The effect of epinephrine on potassium metabolism was examined in six subjects. Each subject participated in four studies as follows: *(1)* potassium chloride infusion (0.75 mEq/kg, i.v.) given over 2 hours, *(2)* epinephrine (0.05 μg/kg·min) plus potassium chloride, *(3)* propranolol (1.43 μg/kg·min) plus epinephrine plus potassium chloride, and *(4)* propranolol plus potassium chloride. The epinephrine infusion with potassium chloride led to a marked improvement in potassium tolerance, which was due to a greater than twofold increase in the extrarenal disposal of potassium ($P < 0.001$). The enhancing effect of epinephrine on extrarenal potassium uptake was completely reversed with the beta-blocking agent propranolol. When propranolol alone was infused with potassium chloride, a significant decrease in the extrarenal disposal of potassium was observed. When potassium chloride was infused alone, 47% of the administered potassium load was excreted in the urine. Epinephrine infusion with potassium chloride markedly inhibited the urinary excretion of potassium (U_KV) to rates that were actually below the basal potassium excretion rate ($P < 0.001$). Propranolol almost completely reversed this effect of epinephrine on U_KV, and when propranolol was infused alone, an enhancement in U_KV ($P < 0.005$) was observed. Insulin adds only a minor contribution to the enhancing effect of epinephrine on extrarenal potassium disposal and does not contribute at all to the inhibitory effect of epinephrine on renal potassium excretion. These results demonstrate that epinephrine ameliorates the rise in plasma potassium concentration following potassium chloride infusion. Because none of the infused potassium was excreted during the 4-hour study period, the improvement in potassium tolerance must result from an enhancement in extrarenal potassium disposal. The ability of propranolol to reverse both the extrarenal and renal effects indicates that the action of epinephrine is mediated via stimulation of the beta receptor.

Epinéphrine et homéostasie du potassium. L'effet de l'épinéphrine sur le métabolisme du potassium a été étudié chez six sujets. Chaque sujet a participé à quatre études de la façon suivante: *(1)* perfusion de chlorure de potassium (0,75 mEq/kg, i.v.) administré en 2 heures, *(2)* épinéphrine (0,05 μg/kg·min) plus chlorure de potassium, *(3)* propranolol (1,43 μg/kg·min) plus épinéphrine plus chlorure de potassium, et *(4)* propranolol plus chlorure de potassium. La perfusion d'épinéphrine avec du chlorure de potassium détermine une augmentation importante de la tolérance au potassium, laquelle est due à une augmentation de plus du double de la disposition extra-rénale du potassium ($P < 0,001$). L'effet d'augmentation par l'épinéphrine de la captation extra-rénale du potassium a été complètement aboli par le bêta bloquant propranolol. Quand le propranolol seul a été perfusé avec du chlorure de potassium, une diminution significative de la disposition extra-rénale de potassium a été observée. Quand le chlorure de potassium est perfusé seul, 47% de la charge administrée sont excrétés dans les urines. La perfusion d'épinéphrine avec le chlorure de potassium a abaissé de façon importante U_KV à des débits inférieurs aux valeurs basales ($P < 0,001$). Le propranolol abolit presque complètement cet effet de l'épinéphrine sur U_KV et quand le propranolol est perfusé seul une augmentation de U_KV ($P < 0,005$) apparaît. L'insuline n'apporte qu'une faible contribution à l'effet d'augmentation par l'épinéphrine de la disposition extra-rénale du potassium et ne contribue pas du tout à l'effet inhibiteur de l'épinéphrine sur l'excrétion rénale de potassium. Ces résultats démontrent que l'épinéphrine minimise l'élévation de la concentration plasma-tique de potassium consécutive à une perfusion de chlorure de potassium. Du fait que le potassium perfusé n'est pas excrété pendant les 4 heures de l'étude il est prouvé que l'amélioration de la tolérance au potassium est la conséquence d'une augmentation de sa disposition extra-rénale. La capacité qu'a le propranolol d'abolir à la fois l'effet rénal et l'effet extra-rénal indique que cette action de l'épinéphrine a pour médiateur la stimulation des récepteurs bêta.

Previous studies from our laboratory have shown that extrarenal tissues play an important role in acute potassium tolerance, with extrarenal mechanisms accounting for the disposal of approximately 50% of an acutely administered potassium load [1, 2]. Both insulin [1] and adrenal hormones [3, 4] appear to play key roles in this extrarenal potassium tolerance. Following adrenalectomy, animals become hyperkalemic and demonstrate a defect in both renal potassium excretion [5] and extrarenal cellular uptake of potassium [3]. Although the renal defect is reversible with exogenous mineralocorticoid administration [3], in recent studies we have been unable to totally correct the extrarenal defect in adrenalectomized rats with aldosterone replacement alone. These results suggest that adrenal medullary hormones, particularly epinephrine, might also play a role in maintaining extrarenal potassium tolerance.

D'Silva was the first to suggest that epinephrine might play a role in potassium homeostasis [6]. He found that an i.v. infusion of epinephrine into anesthetized cats resulted in an initial, transient rise in plasma potassium followed by a prolonged decline of approximately 1 mEq/liter. Similar results have been reported by Todd et al [7, 8] in anesthetized dogs, and these authors further demonstrated that the hypokalemic effect of epinephrine could be prevented with the beta-blocking agent propranolol. More recently, Lum and Lockwood [9, 10] have examined the effect of epinephrine during the infusion of pharmacologic doses of potassium into anesthetized cats. They found that epinephrine ameliorated the rise in plasma potassium concentration and reduced the incidence of hyperkalemia-induced cardiac toxicity.

Little is known, however, about the effect of epinephrine on potassium tolerance in man or the effect of epinephrine on renal potassium handling. Recently, Rosa et al reported an improvement in potassium tolerance with epinephrine and an impair-

ment with propranolol in human subjects [11]. These investigators used very low doses of epinephrine. At higher rates of epinephrine infusion, which produce plasma levels of epinephrine similar to that found during stress in man [16], insulin secretion is stimulated due to the resultant hyperglycemia. What role an increase in plasma insulin concentration following epinephrine-induced hyperglycemia might play in the enhanced potassium tolerance has not been examined. In many of the previous animal studies in which potassium was infused [9, 10], pharmacologic doses were administered, and this resulted in increases in the plasma potassium concentration of 5 to 8 mEq/liter above baseline. Therefore, the present study was undertaken *(1)* to examine the effect of epinephrine on a physiologic increment in plasma potassium concentration, *(2)* to define the renal as well as the extrarenal effects of epinephrine on acute potassium tolerance, *(3)* to determine whether the protective effect of epinephrine is exerted via beta or alpha receptors, *(4)* to define the contribution of insulin to the enhancement in potassium tolerance following epinephrine administration, and *(5)* to determine whether a physiologic increment in potassium concentration is capable of stimulating epinephrine release.

Methods

Subjects. Six healthy volunteers, ranging in age from 18 to 22 years and in ideal body weight from 97 to 118%, were studied. There were five males and one female. No subject had any significant past medical illness, none were taking any medications, and all were consuming a diet containing at least 200 g of carbohydrate per day for 3 days prior to study. Informed, written voluntary consent was obtained from each subject prior to his participation in the study.

Experimental protocol. All studies were performed in the postabsorptive state at 8 A.M. following a 12-hour overnight fast, with subjects remaining recumbent during the study except when voiding. Prior to study, polyethylene catheters were inserted under local xylocaine anesthesia into an antecubital vein for blood sampling and into a femoral vein for the infusion of all test substances. Subjects were given a water load (15 ml/kg) followed by enough deionized water orally to ensure voiding every 30 min. Following the collection of three baseline urine samples, the infusion of test substances was begun. Each subject participated in four studies performed in randomized order and thereby served as his own control. In addition, three subjects served as time controls and were followed for 6 hours without receiving a test substance.

In the first study, potassium chloride was infused via a constant infusion pump (model 975, Harvard Apparatus, Millis, Massachusetts) at a rate designed to deliver 0.75 mEq of potassium per kilogram of body weight over 2 hours. The potassium chloride was dissolved in half-normal saline solution and infused at the rate of 0.74 ml/min. The study was continued for an additional 2 hours after stopping the potassium infusion. In the second study, subjects received the same potassium chloride infusion as in study one. In addition, a constant infusion of epinephrine chloride (adrenalin chloride solution 1:1000, Parke-Davis and Co., Detroit, Michigan) at the rate of 0.05 μg/kg·min was started 30 min prior to beginning the potassium infusion and was continued throughout the 4-hour study period. We have previously shown that this rate of epinephrine administration produces levels similar to those found during stress in man [12]. The epinephrine was dissolved

in half-normal saline and was administered at the rate of 0.27 ml/min. In the third study, potassium chloride and epinephrine were administered as above. In addition, a constant infusion of propranolol hydrochloride (Inderal, Ayerst Laboratories, Inc., New York City) given at the rate of 1.43 μg/kg/min was begun concomitantly with the epinephrine. The propranolol was dissolved in half-normal saline and infused at the rate of 0.27 ml/min. In the fourth study, propranolol (1.43 μg/kg/min) alone was started 30 min prior to beginning the potassium infusion and was continued throughout the 4-hour study period. Two subjects were restudied on a fifth occasion to evaluate what role increased plasma insulin concentration following epinephrine-induced hyperglycemia might play in the improvement in potassium tolerance. In this study, epinephrine infusion (0.05 μg/kg·min) was begun 30 min prior to potassium as described in study two. But, 5 min prior to starting the epinephrine, linear somatostatin (provided by Drs. R. Guillemin and J. Rivier, Salk Institute, San Diego, California) was begun at the rate of 500 μg/hr to inhibit insulin secretion. Simultaneously with somatostatin, an infusion of crystalline procine insulin (Eli Lily Co., Indianapolis, Indiana) was begun at the rate of 0.07 mU/kg·min designed to replace basal insulin levels. Blood pressure, heart rate, and electrocardiogram were monitored at intervals of 15 to 30 min throughout each study.

Following at least three baseline determinations, blood samples were drawn at intervals of 15 to 30 min throughout the study and analyzed for potassium, sodium, glucose, insulin, creatinine, epinephrine, norepinephrine, and bicarbonate concentrations and venous pH. A total of 400 ml of blood was drawn per study, and this was replaced quantitatively with normal saline throughout the study. Studies were performed 2 to 3 weeks apart to allow time to replenish red blood cell losses. Urine samples were collected at 30-min intervals during the study and were analyzed for potassium, sodium, and creatinine.

Analytical determinations. Potassium and sodium concentrations in plasma and urine were determined by flame spectrophotometry (flame photometer, model 143, Instrumentation Laboratory, Lexington, Massachusetts) using lithium as the internal standard. Plasma and urine creatinine concentrations were determined by the method of Jaffe adapted to the autoanalyzer [2]. Methods for the determination of plasma insulin have previously been published [1]. Plasma epinephrine and norepinephrine concentrations were determined by radioenzymatic assay [13] in the laboratory of Dr. R. Hendler. Plasma glucose concentration was determined by the glucose oxidase method (glucose analyzer, Beckman Instrument, Fullerton, California).

Calculations. Clearances of creatinine, potassium, and sodium were calculated according to the formula $C = UV/P$, where U is the urinary concentration, V is the urine volume, and P is the plasma concentration. We have previously shown that basal urinary potassium excretion remains constant for up to 6 hours in subjects infused with saline [14]. To calculate the amount of infused potassium excreted for any given time period, we subtracted the mean basal potassium excretion rate in each subject from the mean rate of potassium excretion during that time period, and multiplied it by the time, in minutes. The sodium excretion was calculated in a similar manner to that for net potassium excretion.

The amount of infused potassium retained within the body during the 4-hour study was calculated by subtracting the net amount of potassium excreted during the 4 hours from the total

amount of potassium administered. The amount of potassium that was disposed of by extrarenal mechanisms was calculated from the difference between the expected rise in plasma potassium concentration (amount of potassium retained ÷ extracellular fluid volume) and the actual rise in the plasma potassium concentration, multiplied by the extracellular fluid volume. In this calculation, the assumption is made that ECF volume remains constant at 20% of body wt.

Potassium tolerance was expressed as the integrated rise in plasma potassium concentration, which was calculated as the area under the curve plotting the rise in plasma potassium with time. This expression of area uses all the data points obtained during potassium loading rather than relying on a single plasma potassium value. This area was calculated using the trapezoidal rule approximation and was carried out by the subroutine QAOIAS of the Harwell Subroutine Library of the Yale University IBM 370/158 computer. Extrarenal potassium tolerance was quantitated by dividing the incremental area in plasma potassium concentration ($mEq/liter \times min$) by the amount of potassium retained (mEq). This value, expressed as minutes per liter, gives a more specific measure of the amount of the potassium load that disappeared from the ECF by extrarenal disposal.

All values are expressed as the means ± SEM. Comparisons of groups was performed with Student's paired t test [15].

Results

Vital signs. During the potassium chloride infusion alone, no change in heart rate or blood pressure was observed. When epinephrine was infused with potassium chloride, a variable increase in heart rate (10 to 15 beats/min) and a widening of pulse pressure (10 to 20 mm Hg) occurred. Subjectively, most subjects reported feelings of tremulousness and a pounding heart beat, which was most marked at the beginning of the epinephrine infusion and subsided after the first 60 min. When propranolol was added to the potassium chloride and epinephrine infusion, no change in heart rate or pulse pressure was observed, and no subjective sensations were reported by any volunteer. When propranolol was infused alone, heart rate decreased by 5 to 10 beats/min without change in blood pressure.

Potassium infusion. During the potassium chloride infusion alone, baseline plasma potassium concentration (3.77 ± 0.11 mEq/liter) rose progressively, reaching a maximum of 0.83 ± 0.09 mEq/liter above baseline at 2 hours (Fig. 1). The potassium chloride infusion was stopped after 2 hours, and thereafter the plasma potassium concentration progressively declined, reaching a value of 0.38 ± 0.14 mEq/liter above basal at the end of the 4-hour study. The incremental area in plasma potassium during the 240-min time period was 126.5 ± 16.2 mEq/liter · min (Fig. 2, top panel). Urinary potassium excretion increased significantly from a mean baseline rate of 37 ± 12 μEq/min to a mean maximum rate of 184 ± 15 μEq/min (Fig. 3) without a change in creatinine clearance (Table 1). Of the infused potassium, 47 ± 4% was excreted during the 4-hour study period (Fig. 4). Mean urinary potassium excretion in the three subjects serving as time controls was 61 ± 23 mEq/min at the onset of study and was unchanged after 6 hours (60 ± 18 mEq/min).

Of the infused potassium that was retained within the body at the end of the 4-hour study period, 24.8 ± 1.2 mEq was translocated out of the ECF by extrarenal mechanisms (Fig. 5),
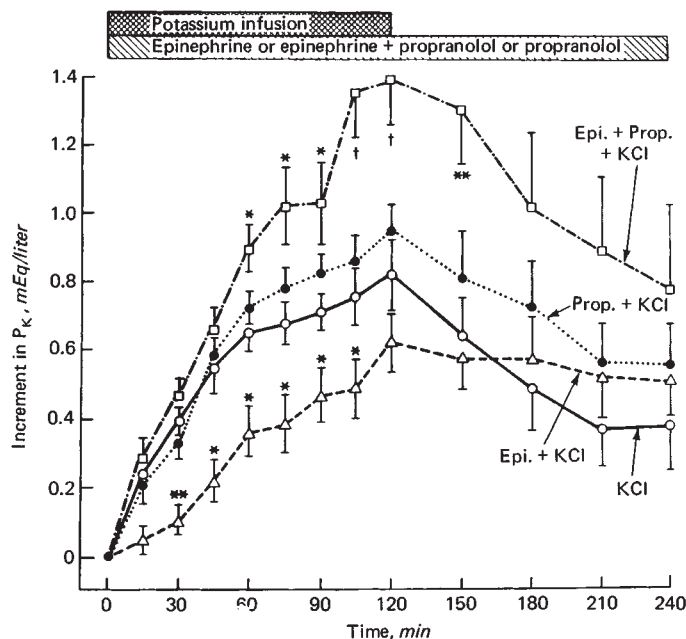

Fig. 1. *Time course of change in the plasma potassium concentration (P_K) with potassium chloride alone (O——O), epinephrine plus potassium chloride (△---△), epinephrine plus propranolol plus potassium chloride (□—·—□), and propranolol plus potassium chloride (●····●). All values represent the mean ± SEM. P values refer to the control group (*P < 0.05, **P < 0.01, †P < 0.001).*

and this represented 82 ± 5% of the retained potassium and 43 ± 5% of the total potassium dose administered. The increment in plasma potassium concentration expressed per amount of potassium retained during the 0 to 240 min was 4.2 ± 0.5 min/liter.

Venous pH (7.34 ± 0.01) and bicarbonate concentration (24 ± 1 mEq/liter) did not change following potassium chloride or in any of the subsequent studies.

Epinephrine plus potassium. When epinephrine was infused alone for 30 min preceding the potassium chloride infusion, the plasma potassium concentration fell from 3.66 ± 0.10 to 3.05 ± 0.06 mEq/liter. This later value was taken as the baseline plasma potassium concentration from which the increment in potassium concentration following potassium chloride infusion was calculated. When the potassium chloride infusion was begun after epinephrine pretreatment, the rise in plasma potassium concentration was significantly less than it was with potassium chloride infusion alone during the first 120 min, $P < 0.001$ (Fig. 1). During the last 2 hours following potassium chloride administration, the increase in plasma potassium concentration above baseline was similar to that observed with the potassium chloride infusion alone. The incremental area in plasma potassium concentration was slightly, although not significantly, less than it was with potassium chloride infusion alone during the 0 to 240 min interval (Fig. 2, top panel).

The mean baseline urinary excretion of potassium (U_KV) was 37 ± 7 μEq/min, which was similar to that with potassium infusion alone (Fig. 3). Following the epinephrine infusion (Fig. 3), U_KV decreased to a mean value of 21 ± 3 μEq/min, which was significantly below the basal excretion rate ($P < 0.001$) and was markedly less than the maximum excretion rate in study one when potassium chloride was infused alone ($P < 0.001$).
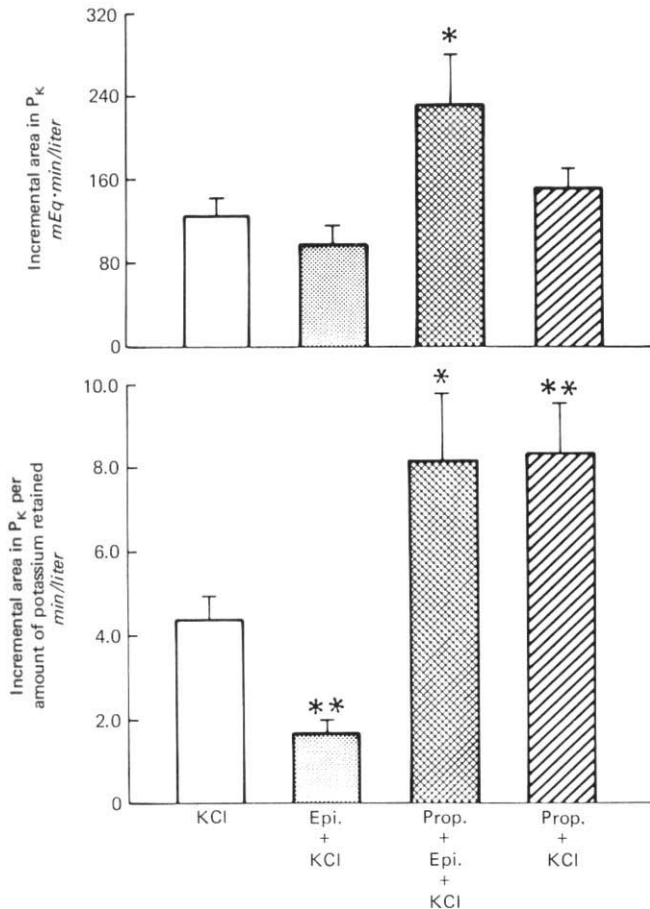
Fig. 2. Top Panel *Integrated rise in plasma potassium concentration (P_K) expressed as the incremental area in plasma potassium concentration above baseline (mEq/liter × min) following potassium chloride alone, epinephrine plus potassium chloride, epinephrine plus propranolol plus potassium chloride, and propranolol plus potassium chloride. All values represent the mean ± SEM. P values refer to the control group.* **Bottom panel** *Incremental area in plasma potassium concentration (mEq/liter × min) per amount of potassium retained (mEq) with potassium chloride, epinephrine plus potassium chloride, epinephrine plus propranolol plus potassium chloride, and propranolol plus potassium chloride. All values represent the mean ± SEM. P values refer to the control group. (*P < 0.02, **P < 0.005).*

Fig. 3. *Time course of change in urinary potassium excretion ($U_K V$) with potassium chloride alone (O——O), epinephrine plus potassium chloride (△---△), epinephrine plus propranolol plus potassium chloride (□—·—□), and propranolol plus potassium chloride (●····●). All values represent the mean ± SEM. P values refer to the control group. (*P < 0.001, **P < 0.02).*

tion did not change significantly from the baseline value of 3.69 ± 0.11 mEq/liter. When the potassium chloride infusion was begun 30 min after starting epinephrine and propranolol, the rise in plasma potassium concentration above baseline was significantly greater than it was with potassium chloride infusion alone during the first 120 min ($P < 0.01$) (Fig. 1) and tended to remain higher for the duration of the study. The incremental area in plasma potassium (Fig. 2, top panel) was also greater with propranolol plus epinephrine compared with potassium chloride alone ($P < 0.02$).

$U_K V$ (Fig. 3) was slightly less than it was with potassium chloride alone during the first 60 min but was not different thereafter. The percentage of the potassium dose excreted (Fig. 4) during the 4-hour study, 31 ± 6%, was significantly less than it was with potassium chloride alone ($P < 0.02$). Creatinine clearance (Table 1) was unaffected by the addition of propranolol.

The total amount of potassium that was translocated out of the extracellular fluid (Fig. 5) was similar to potassium chloride alone and significantly less than it was with epinephrine plus potassium chloride ($P < 0.001$). When the incremental area in potassium is factored by the amount of potassium retained (Fig. 2, bottom panel), it can be seen that propranolol completely blocked the enhancing effect of epinephrine on extrarenal potassium tolerance; the incremental rise per amount of potassium retained was actually higher than it was with potassium chloride ($P < 0.02$).

Propranolol plus potassium chloride. When propranolol was infused alone for 30 min preceding the potassium chloride infusion, the plasma potassium concentration did not change significantly from baseline, 3.75 ± 0.13 mEq/liter. Following the potassium chloride infusion, the rise in plasma potassium concentration (Fig. 1) and also the incremental area in plasma potassium concentration (Fig. 2, top panel) were slightly,

The total amount of potassium excreted over the 4-hour study period fell below that expected if the basal rate of potassium excretion continued unchanged, $P < 0.001$ (Fig. 4). Creatinine clearance was not significantly altered by epinephrine (Table 1).

Despite a decrease in urinary potassium excretion to values below the basal rate of excretion, the plasma potassium concentration actually rose less than it did with potassium chloride alone because the extrarenal disposal of potassium increased by greater than twofold compared to that with potassium chloride alone, $P < 0.001$ (Fig. 5). The incremental area in plasma potassium concentration per amount potassium retained was significantly less than it was with potassium chloride alone during the 0 to 240 min, $P < 0.005$ (Fig. 2, bottom panel).

Propranolol plus epinephrine plus potassium chloride. When propranolol was infused with epinephrine for 30 min preceding potassium chloride infusion, the plasma potassium concentra-
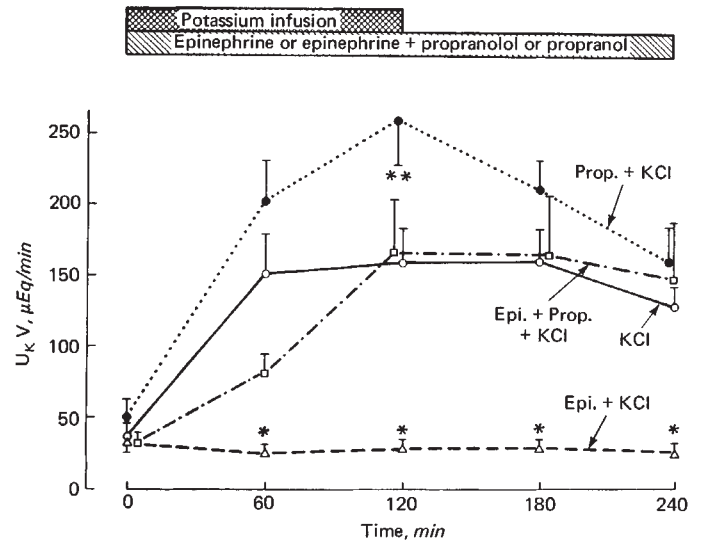
Table 1. Creatinine clearance, baseline sodium excretion, and net sodium excretion following potassium chloride alone, and potassium chloride given with combinations of epinephrine and propranolol[a]

	KCl infusion		Epinephrine + KCl infusion		Epinephrine + propranolol + KCl		Propranolol + KCl	
	Basal	Post infusion	Basal	Post infusion	Basal	Post infusion	Basal	Post infusion
Creatinine clearance, *ml/min*	152 ±7	162 ±12	161 ±14	163 ±13	147 ±8	140 ±8	162 ±15	149 ±8
Sodium excretion, *mEq/min*	92 ±24	229[c] ±40	69 ±16	132[c] ±32	60 ±19	189[c] ±62	120 ±25	269[c] ±31
Net sodium excretion, *mEq*	—	18 ±2	—	8[b] ±3	—	18 ±7	—	12 ±7

[a] Values are the means ± SEM.
[b] $P < 0.02$, compared with all other groups.
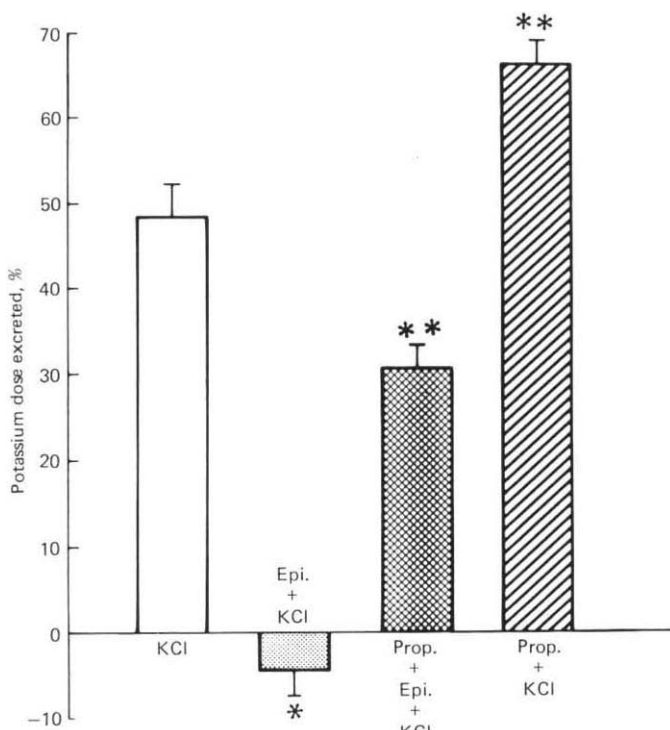[c] This is the maximum increase in $U_{Na}V$.

Fig. 4. *Percentage of the administered potassium dose excreted with potassium chloride alone, epinephrine plus potassium chloride, epinephrine plus propranolol plus potassium chloride, and propranolol plus potassium chloride. All values represent the mean ± SEM. P values refer to the control group (**$P < 0.02$, *$P < 0.001$).*

Fig. 5. *Absolute amount of potassium translocated out of the ECF by extrarenal mechanisms with potassium chloride, epinephrine plus potassium chloride, epinephrine plus propranolol plus potassium chloride, and propranolol plus potassium chloride. All values represent the mean ± SEM. P values refer to the potassium chloride group (*$P < 0.001$).*

although not significantly, higher than they were with potassium chloride alone.

The mean baseline U_KV, 57 ± 16 μEq/min, was similar to the three previous studies. Following the infusion of potassium chloride, the increase in potassium excretion was higher than it was with potassium chloride alone at all time points (Fig. 3), and the percentage of the potassium load excreted (Fig. 4) was greater than it was with potassium chloride alone ($P < 0.02$). Creatinine clearance was unaffected by propranolol (Table 1).

The amount of potassium disposed of by extrarenal mechanisms, 11.9 ± 2.9 mEq, was significantly less than it was with potassium chloride alone, $P < 0.001$ (Fig. 5). Likewise, the incremental area in potassium per amount of potassium retained
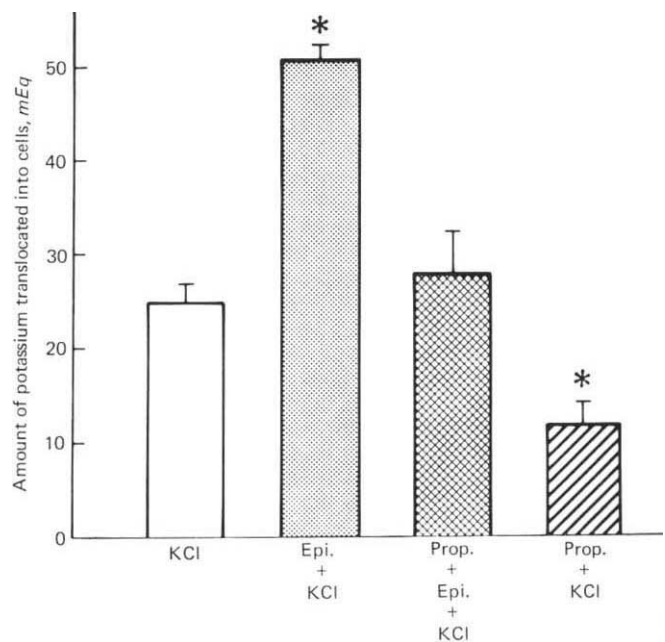
(Fig. 2, bottom panel) during the 4-hour study period was significantly greater than it was with potassium chloride alone ($P < 0.005$).

Sodium. Baseline plasma sodium concentrations were similar in all four studies and were unaffected by any of the experimental maneuvers.

The baseline urinary sodium excretion rates ($U_{Na}V$) were also similar in all four studies. Following the infusion of potassium chloride, $U_{Na}V$ rose significantly in all four groups (Table 1), but the rise with epinephrine plus potassium chloride was significantly less ($P < 0.02$) compared with each of the other three groups.

Glucose. Fasting plasma glucose concentrations were similar in the potassium chloride (85 ± 2 mg/dl), the potassium chloride plus epinephrine (84 ± 3 mg/dl), the potassium chloride plus
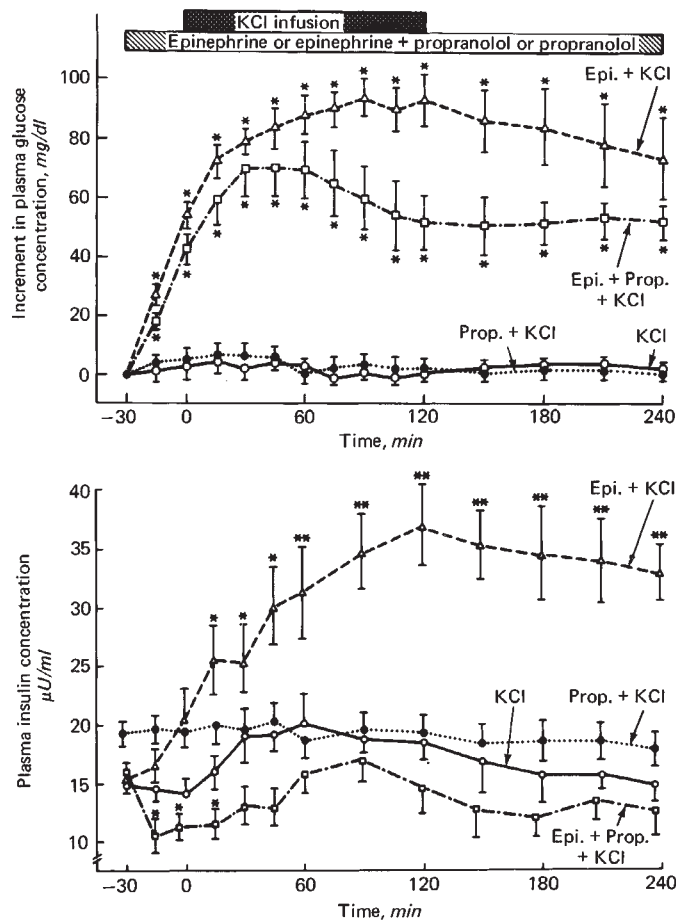
Fig. 6. Top panel *Time course of change in the plasma glucose concentration following potassium chloride alone* (O———O), *epinephrine plus potassium chloride* (△---△), *epinephrine plus propranolol plus potassium chloride* (□—·—□), *and propranolol plus potassium chloride* (●·····●). All values represent the mean ± SEM. The plasma glucose concentrations during the epinephrine and epinephrine-propranolol infusions were significantly higher ($P < 0.001$) than they were with potassium chloride alone during all time intervals. **Bottom Panel** *Time course of change in the plasma insulin concentration following potassium chloride alone* (O———O), *epinephrine plus potassium chloride* (△---△), *epinephrine plus propranolol plus potassium chloride* (□—·—□), *propranolol plus potassium chloride* (●·····●). All values represent the mean ± SEM. *P* values refer to the potassium chloride group (*$P < 0.02$, **$P < 0.001$).

epinephrine and propranolol (80 ± 3 mg/dl), and the potassium chloride plus propranolol (88 ± 3 mg/dl) studies. The plasma glucose concentration remained unchanged during the potassium chloride infusion (Fig. 6, top panel). When epinephrine was infused along with potassium chloride, an immediate and significant rise in the plasma glucose concentration occurred and the hyperglycemia persisted throughout the duration of the study (Fig. 6, top). When propranolol was infused with epinephrine, the rise in plasma glucose concentration was blunted but significant hyperglycemia still remained. Propranolol alone had no effect on the plasma glucose concentration.

Insulin. Baseline plasma insulin concentration was similar in all four studies (Fig. 6, bottom). No change in the plasma insulin concentration occurred following potassium chloride infusion alone. Infusion of epinephrine with potassium chloride resulted
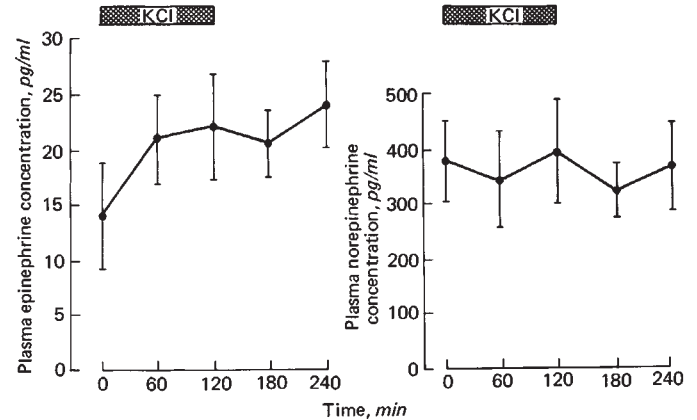

Fig. 7. *Change in plasma epinephrine and plasma norepinephrine concentrations during the infusion of potassium chloride alone.*

in a 15 to 20 μU/ml increase in the plasma insulin concentration (Fig. 6, bottom), which correlated temporally with the rise in plasma glucose concentration (Fig. 6, top). The rise in plasma insulin concentration persisted throughout the 4-hour study period. When propranolol was administered along with epinephrine, an initial small decline in the plasma insulin concentration was observed (Fig. 6, bottom), but thereafter the plasma insulin values were not significantly different from those with potassium chloride alone. Propranolol infusion alone had no effect on the plasma insulin concentration.

Plasma epinephrine and norepinephrine concentrations. Baseline plasma epinephrine and norepinephrine concentrations during the potassium chloride infusion study alone were 16 ± 8 and 420 ± 107 pg/ml, respectively (Fig. 7). Following infusion of potassium chloride, no significant change in either plasma catecholamine concentration was observed.

Somatostatin-insulin plus epinephrine plus potassium. When somatostatin was infused with epinephrine to inhibit insulin secretion and an exogenous insulin infusion was given to maintain basal plasma insulin levels, the mean plasma insulin concentration during the 4-hour study period was maintained at the fasting level (Table 2). In both patients, the incremental area in plasma potassium concentration was slightly higher (19%) than when epinephrine was infused alone. Because the percentage of the administered potassium dose that was excreted was similar in the epinephrine and the epinephrine plus somatostatin-insulin protocols, the incremental plasma potassium area factored by the amount of potassium retained was also slightly higher (14%) when insulin secretion was inhibited with somatostatin.

Discussion

Previous studies in animals, using the infusion of pharmacologic doses of both epinephrine and potassium, have demonstrated that epinephrine ameliorates the rise in plasma potassium concentration and decreases the incidence of fatal cardiac arrythmias [9, 10]. The present study extends these earlier observations to man and documents that physiologic elevations in plasma epinephrine levels, similar to those observed in stress, are capable of blunting the rise in plasma potassium concentration following the infusion of small amounts of potassium. When potassium was administered following pretreat-

Table 2. Summary of potassium data during the infusion of somatostatin-insulin plus epinephrine plus potassium in two patients

	Patient 1		Patient 2	
	EPI	EPI + SRIF + Insulin	EPI	EPI + SRIF + Insulin
Basal P_K, *mEq/liter*	3.65	3.77	3.70	3.89
P_K postepinephrine, *mEq/liter*[b]	3.14	3.27	3.20	3.25
Maximum P_K, *mEq/liter*	3.86	4.17	3.85	4.03
Maximum change in rise of P_K, *mEq/liter*	0.72	0.90	0.65	0.78
Incremental area in P_K, *mEq/liter* × *min*	114.6	136.4	82.6	98.8
K dose excreted, %	−7	−12	−16	−18
K dose retained, %	107	112	116	118
Amount of K translocated into cells, *mEq*	49.5	48.0	53.6	50.0
Retained K translocated into cells, %	87	84	94	85
Incremental P_K area per K retained, *min/liter*	1.88	2.12	1.46	1.68
Basal plasma glucose, *mg/dl*	86	91	85	86
Maximum rise in glucose, *mg/dl*	172	190	176	214
Basal plasma insulin, *μU/ml*	15	17	16	15
Mean plasma insulin,[c] *μU/ml*[c]	32	19	35	14

[a] Abbreviations are: EPI, epinephrine; SRIF, somatostatin and insulin.
[b] Plasma potassium concentration 30 min following epinephrine infusion and immediately prior to starting potassium chloride infusion.
[c] Mean plasma insulin concentration during the 4-hr study period starting with the infusion of potassium chloride.

ment with epinephrine, the rise in plasma potassium concentration was significantly attenuated. This blunted rise in plasma potassium concentration is even more striking when changes in urinary potassium excretion are taken into account. Following potassium chloride infusion alone, 47% of the infused potassium was excreted. This value agrees well with those previously reported under similar experimental conditions [2]. When epinephrine was infused along with potassium chloride, urinary potassium excretion was markedly inhibited and actually fell below baseline values ($P < 0.001$). When the rise in plasma potassium concentration is factored by the amount of infused potassium retained within the body, a greater than twofold increase in the amount of potassium disposed of by extrarenal mechanisms was observed (Fig. 2, bottom). The importance of this protective effect of epinephrine on extrarenal potassium tolerance would assume particular significance during conditions of stress. Under such circumstances, a state of net catabolism exists. This would be expected to result in a net influx of potassium from the intracellular to the extracellular compartment at a time when both insulin secretion [17] and insulin action [18] are significantly impaired. Because stress is known to stimulate epinephrine release, the increased circulating levels of this hormone could exert a protective effect against the development of hyperkalemia.

The mechanism by which epinephrine augments extrarenal disposal of potassium is most likely related to stimulation of beta adrenergic receptors because the augmentation can be blocked by propranolol. Recent studies have demonstrated the presence of beta receptors on both liver and skeletal muscle cells [19, 20], the two major tissues responsible for potassium uptake in man. Because epinephrine infusion was associated with a 15 to 20-μU/ml rise in plasma insulin concentration and because hyperinsulinemia can enhance cellular uptake of potassium [21], we performed additional studies in two patients to define the contribution of insulin to the improvement in potassium tolerance observed following epinephrine. In these studies, somatostatin was used to inhibit endogenous insulin secretion,

and an exogenous insulin infusion was concomitantly given to replace basal insulin levels. When this was done, the incremental area in plasma potassium concentration per amount of potassium retained (14%) was slightly greater than it was when epinephrine was administered alone (Table 2). But the actual values for the incremental rise in plasma potassium concentration per amount of potassium retained in the two subjects (2.12 and 1.68 min/liter) were still markedly less than were the mean values when potassium chloride was infused alone (4.2 ± 0.5 min/liter). Thus, although insulin probably contributes to the enhanced extrarenal uptake of potassium following epinephrine, it does not play the predominant role. The plasma potassium response during the 30-min epinephrine infusion preceding the administration of potassium also suggests that increased insulin secretion does not account for the improved potassium tolerance observed with epinephrine. During this period, the plasma potassium concentration declined by 0.42 ± 0.05 mEq/liter at 15 min and by 0.61 ± 0.06 mEq/liter at 30 min. Yet, the plasma insulin concentration remained unchanged at 15 min and was only slightly elevated at 30 min. In three of six subjects, no rise in plasma insulin concentration occurred during the first 30 min after epinephrine infusion, whereas a significant decline in plasma potassium concentration occurred in all.

An indirect effect of epinephrine, mediated via stimulation of aldosterone secretion, cannot be excluded by the present study. This would seem unlikely, however, because the effect of epinephrine on plasma potassium is immediate, whereas the increase in plasma aldosterone does not occur until 30 to 60 min [22] following epinephrine administration, and the onset of action of aldosterone in stimulating potassium transport is delayed by 60 to 120 min [23].

The ability of epinephrine to enhance potassium tolerance cannot be attributed to enhanced renal excretion of potassium because $U_K V$ decreased markedly following epinephrine infusion. It is unlikely that this decrease in $U_K V$ can be explained by changes in plasma glucose or insulin concentration. In the absence of glycosuria, we are unaware of any direct effect of

hyperglycemia on renal tubular transport of potassium. Although insulin has been reported to depress urinary potassium excretion [24], when insulin secretion was inhibited with somatostatin, the decrease in urinary potassium excretion following epinephrine was similar to that observed when epinephrine was infused without somatostatin. These results suggest that the antikaluretic effect of epinephrine is independent of changes in insulin concentration. This antikaliuretic effect cannot be attributed to a fall in the peritubular capillary potassium concentration perfusing the distal nephron or to a fall in the filtered load of potassium, because the plasma potassium concentration increased following potassium chloride infusion and the GFR was unchanged. Epinephrine is known to decrease renal plasma flow [25]. Therefore, it is possible that the total amount of potassium presented to the distal potassium secretory sites actually diminished, leading to a decrease in the potassium excretion rate, even though the plasma potassium concentration rose.

Lastly, what role the lower plasma potassium concentration may have played in the failure to observe a rise in U_KV following epinephrine should be considered. Baseline plasma potassium concentration, 3.66 mEq/liter, fell to 3.05 after 30 min of epinephrine infusion. At this time the potassium chloride infusion was begun and by 120 min the plasma potassium had risen by 0.6 mEq/liter, that is, it had returned to the basal preepinephrine infusion value. At this time, U_KV had actually decreased significantly ($P < 0.001$) to below the baseline U_KV. Thus, the lower U_KV compared with the potassium chloride group alone could be in large part explicable by the lower plasma potassium concentration. But, the fact that U_KV actually fell below basal levels suggests the possibility that epinephrine may inhibit, either directly or indirectly, renal tubular potassium secretion. Because the current investigation was not designed to directly examine the effect of epinephrine on renal potassium excretion, further studies are needed to delineate this possibility.

The infusion of propranolol in conjunction with epinephrine reversed both the renal (Fig. 3) and extrarenal effects (Fig. 2) of epinephrine on potassium metabolism, indicating that the effect of epinephrine is in large part mediated by stimulation of beta adrenergic receptors. The extrarenal disposal of potassium was actually less during potassium chloride plus propranolol than it was with potassium chloride alone. Two possible explanations could account for this observation. First, it is possible that propranolol not only blocked the effect of the infused epinephrine, but also had an additional action by inhibiting the effect of basal epinephrine levels. This is supported by the studies in which propranolol alone was infused with potassium chloride. Second, part of the deterioration in potassium tolerance following combined epinephrine-propranolol infusion could be the result of an unopposed alpha effect of epinephrine. Additional studies with alpha agonists and antagonists are in progress to answer this question.

The deleterious effects of propranolol on extrarenal potassium tolerance could be explained in several ways. First, it is possible that hyperkalemia stimulates epinephrine release from the adrenal medulla and that propranolol, by blocking this stimulatory effect of potassium could have a detrimental effect on potassium tolerance. Measurements of circulating catecholamines during the potassium chloride infusion, however, failed to demonstrate a significant increase in circulating plasma epinephrine levels. This does not, however, exclude the possibility that an increase in plasma potassium concentration could activate sympathetic nerve fibers innervating muscle and liver cells with local uptake and degradation of epinephrine without a change in circulating plasma levels. Such local epinephrine degradation has been shown to occur by Axelrod and Weinshilborm [26]. It is also possible that basal levels of epinephrine or basal sympathetic nervous system activity are necessary to dispose of an exogenous potassium load normally and that propranolol, by inhibiting the effect of basal epinephrine or by inhibiting basal sympathetic nervous system activity, leads to impaired potassium tolerance. The decrease in the extrarenal disposal of potassium (Fig. 5) when propranolol was infused alone with potassium chloride suggests that this is probably the explanation for the decrease in potassium tolerance following beta blockade. Thus, propranolol not only blocks the effects of exogenously infused epinephrine on cellular potassium uptake, but also inhibits the effect of basal epinephrine levels. These results are similar to the situation with insulin where inhibition of basal insulin secretion by as little as 50% results in a marked impairment in potassium tolerance [1].

The effects of propranolol on renal potassium handling are also opposite to those of epinephrine. Propranolol reversed the inhibitory effect of epinephrine on potassium excretion and, when infused alone with potassium chloride, led to a significant increase in U_KV (Figs. 3 and 4). These results suggest that, even in the basal state, sympathetic nervous system activity plays an important role in potassium homeostasis with beta stimulation enhancing cellular potassium uptake and inhibiting renal potassium excretion. Furthermore, both the renal and extrarenal effects can be reversed by beta blockade.

The current data are in agreement with the recent findings of Rosa et al [11]. These authors demonstrated an improvement in potassium tolerance with epinephrine and an impairment in potassium tolerance with beta blockade. In contrast to the present investigation, urinary potassium excretion was not enhanced with propranolol in that study, possibly due to the lower dose of the drug used. Similarly, the lower dose of epinephrine used in that study could explain their finding of a reduction but not a complete inhibition of urinary excretion of a potassium load. In the current study, the increase in urinary potassium excretion in response to potassium loading was completely prevented with a higher dose of epinephrine, suggesting a dose-related inhibitory effect of epinephrine on urinary potassium excretion.

Summary. The present study documents that elevations of circulating plasma epinephrine concentrations, similar to levels observed in stress, ameliorate the rise in plasma potassium concentration following a potassium chloride infusion. This effect is the result of enhanced extrarenal disposal of potassium and can be reversed by propranolol, indicating that epinephrine's protective effect on potassium tolerance is in large part mediated via stimulation of beta adrenergic receptors.

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