

# Independent Regulation of In Vivo Insulin Action on Glucose Versus $K^+$ Uptake by Dietary Fat and $K^+$ Content

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**Insulin stimulates both glucose and  $K^+$  uptake, and high-fat feeding is known to decrease insulin-stimulated glucose uptake. The purpose of this study was to examine whether insulin's actions on glucose and  $K^+$  uptake are similarly decreased by a high-fat diet. Wistar rats were fed a standard control (12.2% fat;  $n = 6$ ) or high-fat (66.5% fat;  $n = 13$ ) diet for 15 days. Because  $K^+$  content was 1% in the control and 0.5% in the high-fat diet and because the rats ate less of the high-fat diet, we also compared the high-fat diet with 0.5%  $K^+$  (HFD;  $n = 7$ ) to a high-fat diet supplemented with 1.5%  $K^+$  (HFD+K;  $n = 6$ ).  $K^+$  intake was matched between the control and HFD+K groups ( $246 \pm 8$  vs.  $224 \pm 2$  mg/day), but was lower in the HFD group ( $78 \pm 10$  mg/day;  $P < 0.05$ ). Insulin-stimulated glucose and  $K^+$  uptake were determined by hyperinsulinemic ( $5 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) glucose and  $K^+$  clamps. The HFD depressed both insulin-stimulated glucose uptake compared to the control ( $133 \pm 5$  vs.  $166 \pm 7 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ;  $P < 0.05$ ) and  $K^+$  uptake ( $5.5 \pm 0.9$  vs.  $8.9 \pm 1.0 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ;  $P < 0.05$ ) compared to the control. However, insulin-stimulated  $K^+$  uptake was unchanged in the HFD+K versus in the control group ( $10.0 \pm 0.6$  vs.  $8.9 \pm 1.0 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ;  $P > 0.05$ ), whereas insulin-stimulated glucose uptake in the HFD+K group was decreased to a rate ( $137 \pm 9 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ), similar to that of the HFD group. We concluded that the decrease in insulin-stimulated  $K^+$  uptake during high-fat feeding was a result of decreased  $K^+$  intake, and that insulin's actions on glucose uptake and  $K^+$  uptake are independently regulated by dietary fat and  $K^+$  content, respectively. *Diabetes* 51:915–920, 2002**

**E**xtracellular  $K^+$  levels are tightly regulated in mammals (1,2). This regulation is critical for normal cardiac and neuromuscular functions, because the extracellular  $K^+$  level is a major determinant of the membrane potential. The maintenance of chronic  $K^+$  balance is regulated primarily by the kid-

neys (3). The kidneys have a remarkable capacity to regulate  $K^+$  excretion by secreting or actively reabsorbing  $K^+$  to match  $K^+$  intake (2,4). However, the adaptation of the kidneys to altered  $K^+$  balance is slow, and extrarenal tissues must play a significant role in the acute regulation of extracellular  $K^+$  (1). During the first 4–6 h after an acute  $K^+$  load, only about half of the  $K^+$  load appears in the urine (1,5), indicating that extrarenal tissues rapidly take up the rest of  $K^+$  load. A major component of extrarenal regulation of extracellular  $K^+$  is insulin's action to stimulate cellular  $K^+$  uptake (5,6), which plays an important role in preventing an excessive rise in extracellular  $K^+$  level after a meal (i.e., during  $K^+$  intake).

Although insulin's action on glucose metabolism has been extensively studied, relatively less attention has been given to insulin's action on cellular  $K^+$  uptake, in part because of limited quantitative methodology. Recently, we developed a novel technique for quantifying in vivo insulin action on cellular  $K^+$  uptake, termed the " $K^+$  clamp" (7). In this method, plasma  $K^+$  is maintained constant during insulin infusion by varying exogenous  $K^+$  infusion, and that the  $K^+$  infusion rate required to clamp plasma  $K^+$  is a measure of insulin action to increase cellular  $K^+$  uptake. This approach is analogous to the glucose clamp technique (8), which has been widely used in studies of insulin action on glucose metabolism in vivo. Using this approach, in combination with the glucose clamp, we previously demonstrated that insulin action on cellular  $K^+$  uptake was selectively (i.e., without changes in insulin action on glucose uptake) decreased after a short-term  $K^+$  deprivation (7).

Of the many homeostatic systems of the body, the  $K^+$  and glucose homeostatic systems are unique in that they share acute regulation by insulin. This feature suggests the potential for interactions or cross-talk between the two systems. Insulin resistance with respect to glucose metabolism is usually associated with hyperinsulinemia because pancreatic  $\beta$ -cells increase insulin secretion to compensate for insulin resistance (9). It is conceivable that the resulting hyperinsulinemia has a substantial impact on  $K^+$  homeostasis (e.g., provoking hypokalemia) unless insulin's action on  $K^+$  uptake is similarly dampened. So, the question arises as to whether resistance to insulin's action on glucose uptake is accompanied by or leads to resistance to insulin's action on  $K^+$  fluxes. Although glucose and  $K^+$  transport into cells are independent (10–12), there is evidence for shared signaling mechanisms. For example, wortmannin, an inhibitor of phosphatidylinositol (PI) 3-ki-

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FFA, free fatty acid; GINF, glucose infusion rate; KINF,  $K^+$  infusion rate; PI, phosphatidylinositol.

nase, inhibits insulin stimulation of both glucose and K<sup>+</sup> transport in 3T3-L1 fibroblasts (13). Therefore, one possibility is that insulin resistance occurs simultaneously in both systems because of an alteration in shared signaling mechanisms. Alternatively, insulin resistance may occur in one system and provoke insulin resistance in the other system. For example, insulin resistance of glucose uptake results in hyperinsulinemia, which may cause an adaptation of the K<sup>+</sup> homeostatic system such that insulin action on K<sup>+</sup> uptake is dampened to prevent hypokalemia. Finally, it is also possible that insulin action on glucose and K<sup>+</sup> homeostasis are independently regulated.

High-fat feeding is a well-established model of insulin resistance with respect to glucose metabolism (14,15). The goal of the present study was to examine whether impaired insulin action on glucose uptake in rats fed a high-fat diet was accompanied by impaired insulin action on cellular K<sup>+</sup> uptake using the glucose and K<sup>+</sup> clamp techniques.

## RESEARCH DESIGN AND METHODS

**Animals and diets.** Male Wistar rats weighing 200–225 g were obtained from Simonsen (Gilroy, CA) and were housed for at least 6 days before the study. Animals were housed under controlled temperature (22 ± 2°C) and lighting (12-h light [0600–1800] and 12-h dark [1800–0600]) conditions, and had free access to water and food. Animals were fed a control diet (12% fat; TD 8604, Harlan Teklad, Madison, WI; *n* = 7) or a standard high-fat diet (66.5% fat; Harlan Teklad) for 15 days. Because the K<sup>+</sup> content was different between the control and high-fat diets (1.0 vs. 0.5%) and because less food is consumed with high-fat diets, the high-fat diets in this study were given without K<sup>+</sup> supplementation (HFD; 0.5% K<sup>+</sup>; TD94106; *n* = 7) as well as with K<sup>+</sup> supplementation (HFD+K; 1.5% K<sup>+</sup>; TD99478; *n* = 6) to match K<sup>+</sup> intake to that of the control group. Diets were stored at 4°C, and diets in animal cages were replaced every 3 days. Body weight and food and water consumption were measured every 3 days. All procedures were approved by the Institutional Animal Care and Use Committee at the University of Southern California.

**Catheterization.** At least 4 days before experiments, animals were placed in individual cages with wire floors. The distal one-third of each rat's tail was drawn through a hole placed low on the side of the cage and secured there with a rubber stopper. This arrangement was required to protect tail blood vessel catheters during experiments (15,16). Animals were free to move about and were allowed unrestricted access to food and water. Two tail vein infusion catheters were inserted the day before the experiments, and one tail artery blood sampling catheter was inserted 6 h before the start of the experiments (i.e., ~0700). Catheters were placed percutaneously during local anesthesia with lidocaine while rats were restrained in a towel. Animals were returned to their cages after catheter placement with tails secured as described above and were free to move about during the experiments. Patency of the arterial catheter was maintained by a slow (0.016 ml/min) infusion of heparinized saline (10 units/ml).

**Simultaneous glucose and K<sup>+</sup> clamps.** Food was removed from the cage at 0700. At 1300, basal blood samples were taken from the tail artery. Experiments began with a constant infusion of porcine insulin (22 pmol · kg<sup>-1</sup> · min<sup>-1</sup>; Novo Nordisk, Princeton, NJ) through a tail vein catheter to raise plasma insulin levels to within a physiological range; the infusion was continued for 2.5 h. During the infusion, blood samples (60 μl) were collected at 10-min intervals for the immediate measurement of plasma glucose and K<sup>+</sup> concentration. Dextrose (20%) and KCl (150 mmol/l) solutions were infused together (via a Y-connector) and infused through a tail vein catheter at variable rates to maintain plasma glucose and K<sup>+</sup> at basal levels. Also, [<sup>3</sup>H]glucose (purified by high-performance liquid chromatography; Du Pont, Boston, MA) was infused at a rate of 0.2 μCi/min throughout the clamp for the estimation of insulin-stimulated whole-body glucose fluxes. Blood samples (60 μl) for measurements of plasma [<sup>3</sup>H]glucose concentrations were taken every 10 min during the final 30 min of the clamp. Additional blood samples (80 μl) were obtained for the determination of plasma insulin and free fatty acid (FFA) concentrations at 0, 30, 90, and 150 min.

To avoid contamination of urine passed during the experiments by fecal K<sup>+</sup>, a mesh screen was placed under the wire floor to separate feces from passed urine. The urine passed before the experiment was collected and removed by paper towels placed on the mesh screen. At the end of the clamp,

animals were anesthetized with sodium pentobarbital, their urine was collected from the urinary bladder, and the floor of the cage was rinsed with water, which was then collected to measure urinary K<sup>+</sup> excretion during the experiment (16). Animals were killed by an overdose of sodium pentobarbital immediately after the urine collection.

**Analysis.** Plasma glucose was analyzed during the clamps using 10 μl plasma by a glucose-oxidase method on a Beckman Glucose Analyzer II (Beckman, Fullerton, CA). Plasma and urine K<sup>+</sup> levels were determined by flame photometry using a Radiometer FLM 3, as previously reported (17). Plasma insulin levels during the clamps were measured by radioimmunoassay using a porcine insulin radioimmunoassay kit from Linco Research (St. Charles, MO). For the determination of plasma [<sup>3</sup>H]glucose, plasma was deproteinized with ZnSO<sub>4</sub> and Ba(OH)<sub>2</sub>, dried to remove <sup>3</sup>H<sub>2</sub>O, resuspended in water, and counted in scintillation fluid (Ready Safe, Beckman). Plasma FFA concentrations were determined using an acyl-CoA oxidase-based colorimetric kit (Wako, Osaka, Japan).

**Calculations and statistical analysis.** Whole-body glucose uptake was determined as the ratio of the [<sup>3</sup>H]glucose infusion rate (dpm/min) to the specific activity of plasma glucose (dpm/μmol) during the final 30 min of the clamp. Insulin's action to stimulate cellular K<sup>+</sup> uptake was represented by the K<sup>+</sup> infusion (KINF) during the final 30 min of clamp or total amount of K<sup>+</sup> infused during the entire clamp. Data are expressed as means ± SE. The significance of the differences in mean values between groups was evaluated using the one-way ANOVA, followed by ad hoc analysis using Tukey's test. Differences were considered significant at *P* < 0.05.

## RESULTS

The animals maintained on the high-fat diets consumed less food compared to the control group (Fig. 1A). However, calorie intake was identical between the control and high-fat-fed rats because of the higher calorie content of the high-fat diets (Fig. 1B). There was a threefold difference in K<sup>+</sup> intake between the control group and high-fat-fed groups, arising from a 50% lower dietary K<sup>+</sup> content (1.0 vs. 0.5%) and ~40% less food consumption in the high-fat-fed rats. Increasing the K<sup>+</sup> content in the high-fat diet from 0.5 to 1.5% (HFD+K group) resulted in matched K<sup>+</sup> intake between the control and HFD+K rats (Fig. 1C). After the 15-day feeding period, there was no significant difference in body weight among the three groups (Table 1). High-fat feeding did not alter basal plasma glucose or FFA concentrations, except that the HFD+K diet slightly increased plasma glucose (*P* < 0.05). Importantly, the threefold reduction in K<sup>+</sup> intake in the HFD group, compared with the control or HFD+K group, did not decrease basal plasma K<sup>+</sup> concentrations, demonstrating the existence of an effective homeostatic mechanism that maintained the plasma K<sup>+</sup> level in the face of markedly lower K<sup>+</sup> intake.

Hyperinsulinemic-euglycemic/eukalemic clamps were conducted in the three experimental groups. Insulin was infused at a constant rate to raise plasma insulin levels within a physiological range, and plasma glucose and K<sup>+</sup> concentrations were maintained at basal levels (~7.5 mmol/l and ~4.1 mEq/l) by exogenous glucose and K<sup>+</sup> infusions (Fig. 2). Plasma insulin during the clamps showed a tendency to be higher in the high-fat-fed rats (625 ± 29 and 666 ± 27 pmol/l for HFD and HFD+K groups, respectively, vs. 570 ± 37 pmol/l for control group; *P* > 0.05). Plasma FFA concentrations decreased during the clamps in all groups, but the clamp FFA levels were lower in control than in high-fat-fed rats (0.09 ± 0.01 vs. 0.15 ± 0.01 mmol/l for control vs. both HFD and HFD+K; *P* < 0.05).

As expected, the glucose infusion rate (GINF) required to maintain basal glucose levels during insulin infusion was lower in high-fat-fed rats (*P* < 0.05) (Fig. 2B). K<sup>+</sup>

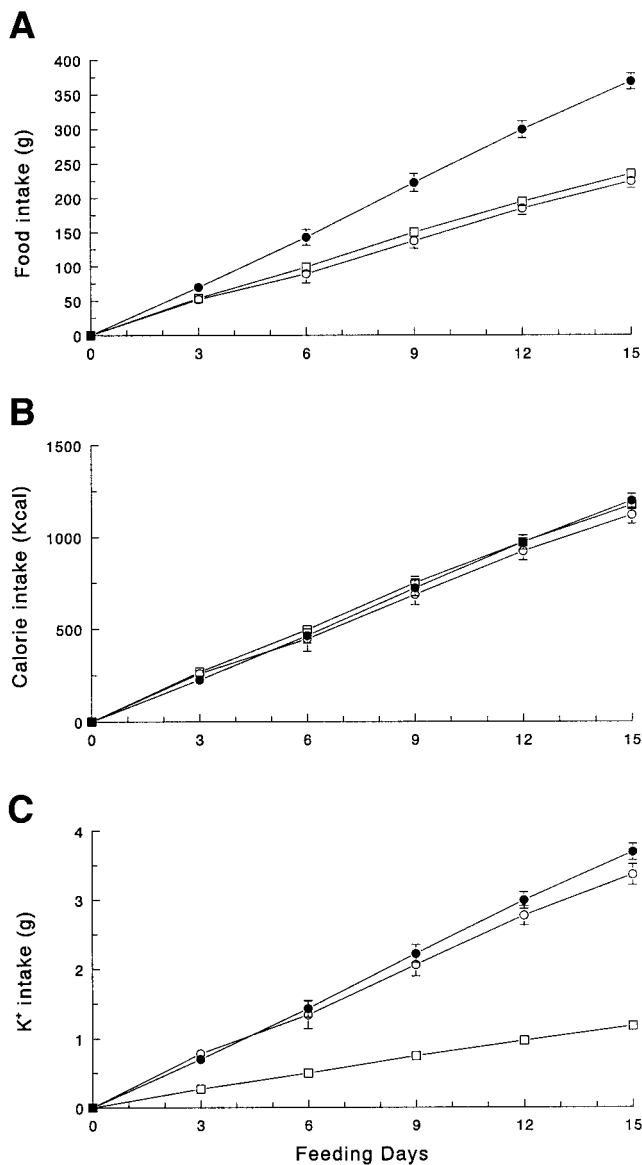


FIG. 1. Cumulative intake of food (A), calories (B), and K<sup>+</sup> (C) during the 15-day feeding period in the control (●), HFD (□), and HFD+K (○) groups. Data are means ± SE for six or seven experiments.

supplementation in high-fat-fed rats did not change the GINF, indicating that insulin action on glucose metabolism is independent of K<sup>+</sup> intake. The KINF required to maintain basal K<sup>+</sup> levels was also decreased in the HFD group compared with the control group ( $P < 0.05$ ) (Fig. 2D). However, the KINF was restored to control values in HFD+K rats, thereby indicating that the low KINF in the HFD group was attributable to low K<sup>+</sup> rather than high-fat intake.

TABLE 1  
Basal metabolic parameters after the 15-day feeding period

Group	<i>n</i>	Body weight (g)	Plasma glucose (mmol/l)	Plasma K <sup>+</sup> (mEq/l)	Plasma FFA (mmol/l)
Control	6	317 ± 7	7.9 ± 0.1	4.2 ± 0.1	0.48 ± 0.03
HFD	7	311 ± 7	8.1 ± 0.1	4.0 ± 0.1	0.47 ± 0.02
HFD+K	6	319 ± 6	8.5 ± 0.1*	4.1 ± 0.1	0.47 ± 0.03

Data are means ± SE. \* $P < 0.05$  vs. control.

Consistent with the GINF data, insulin-stimulated whole-body glucose uptake, assessed using the tracer dilution technique, was lower in high-fat-fed rats regardless of K<sup>+</sup> supplementation ( $P < 0.05$ ) (Fig. 3A). On the other hand, the total amount of K<sup>+</sup> infused during the clamps, reflecting insulin's action to stimulate cellular K<sup>+</sup> uptake, was decreased in the HFD group ( $P < 0.05$ ), but was restored to control values in the HFD+K group (i.e., with K<sup>+</sup> supplementation) (Fig. 3B). These data clearly demonstrate that insulin's action on glucose uptake was regulated by dietary fat, but not by K<sup>+</sup> intake, whereas insulin's action on K<sup>+</sup> uptake was regulated by K<sup>+</sup> intake independent of fat intake.

The kidneys have a remarkable capacity to adjust K<sup>+</sup> excretion to match K<sup>+</sup> intake. Urinary K<sup>+</sup> excretion during the K<sup>+</sup> clamp was substantially reduced in the HFD group compared with the control group ( $346 \pm 43$  vs.  $610 \pm 51$  μmol;  $P < 0.05$ ), but was restored to normal values in the HFD+K group ( $662 \pm 52$  μmol). Interestingly, there was a significant correlation between urinary K<sup>+</sup> excretion and K<sup>+</sup> infusion (reflecting insulin-stimulated cellular K<sup>+</sup> uptake) during the clamps ( $r = 0.84$ ,  $P < 0.001$ ) (Fig. 4). These data may indicate that the kidneys' function to excrete K<sup>+</sup> and insulin's action to promote cellular K<sup>+</sup> uptake are similarly regulated in response to change in K<sup>+</sup> intake.

## DISCUSSION

The present study demonstrated that high-fat feeding (without K<sup>+</sup> supplementation) results in decreases in insulin's actions on glucose and K<sup>+</sup> uptake. Interestingly, K<sup>+</sup> supplementation in high-fat-fed rats restored insulin's action on K<sup>+</sup> uptake, but not on glucose uptake, to control levels. These data clearly indicate that the decreased insulin action on K<sup>+</sup> uptake in high-fat-fed rats was attributable to low K<sup>+</sup> intake rather than high-fat intake, and that when K<sup>+</sup> intake was matched, insulin's action on glucose uptake was selectively (i.e., without change in insulin action on K<sup>+</sup> uptake) impaired by high-fat feeding. Thus insulin's actions on glucose and K<sup>+</sup> uptake were independently regulated by dietary fat and K<sup>+</sup> content, respectively.

It was interesting to note that calorie intake was exactly matched between control and high-fat-fed rats, despite markedly different food consumption and caloric contents of the diets. This might have occurred coincidentally, but it is more likely that food consumption was tightly controlled by daily caloric intake or energy balance. Dietary K<sup>+</sup> content did not affect food consumption, calorie intake, weight gain, or insulin action on glucose uptake in high-fat-fed rats. In contrast, low K<sup>+</sup> intake in high-fat-fed rats resulted in specific changes in the K<sup>+</sup> homeostatic

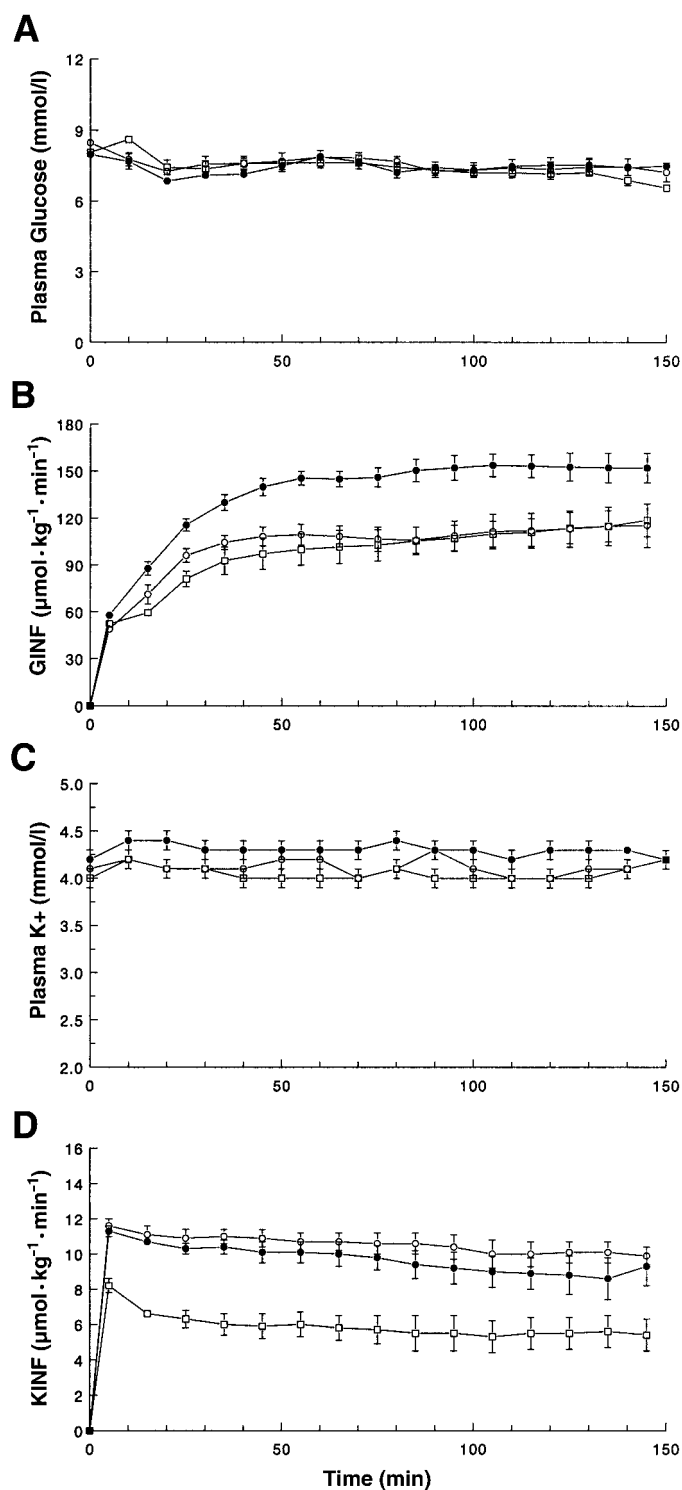


FIG. 2. Plasma glucose (A) and K<sup>+</sup> (C) concentrations and glucose (B) and K<sup>+</sup> (D) infusion rates during the 150-min hyperinsulinemic-euglycemic/eukalemic clamps in the control (●), HFD (□), and HFD+K (○) groups. Data are means ± SE for six or seven experiments.

system, including insulin action on cellular K<sup>+</sup> uptake and urinary K<sup>+</sup> excretion. Interestingly, there was a strong correlation between the changes in these parameters (Fig. 4). It is important to note that the regression line passes through the origin, indicating that relative changes in these parameters were identical. These data suggest the possibility that the kidneys' function to excrete K<sup>+</sup> and insulin's

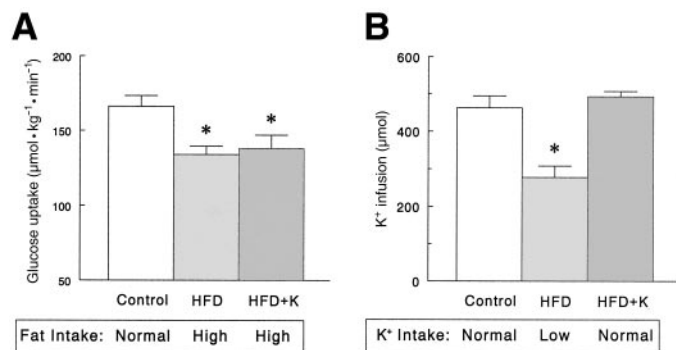


FIG. 3. Insulin-stimulated glucose uptake (A) and total amount of K<sup>+</sup> infused during the hyperinsulinemic glucose/K<sup>+</sup> clamp (B) in the control, HFD, and HFD+K groups. Insulin-stimulated glucose uptake was estimated using the tracer dilution technique with [<sup>3</sup>H]glucose. K<sup>+</sup> infusion during the K<sup>+</sup> clamp represents insulin action to stimulate cellular K<sup>+</sup> uptake. Data are means ± SE for six or seven experiments. \**P* < 0.05 vs. control.

action to promote cellular K<sup>+</sup> uptake are similarly (or concertedly) regulated in response to altered K<sup>+</sup> intake. It is also important to note that these changes occurred without any change in basal (postabsorptive) plasma K<sup>+</sup> levels. Therefore, the body must have a way to sense low K<sup>+</sup> intake independent of basal plasma K<sup>+</sup> level, and this sensing possibly triggers the concerted efforts of the kidneys and muscle (the major target tissue for insulin action) to conserve extracellular K<sup>+</sup>.

Our previous study (7) demonstrated that insulin at physiological concentrations, similar to that in the present study, had no significant effect on urinary K<sup>+</sup> excretion; therefore, most of the K<sup>+</sup> infused during the K<sup>+</sup> clamp should be attributed to insulin's action to promote K<sup>+</sup> uptake in insulin-sensitive tissues, mainly skeletal muscle (7,18). Insulin stimulates K<sup>+</sup> transport in skeletal muscle, and this action is likely mediated by stimulation of Na-K-ATPase, the sodium pump (6,19). Insulin may also stimulate K<sup>+</sup> transport in muscle by activating the bumetanide-sensitive Na-K-Cl co-transporter (13,20) or other K-Cl co-transporters (21). Further studies are required to determine the relative contributions of these transporters to insulin-stimulated cellular K<sup>+</sup> uptake in vivo.

The selective impairment of insulin action on glucose

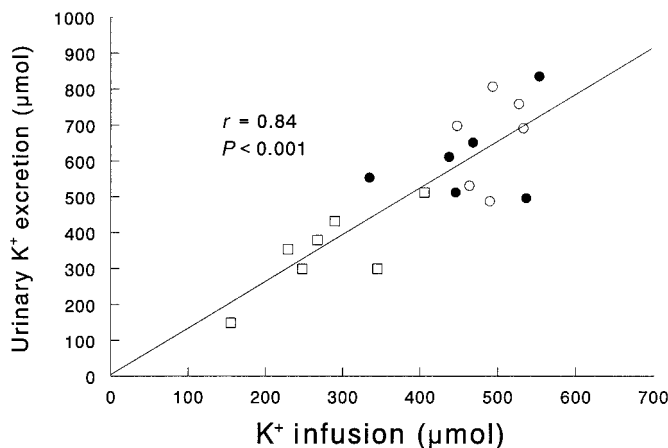


FIG. 4. Correlation between urinary K<sup>+</sup> excretion and K<sup>+</sup> infusion required to clamp plasma K<sup>+</sup> during the 150-min hyperinsulinemic-eukalemic clamps. The *r* value was calculated using the combined data from all three groups. ●, control; □, HFD; ○, HFD+K.

versus  $K^+$  uptake has implications for signaling mechanisms in stimulating glucose and/or  $K^+$  transport. Insulin increases glucose and  $K^+$  transport in insulin-sensitive cells mainly by stimulating translocation of GLUT4, the insulin-responsive glucose transporter, and Na-K-ATPase  $\alpha 2$ , from distinct intracellular storage sites to the surface membranes (6,22,23). Although both GLUT4 and the sodium pump are translocated by insulin from intracellular membranes to the plasma membrane, the two transporters appear to be localized to distinct, separate intracellular vesicles (24). Despite extensive studies, the insulin-signaling pathways for GLUT4 or sodium pump translocation have not been fully elucidated. However, it is now established that activation of PI 3-kinase is crucial for insulin stimulation of GLUT4 translocation and glucose transport (25,26). Previous studies have demonstrated that insulin-stimulated PI 3-kinase activity was reduced in high-fat-fed rats, and this reduction in activity was suggested to be responsible for impaired insulin action on glucose uptake (27,28). If this is the case, the intact insulin action on  $K^+$  uptake in HFD+K rats suggests that insulin stimulation of  $K^+$  transport is independent of PI 3-kinase, although we cannot exclude the possibility that only a permissive activation of PI 3-kinase is required for the stimulation of cellular  $K^+$  uptake, and even impaired PI 3-kinase activation is still sufficient for full stimulation of  $K^+$  uptake. In this regard, Sweeney et al. (13) reported that PI 3-kinase inhibitors attenuated insulin stimulation of  $K^+$  transport in 3T3-L1 fibroblasts (although these cells do not express the insulin-sensitive  $\alpha 2$  sodium pump found in muscle). Whether PI 3-kinase activation is required for insulin stimulation of  $K^+$  transport was not addressed in the present study. However, the present study does provide distinct models of insulin resistance in which insulin action on glucose uptake or  $K^+$  uptake is selectively altered. Studying changes in insulin-signaling events, combined with direct assessment of glucose and  $K^+$  transport, in muscles of these rats would allow researchers to delineate shared upstream versus specific downstream signaling mechanisms for glucose versus  $K^+$  transporter redistribution.

Impaired insulin action on  $K^+$  fluxes has been reported in obesity (29) and in adolescents with type 1 diabetes (30), and both obesity and type 1 diabetes are known to be associated with insulin resistance with respect to glucose metabolism. On the other hand, Alvestrand et al. (31) showed that insulin-mediated  $K^+$  uptake was not altered in uremia, whereas insulin-mediated glucose uptake was markedly impaired. Thus there is evidence for an association (29,30) as well as a dissociation (12,31) of resistance to insulin action on glucose versus  $K^+$  regulation. In those studies, however, insulin action on  $K^+$  fluxes in vivo was studied mainly by observing decreases in plasma  $K^+$  levels or measuring  $K^+$  uptake by specific organs (e.g., liver) during insulin infusion (29–32). Using those approaches, plasma  $K^+$  levels fall during insulin infusion, and such changes may affect  $K^+$  fluxes directly (i.e., because of the effects of  $K^+$  level per se) or indirectly (by triggering other mechanisms, such as involving hormones or altered membrane potentials) and confound the results. The  $K^+$  clamp technique allows us to avoid such confounding effects. The combination of glucose and  $K^+$  clamp techniques will

allow the study of the relationship between insulin action on glucose versus  $K^+$  uptake in various pathological states to understand the interactions between the  $K^+$  and the glucose homeostatic systems.

In conclusion, the present data indicate that the low  $K^+$  intake in typical high-fat diets leads to decreased insulin action on cellular  $K^+$  uptake and that high-fat feeding, when  $K^+$  intake was matched, had a selective effect to impair insulin's action on glucose uptake. Thus insulin's action on glucose uptake was regulated by dietary fat content, but not  $K^+$  content, whereas insulin's action on  $K^+$  uptake was regulated by dietary  $K^+$  content, but not fat content.

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