Kidney International, Vol. 37 (1990), pp. 793–798

CLINICAL INVESTIGATION

Adrenergic modulation of potassium metabolism in uremia

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Adrenergic modulation of potassium metabolism in uremia. The effect of chronic beta adrenergic blockade on potassium homeostasis during moderate intensity exercise (40% of VO_2 max) was examined in seven end-stage renal patients who were being maintained on chronic dialysis treatment. Subjects participated in three study protocols: 1) exercise alone, 2) exercise plus propranolol (a nonselective beta-1, beta-2 antagonist), and 3) exercise plus metoprolol (a specific beta-1 antagonist). The basal potassium concentration was similar in all three studies and averaged 4.95 ± 0.12 mEq/liter. During Study 1 (exercise alone), plasma potassium rose by 0.26 ± 0.09 mEq/liter. During exercise with propranolol, plasma K concentration rose significantly higher (Δ plasma K = 0.44 ± 0.26 mEq/liter; $P < 0.05$ vs. exercise alone). In contrast, the rise in plasma K during exercise with metoprolol (Δ plasma K = 0.20 ± 0.08 mEq/liter) was similar to that observed with exercise alone. Differences in potassium homeostasis between metoprolol and propranolol could not be explained by differences in hemodynamic parameters, levels of potassium regulatory hormones, or acid base status. Thus, the higher rise in potassium concentration during exercise with propranolol could only be explained by adrenergic blockade at the beta-2 receptor site. These results support the concept that adrenergic control of extrarenal potassium homeostasis in dialysis patients is mediated at the beta-2 receptor. Since a deterioration in potassium homeostasis during exercise is observed with beta-2, but not beta-1 blockade, selective beta-1 adrenergic blocking agents may be safer in dialysis patients.

Extrarenal tissues play a major role in the regulation of acute potassium disposal [1]. During the first hours following potassium administration in humans, more than 50% of an infused or ingested potassium load is retained within the body and of the retained potassium approximately 75 to 80% is translocated into cells [1]. Several hormones, particularly insulin [2–4] and catecholamines [5, 6], have been shown to modulate extrarenal potassium homeostatasis.

Recent studies have shown that beta adrenergic stimulation increases, while beta adrenergic inhibition decreases extrarenal potassium tolerance [7, 8]. Furthermore, results from animal studies indicate that the effect is mediated by the beta-2 adrenergic receptor [9]. These studies have potential clinical importance concerning the use of beta adrenergic blocking agents in the treatment of patients who are prone to develop hyperkalemia, such as Type 1 diabetic individuals and uremic subjects who are being maintained on chronic dialysis treatment [10, 11]. However, few studies have examined the effect of beta adrenergic blockade during physiologic conditions which are likely to be associated with the development of hyperkalemia. We recently have demonstrated that the serum potassium concentration rises higher in Type I diabetic subjects during exercise on chronic nonselective beta adrenergic blockade (propranolol) compared to selective beta-1 blockade (metoprolol) [10]. The present study was undertaken to examine this phenomenon in dialysis patients. Physical exercise was chosen as a physiological stimulus to induce hyperkalemia, since it is likely to be a part of the patient's every day life and it is known to induce a predictable and transient increase in plasma potassium levels. Furthermore, many dialysis patients are encouraged to exercise to improve their sense of well being and their functional capacity.

Received for publication October 27, 1988
and in revised form August 25, 1989
Accepted for publication September 1, 1989

Methods

Subjects

Seven nondiabetic patients on maintenance dialysis treatment (3 hemodialysis, 4 CAPD) volunteered to participate in the study. There were three females and four males with a mean age of 37 ± 1 years (range 33 to 40 years). All subjects were within 20% of their ideal body weight, based on the medium frame individuals of the Metropolitan Life Insurance Table, 1959. Mean height and weight were 166 ± 4 cm and 68 ± 4 kg, respectively. Serum urea nitrogen was 72 ± 10 mg/dl (range 47 to 116) and serum creatinine was 16.1 ± 1.0 mg/dl (range 9.5 to 20). No subject had any evidence of hepatic, cardiovascular, endocrine, or other major organ system disease nor was there a family history of diabetes in any subject. Except for vitamin supplementation and phosphate binders, dialysis subjects consumed no medications for at least seven days prior to their participation in the study. For at least three days prior to the study all subjects consumed a weight maintaining diet containing at least 200 grams of carbohydrate per day. None of the uremic subjects was on a protein restricted diet. In the CAPD subjects, all fluid was drained from the peritoneal cavity at 12 midnight on the evening prior to study. Dialysis was resumed as usual after completion of the exercise protocol. In the hemodialysis subjects, studies were performed the day following a hemodialysis session. The purpose, nature and potential risks of the study were explained to each subject before obtaining his/her voluntary written consent. The experimental protocol was reviewed and approved by the Human Investigation Committee of the Yale University School of Medicine.

Experimental design

Each subject initially had his or her maximum aerobic capacity determined on a bicycle ergometer. The mean VO_2 max averaged 20 ± 1 ml/kg · min (range 16 to 25). Subsequently, all subjects participated in three separate study protocols, which were performed at 8 a.m. after a 10 to 12 hour overnight fast. On the morning of the study a small polyethylene catheter was inserted into an antecubital vein before the start of exercise. Blood samples were obtained without a tourniquet at 5 to 10 minute intervals in the basal period, and throughout the exercise and recovery periods. Exercise was performed in the sitting position on a bicycle ergometer. The intensity of exercise was adjusted to represent 40% of each subjects VO_2 max. Electrocardiographic tracings and blood pressure were monitored throughout the basal, exercise and recovery period.

Study one: Exercise alone. After a thirty-minute basal period, each subject exercised for forty minutes, and this was followed by a thirty-minute recovery period.

Study two: Exercise plus chronic propranonol administration. Subjects received 40 mg of propranolol orally every 12 hours for three days prior to exercise. The last dose of propranolol was administered at 8 a.m. on the day of the study. Exercise was performed as in study 1.

Study three: Exercise plus chronic metoprolol administration. Subjects received selective beta-1 doses of metroprolol, 50 mg every 12 hours, for three days prior to exercise. The last dose of metoprolol was administered at 8 a.m. on the day of the study. Exercise was performed as in study 1.

The propranolol and metoprolol were administered in a double blinded manner so that neither the subjects nor the investigators knew which medication was being consumed. The order of propranolol/metoprolol administration was randomized and a washout period of two to three weeks was allowed between the metoprolol and propranolol studies.

Analytical determinations

Plasma potassium concentration was determined by flame photometry with lithium as an internal standard (Flame Photometer 443, Instrumentation Laboratory, Watertown, Massachusetts, USA). Plasma insulin concentration was determined by standard radioimmunoassay procedures [12]. Plasma glucagon concentration was determined by radioimmunoassay using the 30 K antibody of Unger [13]. Samples of epinephrine and norepinephrine were collected in glutathione and analyzed by a radioenzymatic method (Cat-a-Kit, Upjohn, Kalamazoo, Michigan, USA). Plasma aldosterone concentration was determined by radioimmunoassay (Coat-a-Count, Diagnostic Product, Los Angeles, California, USA) after chromatographic purification according to the method of Buhler, Sealy and Laragh [14]. Bicarbonate concentration was determined on an acid base analyzer (ABL 30, Radiometer, Copenhagen, Denmark). Plasma glucose concentration was measured using the glucose oxidase method (Glucose Oxidase Analyzer, Beckman Instruments, Fullerton, California, USA).

Statistical analysis

All data are expressed as the mean ± SEM. Statistical comparisons were performed using the two way analysis of variance with repeated measures and paired Student's *t*-test analysis.

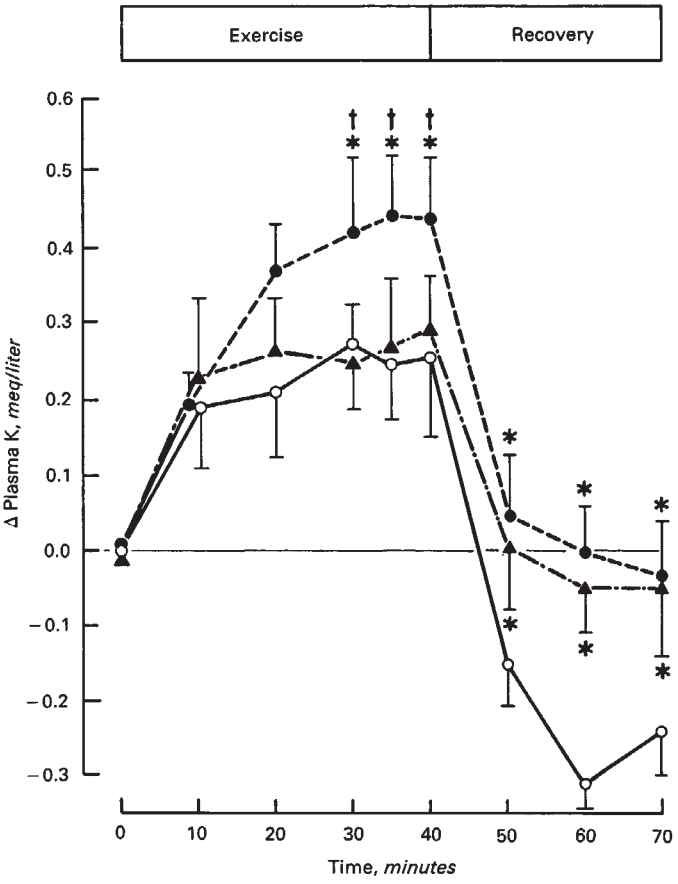

Fig. 1. *Time course of change in plasma potassium concentration in dialysis subjects during exercise alone (open circles), exercise plus propranolol (closed circles), and exercise plus metoprolol (closed triangles).* All values represent the mean ± SEM. *$P < 0.05$ vs. control study. †$P < 0.05$ vs. metoprolol study.

Results

Plasma potassium concentration

The basal plasma potassium concentration was similar in all three studies and averaged 4.82 ± 0.27, 4.99 ± 0.27 and 4.89 ± 0.27 mEq/liter in studies 1, 2, and 3, respectively. With the onset of exercise alone there was a prompt rise in plasma potassium concentration which reached a plateau value that was 0.26 ± 0.9 mEq/liter above baseline during the 30 to 40 minute time interval (Fig. 1). When exercise was stopped, the plasma potassium concentration decreased to levels that were 0.20 to 0.25 mEq/liter below the basal value (Fig. 1).

After chronic propranolol administration, the increase in plasma potassium concentration during both the exercise and post-exercise recovery periods was approximately twice as great as during the control study. During the 30 to 40 minute time interval the mean increment in plasma potassium concentration was 0.43 ± 0.09 mEq/liter ($P < 0.05$ vs study 1). During the 30 minute recovery period the plasma potassium also remained higher ($P < 0.05$) than during the control study (Fig. 1).

Table 1. Plasma hormone, glucose, and bicarbonate concentrations during the basal, exercise, and post exercise recovery periods during the three experimental protocols

	Basal	Exercise		Recovery
	0	20′	40′	70′
Epinephrine *pg/ml*				
Control	87 ± 24		160 ± 44[b]	75 ± 20
Propranolol	57 ± 12		187 ± 66[b]	87 ± 19
Metoprolol	64 ± 21		188 ± 27[b]	70 ± 20
Norepinephrine *pg/ml*				
Control	633 ± 188		1043 ± 280[b]	682 ± 189
Propranolol	782 ± 159		1346 ± 258[b]	894 ± 202
Metoprolol	771 ± 245		1723 ± 389[b]	662 ± 158
Insulin *μU/ml*				
Control	17 ± 3	17 ± 3	16 ± 2	16 ± 2
Propranolol	22 ± 5	22 ± 5	25 ± 4[c]	24 ± 4[c]
Metoprolol	20 ± 5	18 ± 4	19 ± 4	21 ± 5
Glucagon *pg/ml*				
Control	447 ± 58	463 ± 41	469 ± 47	469 ± 40
Propranolol	462 ± 42	417 ± 16	454 ± 17	448 ± 29
Metoprolol	472 ± 93	449 ± 52	434 ± 43	450 ± 66
Aldosterone *mg/ml*				
Control	24 ± 2	34 ± 3[a]	46 ± 7[b]	28 ± 3
Propranolol	22 ± 3	39 ± 4[a]	52 ± 11[b]	33 ± 6
Metoprolol	38 ± 5	58 ± 11[b]	69 ± 11[b]	50 ± 11[c,d]
Bicarbonate *mEq/liter*				
Control	22 ± 2	21 ± 2	20 ± 2	21 ± 2
Propranolol	20 ± 2	20 ± 2	19 ± 2	20 ± 2
Metoprolol	21 ± 2	19 ± 2	19 ± 1	21 ± 2
Glucose *mg/dl*				
Control	77 ± 3	79 ± 4	80 ± 3	76 ± 3
Propranolol	82 ± 3	80 ± 3	81 ± 5	74 ± 3
Metoprolol	83 ± 2	85 ± 4	82 ± 4	78 ± 3

All values represent the mean ± SEM.
[a] $P < 0.05$ vs. basal
[b] $P < 0.01$ vs. basal
[c] $P < 0.05$ vs. control
[d] $P < 0.05$ vs. metoprolol

In contrast, when exercise was performed after chronic metoprolol administration, the increment in plasma potassium concentration during exercise was similar to that observed during the control study and significantly lower ($P < 0.05$) than when exercise was performed after propranolol administration (Fig. 1). During the recovery period with metoprolol, plasma potassium concentration did not fall significantly below basal levels.

Plasma hormone, glucose, bicarbonate concentrations

The fasting plasma insulin concentration in the uremic patients was similar in the three studies and averaged 20 ± 4 μU/ml; no change in plasma insulin levels was observed during the exercise and recovery periods in any of the three experimental protocols (Table 1). The fasting plasma glucagon concentration was similar in the three studies and averaged 461 ± 63 pg/ml; no significant change from baseline was observed in any of the three experimental studies during the exercise or recovery periods (Table 1). Basal catecholamine concentrations were similar in all studies and rose approximately twofold above baseline during exercise ($P < 0.01$; Table 1). During the post-exercise recovery period both plasma epinephrine and norepinephrine concentrations returned to basal levels. Basal plasma aldosterone levels were similar in all three studies, rose approximately twofold during all three exercise protocols ($P < 0.01$), and tended to return to baseline during the recovery period (Table 1). The fasting plasma glucose concentrations were similar in the three studies and averaged 81 ± 3 mg/dl; no change from baseline was observed during the exercise or recovery periods (Table 1). Similarly, plasma bicarbonate levels were nearly identical in each study and did not change significantly during exercise. Further details concerning the metabolic effects of exercise in these patient form the basis of a separate report [15].

Blood pressure and heart rate

Exercise was associated with a significant increase in systolic blood pressure and heart rate. When exercise was performed with either propranolol or metoprolol, no increase in systolic blood pressure was observed. Basal blood pressure was unaffected by either chronic propranolol or metoprolol administration. The basal heart rate was significantly reduced by chronic beta adrenergic blockade and the exercise-induced tachycardia was blunted by both agents (Table 2).

Discussion

In the present study, the effect of chronic beta adrenergic blockade on extrarenal potassium disposal in stable dialysis patients was examined. The maintenance of *chronic* potassium homeostasis is, in large part, regulated by the kidney [16]. In

Table 2. Arterial blood pressure and heart rate during the basal state, at the end of the 40 minute exercise period, and at the end of the 30 minute post-exercise recovery period

		Basal	Exercise	Recovery
Control				
Blood pressure	Systolic	123 ± 5	143 ± 5[b]	123 ± 5
mm Hg	Diastolic	82 ± 3	82 ± 2[b]	81 ± 1
Heart rate *beats/min*		74 ± 2	126 ± 3[b]	81 ± 3
Propranolol				
Blood pressure	Systolic	120 ± 5	125 ± 5[a]	112 ± 6[a]
	Diastolic	78 ± 5	78 ± 5	71 ± 5
Heart rate		63 ± 3[a]	99 ± 6[a,b]	75 ± 3[a]
Metoprolol				
Blood pressure	Systolic	118 ± 5	119 ± 4[a]	118 ± 3[a]
	Diastolic	74 ± 2	70 ± 3[a]	70 ± 3[a]
Heart rate		63 ± 3[a]	90 ± 5[a]	72 ± 4[a]

All values represent the mean ± SEM.
[a] $P < 0.05$ vs. the control study
[b] $P < 0.01$ vs. basal

normal subjects more than 90% of the daily potassium intake is excreted via the renal route [14]. In contrast, acute potassium intake is dependent upon extrarenal mechanisms [1]. In patients without significant renal function and urine output, it is obvious that extrarenal tissues, liver and muscle [2], must play an even more important role in potassium homeostasis if extremes of hyperkalemia are to be prevented. This is a serious concern in the clinical management of patients with end-stage renal disease and represents one of the most common indications for the initiation of dialysis treatment [17]. Several hormones, including insulin, catecholamines and aldosterone, have been shown to modulate extrarenal potassium homeostasis [1].

Rosa et al [5] and DeFronzo, Bia and Birkhead [6] were amongst the first to demonstrate that, in humans, epinephrine administration improves potassium tolerance during intravenous potassium infusion. The potassium lowering effect of epinephrine could not be explained by changes in renal potassium excretion, and both groups concluded that epinephrine improved potassium tolerance by increasing its extrarenal disposal. Since the hypokalemic action of epinephrine could be blocked by propranolol, the effect of the catecholamine on extrarenal potassium tolerance was felt to be mediated via the beta adrenergic receptor [5, 6]. This conclusion is consistent with in vitro studies in skeletal muscle [18]. Recent in vivo studies employing an acutely nephrectomized rat model [9] have shown that the protective effect of physiologic doses of epinephrine on potassium tolerance following potassium infusion could by mimicked by the administration of a selective beta-2 but not by a beta-1 agonist. Conversely, both nonselective beta-1, beta-2 and selective beta-2 antagonists caused a deterioration in extrarenal potassium tolerance. Selective beta-1 blocking agents, such as metoprolol, did not affect extrarenal potassium tolerance. These results confirm previous findings and indicate that the beta-2 adrenergic receptor plays a primary role in extrarenal potassium disposal. With respect to this [19], recent reports have demonstrated that nebulized albuterol, a selective beta-2 agonist, causes a significant and dose dependent decline in plasma potassium concentration in hemodialysis patients [20]. This provides a reasonable alternative for the acute treatment of serious hyperkalemia in this patient population. These observations have important clinical implications for patients with impaired potassium homeostatic mechanisms, such as diabetic and dialysis subjects, who often are treated with beta adrenergic blocking agents.

A few preliminary studies have suggested that the plasma potassium concentration may be higher in dialysis patients on propranolol [11]. However, few studies have attempted to assess whether the beta adrenergic nervous system plays a regulatory role in potassium homeostasis under physiologic conditions, such as stress and exercise, which may be encountered in every day life. Aerobic physical exercise is associated with a significant rise in the plasma potassium concentration, the magnitude of which is related to the work load and the duration of physical activity. The regulation of extrarenal potassium homeostasis is multifactorial, with the beta-2 receptor playing an important role in the transfer of potassium across the cell membrane [1, 5, 7], while the beta-1 receptor appears to regulate blood flow to muscle and liver [21, 22], the two tissues primarily responsible for extrarenal potassium uptake. Because both beta-1 and beta-2 receptors are involved in the regulation of potassium metabolism and because the sensitivity of each of these receptors can be regulated (either negatively or positively) by any of the myriad of metabolic/endocrine/cardiovascular/neurogenic derangements that occur in uremia, we felt that it was important to examine the effect of beta-adrenergic blockade on potassium homeostasis in dialysis patients whose only mechanism of potassium disposal is via the extrarenal route. In healthy young adults it has been shown that both selective and non-selective beta blockade impair potassium homeostasis during moderate aerobic exercise, although the impairment was less severe with beta-1 blockade and primarily involved the post-exercise recovery period. These observations are consistent with the concept that the beta-2 receptor is primarily involved with cellular potassium transfer, whereas the beta-1 receptor regulates blood flow to tissues that govern potassium uptake.

In the present study we have examined the effect of selective (metoprolol) and nonselective (propranolol) beta adrenergic antagonists on the exercise-induced rise in plasma potassium concentration in end-stage renal failure patients who were being maintained on chronic dialysis. Since urine output was absent or negligible in all subjects, any differences in the plasma potassium concentration between the control and experimental studies must be due to an impairment in extrarenal potassium metabolism. As can be seen in Figure 1, three days of propranolol administration was associated with a twofold greater increment in the plasma potassium concentration compared to the control study. In contrast, metoprolol caused no deterioration in potassium tolerance during the exercise period, although the plasma potassium concentration failed to decline below basal levels during the post-exercise recovery period. These results are different from those previously reported by us [10] as well as by others [23] in healthy young subjects in whom metoprolol significantly affected the post-exercise decline in plasma potassium concentration. These findings suggest a diminished impact of beta-1-mediated cardiovascular adaptations with an increase in muscle/liver blood flow.

However, before concluding that the deleterious effect of propranolol is mediated by a beta-mediated phenomenon, it is important to consider other factors that are known to affect

extrarenal potassium metabolism. Small increases in the plasma insulin concentration (20 to 40 μU/ml) have been shown to enhance both splanchnic and peripheral (muscle and adipocyte) potassium uptake [2]. Conversely, a decline in insulin concentration below basal levels impairs potassium tolerance [3]. In normal subjects a decline in insulin levels during exercise is usually observed, and this may contribute to the observed rise in plasma potassium concentration. However, in the present study there was no significant change in the plasma insulin concentration during either the exercise or post-exercise recovery period in any of the three experimental protocols. Thus, it is unlikely that alterations in insulin metabolism play any role in the impaired potassium tolerance observed following propranolol administration.

Circulating catecholamine levels also can affect extrarenal potassium metabolism [5, 6]. Since the plasma epinephrine and nonepinephrine concentrations rose to the same extent during the control study and during the two studies performed with beta adrenergic blockade, it is unlikely that either hormone can explain the deterioration in potassium tolerance observed with propranolol. Plasma aldosterone levels also rose in response to exercise. This was not unexpected since both potassium and cathecolamines stimulate aldosterone secretion [24]. Although aldosterone can affect extrarenal potassium tolerance [25], no differences in the plasma aldosterone concentrations between any of the three studies were observed. It also is unlikely that changes in acid base balance can explain the excessive rise in plasma potassium concentration following propranolol since the venous bicarbonate concentration remained constant in all three experimental protocols during both exercise and recovery periods. Lastly, since propranolol and metoprolol blocked the exercise induced rise in blood pressure and pulse to the same extent, it is unlikely that a difference in hemodynamics can explain the differing results during exercise between these agents. We can, therefore, reasonably conclude that the deterioration in potassium homeostasis with propranolol administration can be ascribed to beta-2 adrenergic blockade.

During recovery there was a fall in plasma potassium concentration of approximately 0.3 mEq/liter below baseline in the control study; this decline was similar to that previously reported by us in normal subjects [10] and most likely related to the persistently elevated levels of epinephrine. This fall below baseline was not observed with either beta blocking agents and is consistent with a beta-1 blockade induced decrease in blood flow to muscle and liver in the recovery period. The mild decrease in blood pressure and pulse during the recovery period with beta blockade compared to the control study supports this interpretation.

In conclusion, nonspecific beta adrenergic blockade with propranolol causes a deterioration in extrarenal potassium metabolism during exercise in stable dialysis patients. In contrast, metoprolol, a specific beta-1 adrenergic antagoinst, does not impair extrarenal potassium homeostasis. Exercise is frequently encouraged in dialysis patients since a number of studies have demonstrated that it can dramatically improve functional capacity in these patients [26, 27]. The current results suggest that, in dialysis patients who must be started on a beta blocking agent, selective beta-1 adrenergic blocking agents may be a safer choice.

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