Effect of sodium intake on insulin sensitivity

DANIEL S. DONOVAN, CAREN G. SOLOMON, ELLEN W. SEELY, GORDON H. WILLIAMS, AND DONALD C. SIMONSON
Endocrine-Hypertension Division, Brigham and Women's Hospital, Joslin Diabetes Center, and Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115

Donovan, Daniel S., Caren G. Solomon, Ellen W. Seely, Gordon H. Williams, and Donald C. Simonson. Effect of sodium intake on insulin sensitivity. *Am. J. Physiol.* 264 (*Endocrinol. Metab.* 27): E730-E734, 1993.—To examine the effects of sodium intake on insulin sensitivity, we performed euglycemic insulin clamp studies (40 $mU \cdot m^{-2} \cdot min^{-1}$) in eight healthy normotensive nondiabetic white males (age = 36 ± 5 yr; wt = 66 ± 3 kg) after 5 days on high (200 meq/day)- and low (10 meq/day)-sodium diets administered in random order. High sodium intake was associated with significantly greater urinary sodium excretion (160 ± 7 vs. 8 ± 2 meq/day; $P < 0.0001$), suppression of plasma aldosterone (7 ± 3 vs. 38 ± 6 ng/dl; $P < 0.001$) and renin (1.5 ± 0.2 vs. 6.0 ± 0.9 $ng \cdot ml^{-1} \cdot h^{-1}$; $P < 0.005$) levels, but no change in blood pressure (116 ± 3/63 ± 2 vs. 114 ± 3/64 ± 2 mmHg; P = not significant). The rate of glucose infusion during the clamp was significantly reduced during the high- vs. low-sodium diet (279 ± 19 vs. 334 ± 24 $mg \cdot m^{-2} \cdot min^{-1}$; $P < 0.01$). This impairment in insulin sensitivity was not related to changes in serum potassium, epinephrine, norepinephrine, cortisol, or growth hormone but was highly correlated with an increment in circulating free fatty acid levels during high sodium intake ($r = 0.82$, $P < 0.05$). These data suggest that *1*) high sodium intake may exacerbate insulin resistance by increasing circulating free fatty acids, and *2*) differences in sodium intake may influence measures of insulin sensitivity in other disease states.

blood pressure; insulin resistance; insulin clamp; free fatty acids

EPIDEMIOLOGICAL STUDIES have revealed that impaired glucose tolerance and diabetes are commonly associated with essential hypertension (15, 31). More recently, insulin resistance has been directly demonstrated in nonobese and obese patients with essential hypertension utilizing the euglycemic insulin clamp technique (10) or the insulin suppression test (33). These findings raise the possibility that insulin resistance and/or hyperinsulinemia may play an important etiologic role in the pathogenesis of hypertension.

Although the precise physiological mechanisms underlying this relationship remain unclear, several hypotheses have been proposed. There is evidence that hyperinsulinemia can lead to sympathetic nervous system activation (26), thereby increasing cardiac contractility and peripheral vascular resistance. It is also well documented that the acute administration of insulin increases renal reabsorption of sodium (4), potentially leading to a state of volume overload. This physiological mechanism takes on additional importance in view of the fact that ~50% of the hypertensive population exhibits salt sensitivity, i.e., exaggerated changes in blood pressure in response to changes in salt intake (34). On the basis of this information, it has been proposed that insulin resistance and/or hyperinsulinemia may be a particularly important factor in the pathogenesis of salt-sensitive forms of hypertension.

Despite the well-documented effects on insulin on sodium homeostasis, the converse relationship, that of sodium intake on insulin sensitivity, has not been carefully examined. One recent report noted a hyperinsulinemic response to oral glucose loading in salt-sensitive normotensive subjects but not in salt-resistant subjects (29), whereas another report found an increased glycemic response to oral glucose loading in hypertensive patients on a low-sodium diet (14). The present study was designed to determine the effects of dietary sodium intake on insulin sensitivity in healthy normal subjects utilizing the euglycemic insulin clamp technique and to examine the physiological mechanisms responsible for any observed changes in insulin action.

METHODS

Subjects. Eight healthy white male subjects were studied. The subjects had a mean age of 36 ± 5 (SE) yr and were of normal weight (mean = 66 ± 3 kg). Body mass index ranged from 17.6 to 23.7 (mean = 21.0 ± 0.6) kg/m^2. None had a personal or family history of hypertension or diabetes, and none was taking any medications. The protocol was approved by the Committee for the Protection of Human Subjects from Research Risks at Brigham and Women's Hospital, and each subject gave voluntary informed written consent before participating.

Procedures. All subjects were admitted to the Clinical Research Center at Brigham and Women's Hospital and were placed on a constant isocaloric diet containing 300 g carbohydrate, 1,000 mg calcium, 100 meq potassium, and either 200 meq sodium or 10 meq sodium/day for 5 days. Each subject received both the high- and low-sodium diets in random consecutive order. Urine samples (24 h) for sodium and potassium were collected each day throughout the study.

At the end of each 5-day period of high or low sodium intake (when sodium balance had been achieved), each subject received a 3-h euglycemic insulin clamp as previously described (6). In brief, after an overnight fast, an intravenous catheter was placed in an antecubital vein for the infusion of glucose and insulin, and a second catheter was placed retrogradely in a dorsal hand vein for blood sampling. The hand bearing the blood sampling catheter was kept in a warming box heated to 70°C to ensure arterialization of venous blood (16). After the collection of baseline samples, a primed continuous infusion of crystalline insulin was administered at a rate of 40 $mU \cdot m^{-2} \cdot min^{-1}$. The plasma glucose was measured at 5-min intervals and was maintained at 90 mg/dl by a variable infusion of 20% dextrose. The amount of glucose infused in milligrams per square meter per minute during the last 120 min of the clamp was used as an index of insulin sensitivity.

Before each clamp study, basal blood pressure was measured using an automated blood pressure recorder (Dinamap, Critikon, Tampa, FL). The systolic, diastolic, and mean arterial blood pressures were recorded at 2-min intervals for 1 h.

Biochemical analyses. Plasma glucose concentrations were measured by the glucose oxidase method with a glucose reflectometer (Lifescan, Mountain View, CA). Plasma insulin (32), renin activity (8), angiotensin II (8), catecholamines (18),

cortisol (ICN Biomedicals/Clinical Assays Gammacount, Costa Mesa, CA), and growth hormone (Nichols Allegro HGH Kit, San Juan Capistrano, CA) were measured by radioimmunoassay as previously described. Free fatty acids were extracted by chloroform-methanol, separated by thin-layer chromatography, and quantitated by gas-liquid chromatography.

Statistical analysis. The CLINFO computer software package was used to collate and analyze the data. Data are expressed as means ± SE. Statistical methods included paired t test for hypothesis testing of paired data and regression analysis to evaluate the relationship between variables. The null hypothesis was rejected at a P value ≤0.05.

RESULTS

The mean systolic, diastolic, and mean arterial pressures did not differ significantly on the two diets and remained in the normal range despite substantial differences in dietary sodium intake (Table 1). Mean weight was slightly but significantly higher on the high-sodium diet compared with the low-salt diet, most likely reflecting a state of modest fluid retention that accompanies increased sodium intake.

Mean 24-h urinary sodium excretion was significantly different on the low-sodium and high-sodium diets and appropriately reflected the dietary sodium intake (Table 1). As expected, the mean basal aldosterone and plasma renin activity levels were significantly higher on the low-sodium diet, further confirming the effects of the different dietary sodium intakes.

There were no significant differences in fasting plasma glucose or insulin levels with changes in sodium intake (Table 1). Similarly, the mean levels of insulin [57 ± 1 vs. 61 ± 3 μU/ml; P = not significant (NS)] and glucose (93 ± 1 vs. 92 ± 1 mg/dl; P = NS) achieved during the insulin clamp studies did not differ during the high- and low-sodium diets. The time course of the plasma glucose levels and rates of glucose infusion during the clamp studies are shown in Fig. 1. Despite similar circulating insulin levels, the rate of glucose uptake during the final 120 min of the clamp was 16% lower on the high-sodium diet compared with the low-sodium diet (279 ± 19 vs. 334 ± 24 $mg \cdot m^{-2} \cdot min^{-1}$; $P < 0.01$; Fig. 2).

The basal counterregulatory hormone responses to changes in sodium intake are summarized in Table 2. There were no significant differences in epinephrine, norepinephrine, or growth hormone between the two diets. As would be expected on the basis of volume expansion, dopamine was significantly increased on the high-sodium

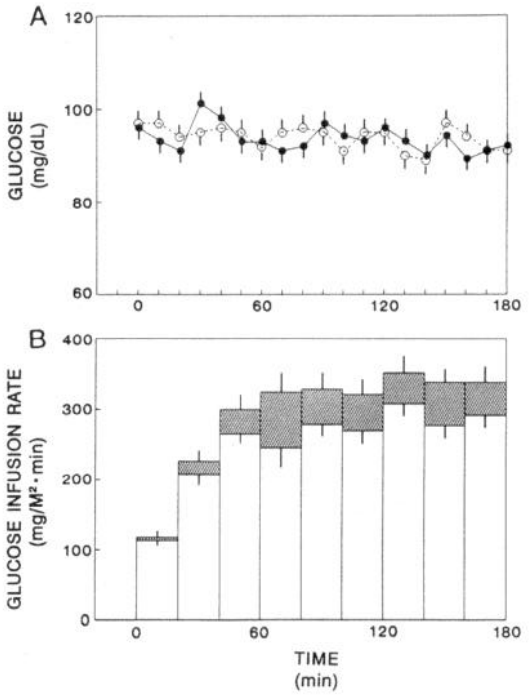

Fig. 1. *A*: plasma glucose levels during insulin clamp studies performed during low sodium intake (10 meq/day; filled circles) or high sodium intake (200 meq/day; open circles). *B*: rates of glucose infusion at 20-min intervals during insulin clamp studies performed during low sodium intake (10 meq/day; hatched bars) or high sodium intake (200 meq/day; open bars).

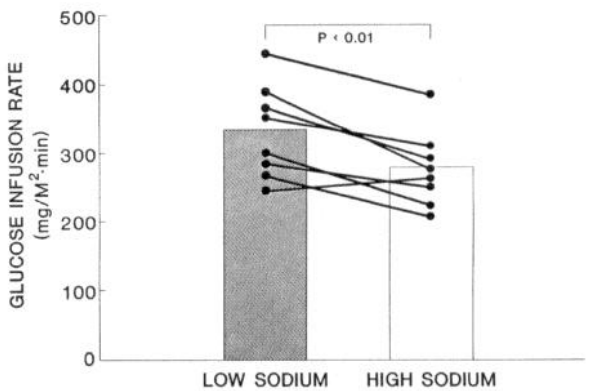

Fig. 2. Steady-state glucose infusion rate during final 120 min of insulin clamp study after 5 days of low (10 meq/day) or high (200 meq/day) sodium intake.

Table 1. *Physical and biochemical responses to sodium intake*

	Low Sodium	High Sodium
Systolic blood pressure, mmHg	114±3	116±3
Diastolic blood pressure, mmhg	64±2	63±2
Mean arterial pressure, mmHg	79±2	79±2
Weight, kg	66±3	67±3*
Urine sodium, meq/day	8±2	160±8‡
Aldosterone, ng/dl	38±6	7±3‡
Plasma renin activity, $ng \cdot ml^{-1} \cdot h^{-1}$	6.0±0.9	1.5±0.2†
Fasting plasma glucose, mg/dl	96±2	97±2
Fasting plasma insulin, μU/ml	5.1±1.5	4.8±1.4

Values are means ± SE. * $P < 0.05$ vs. low sodium. † $P < 0.01$ vs. low sodium; ‡ $P < 0.001$ vs. low sodium.

vs. low-sodium diet (50 ± 7 vs. 28 ± 5 pg/ml; $P < 0.01$). Mean basal cortisol levels were slightly, but significantly, lower on the high-sodium diet (10 ± 1 vs. 13 ± 1; $P < 0.05$).

Basal serum potassium levels on the day of the insulin clamp study were not significantly different on the high- vs. low-sodium diets (4.2 ± 0.1 vs. 4.3 ± 0.1 meq/l; P = NS). Although serum potassium levels decreased significantly during the clamp studies (Fig. 3), there were no differences between potassium concentrations at the end of the 3-h period of insulin and glucose infusion (3.8 ± 0.1 vs. 3.7 ± 0.1 meq/l; P = NS) on the high- and low-sodium intake. The 24-h urinary potassium excretion was nearly identical on the two diets (78 ± 4 vs. 79 ± 4

Table 2. *Basal counterregulatory hormone responses to sodium intake*

	Low Sodium	High Sodium
Epinephrine, pg/ml	29±7	33±11
Norepinephrine, pg/ml	307±85	273±56
Dopamine, pg/ml	28±5	50±7†
Growth hormone, ng/ml	2.0±0.3	4.1±1.3
Cortisol, μg/dl	13±1	10±1*

Values are means ± SE. * $P < 0.05$ vs. low sodium. † $P < 0.01$ vs. low sodium.

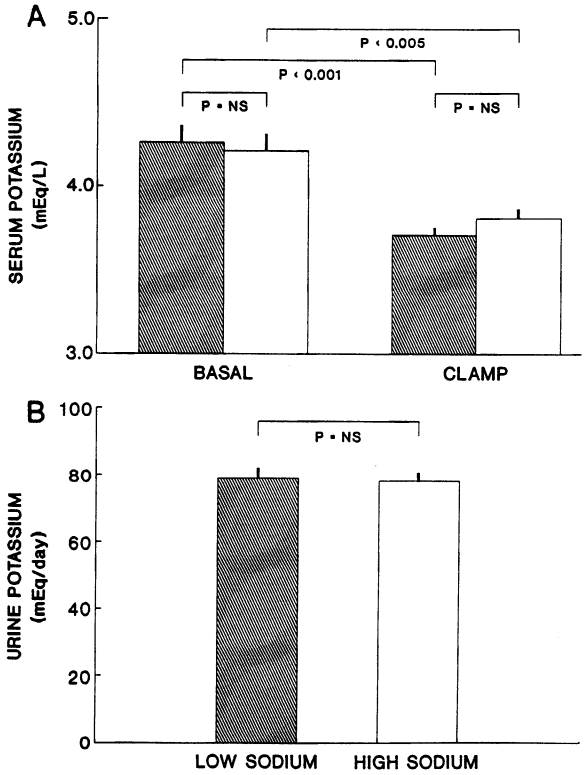

Fig. 3. Serum potassium levels in basal state and at end of insulin clamp study (*A*) and 24-h urinary potassium excretion (*B*) after 5 days of low (10 meq/day; hatched bars) or high (200 meq/day; open bars) sodium intake. NS, not significant.

meq/day on high vs. low sodium; P = NS).

The mean basal free fatty acid levels were significantly increased during the 200 meq/day sodium diet when compared with the 10 meq/day sodium diet (147 ± 17 vs. 117 ± 15 μmol/l; $P < 0.05$). The higher free fatty acid levels during high-sodium intake was observed for all of the major circulating fatty acid moieties, including palmitic (31 ± 5 vs. 24 ± 3 μmol/l; $P < 0.05$), stearic (17 ± 2 vs. 14 ± 2 μmol/l; $0.10 < P < 0.05$), oleic (49 ± 7 vs. 36 ± 6 μmol/l; $P < 0.05$), and linoleic (30 ± 3 vs. 24 ± 3 μmol/l; $P < 0.05$) acids. This change occurred despite the fact that diets were of constant composition (except for sodium content) on each of the 10 study days. There was a significant inverse correlation between the change in glucose uptake during the clamp and the change in basal free fatty acid levels ($r = -0.82$; $P < 0.05$; Fig. 4).

DISCUSSION

Our study indicates that higher dietary intake of sodium causes a significant decrement in insulin sensitivity, as measured by the euglycemic insulin clamp technique. There are several factors known to adversely affect insulin sensitivity, including fasting, stress, immobilization, or changes in the carbohydrate or fat content of the diet (22). These factors can be eliminated as potential explanations on the basis of the controlled and randomized design of our study. Similarly, none of our subjects had diabetes, essential hypertension, obesity, or other disease states known to be associated with insulin resistance.

Changes in levels of counterregulatory hormones may lead to alterations in insulin action. Catecholamines have been documented to cause changes in insulin sensitivity by increasing hepatic glucose production as well as decreasing peripheral glucose utilization (7, 27). However, we observed no significant differences in the levels of epinephrine or norepinephrine during the change in sodium intake. Although high doses of dopamine or dopamine analogues may also decrease insulin sensitivity, the magnitude of the increase in plasma dopamine levels that was observed on the high-salt diet was well below the levels that have previously been described to cause changes in insulin action (28). Growth hormone and cortisol can also lead to impairment of insulin action at both hepatic and extrahepatic sites (17, 23, 24). However, basal growth hormone levels did not differ between the two diets, and basal cortisol levels actually decreased significantly on the high-sodium diet. Therefore, changes in either of these two hormones appears unlikely to account for the observed decrement in insulin sensitivity on the high-sodium diet.

Many studies have examined the effects of changes in serum potassium levels on glucose metabolism. Impaired carbohydrate tolerance has been noted with thiazide diuretic use and can be prevented by maintenance of potassium levels (1, 13, 25). However, in our study, changes in sodium intake did not lead to significant alterations in serum potassium levels, and urinary potassium excretion was nearly identical during the two different sodium diets. As previously demonstrated, insulin infusion during the clamp leads to a fall in serum potassium levels (3); however, the magnitude of this fall was quite similar on

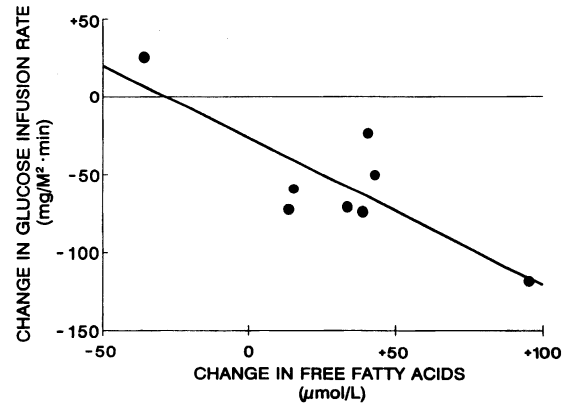

Fig. 4. Change in glucose infusion rate during insulin clamp study vs. change in basal free fatty acid levels after high and low sodium intake. Change for each variable is calculated as value during high-sodium diet minus value during low-sodium diet ($r = -0.82$; $P < 0.05$).

the two different diets. Thus changes in potassium homeostasis do not appear to explain the observed fall in insulin sensitivity with high sodium intake.

Elevated levels of free fatty acids have been proposed to cause insulin resistance via substrate competition, leading to an increased rate of free fatty acid oxidation and inhibition of key rate-limiting enzymes involved in glycolysis and glucose oxidation (20, 21). This cycle, first proposed by Randle et al. (20, 21), is thought to contribute in part to the insulin resistance seen in individuals with non-insulin-dependent diabetes and in some patients with obesity (12) and can be demonstrated during intralipid infusion in healthy volunteers (9). Our data are consistent with these previous studies in that we observed a strong and significant inverse correlation between changes in basal free fatty acid levels and changes in insulin sensitivity on the two different diets (Fig. 4). Of note, the only subject who did not demonstrate this rise in free fatty acid levels with high-sodium intake was the same subject who did not exhibit a decrement in glucose disposal on the high-sodium diet.

The mechanism by which changes in sodium intake might influence circulating free fatty acid levels are not entirely clear. Goodfriend et al. (11), in a study involving both normal and hypertensive subjects, noted that dietary sodium loading caused a 33% rise in total free fatty acid levels, whereas saline infusion led to a 60–100% rise in fatty acid levels. Insulin levels, however, were significantly lower after sodium loading. Although we did not perform dynamic tests of insulin secretion, basal insulin levels were nearly identical during the two sodium diets in our study. The period of overnight fasting before each clamp study was also identical and, therefore, unlikely to contribute to the difference in basal free fatty acid levels.

The specific tissues involved in the insulin resistance caused by high-sodium intake also cannot be directly determined from this initial study. Although we did not measure rates of hepatic glucose production, the fact that fasting plasma glucose and insulin levels were unchanged despite changes in sodium intake makes it unlikely that substantial alterations occurred in the rates of basal glucose production or utilization. Furthermore, the plasma insulin levels that were achieved during the clamp have been shown previously to be sufficient to inhibit endogenous glucose output in healthy individuals as well as in patients with diabetes and essential hypertension (10). These data would suggest that peripheral tissues, primarily muscle, are likely to be the primary site of the alteration in insulin action.

Only two previous studies have attempted to examine changes in carbohydrate metabolism during changes in salt intake. Sharma et al. (29) studied 25 healthy normotensive men who received both 260 and 20 mmol/day sodium diets followed by an oral glucose tolerance test. They classified 10 of their subjects as "salt sensitive" using the criteria of a 3 mmHg drop in mean arterial pressure on the low-sodium diet. These subjects had a hyperinsulinemic and hyperglycemic response to the oral glucose load, suggesting the presence of insulin resistance, whereas the "salt-resistant" subjects had decreased insulin levels on the high-salt diet. If we apply the blood pressure criteria of Sharma et al. (30) to our volunteers, only two of our subjects would be considered salt sensitive. Nevertheless, we found a consistent deterioration in insulin sensitivity during high-sodium intake, regardless of blood pressure response. It is possible that this discrepancy is explained by the fact that the glycemic and insulinemic response to oral glucose loading as in the study of Sharma et al. (29) does not directly examine insulin sensitivity and could fail to detect changes of the magnitude that we observed.

Another study (14) investigated the effect of low (34 mmol/day)- and high-sodium (340 mmol/day) diets on oral glucose tolerance in 15 subjects with hypertension and noted that the insulinemic and glycemic responses to an oral glucose load were elevated when sodium intake was restricted. These results suggest that there may be a difference in the response of insulin sensitivity to sodium intake between normotensive and hypertensive subjects. However, as already noted, the oral glucose tolerance test is a relatively imprecise and insensitive means of assessing insulin resistance.

In summary, our data suggest that the decrement in insulin sensitivity that we observed on a high-salt diet may represent a normal physiological response to dietary salt loading. This decrement was unrelated to changes in counterregulatory hormones or potassium homeostasis but was associated with changes in free fatty acid metabolism. To put the magnitude of this effect into perspective, the 16% change in insulin sensitivity between the high- and low-salt diets is quantitatively similar to the differences in insulin sensitivity observed before and after weight loss, exercise (4), or antihypertensive treatment (19) but is clearly less than the difference between hypertensive and/or diabetic patients and healthy volunteers (5, 10).

These findings may help provide new insight into the role of insulin resistance in the pathogenesis of essential hypertension. Because ~50% of patients with essential hypertension exhibit some degree of sodium sensitivity, this may represent an exaggeration of this normal physiological response. Thus high-sodium intake, per se, may induce insulin resistance and/or hyperinsulinemia, thereby initiating a series of metabolic consequences that raise arterial blood pressure. Further, the results of this investigation strongly suggest that dietary sodium intake be taken into consideration in future studies of insulin sensitivity and hypertension.

This study was supported in part by National Institutes of Health (NIH) research Grants DK-43505 (to D. C. Simonson) and HD-24499 (to E. W. Seely), General Clinical Research Center at Brigham and Women's Hospital Grant RR-02635, Diabetes and Endocrinology Research Center at Joslin Diabetes Center Grant DK-36836, NIH training Grants HL-07609 and DK-07529, and by grants from the American Diabetes Association (to D. C. Simonson and G. H. Williams). Data were analyzed in a CLINFO facility supported by NIH Grant RR-02635.

Address for reprint requests: D. C. Simonson, Section of Diabetes and Metabolism, Brigham and Women's Hospital, 221 Longwood Ave., Boston, MA 02115.

Received 23 April 1992; accepted in final form 8 December 1992.

REFERENCES

1. **Andersson, O. K., T. Gudbrandsson, and K. Jamerson.** Metabolic adverse effects of thiazide diuretics: the importance of normokalaemia. *J. Intern. Med.* 229, *Suppl.* 2: 89–96, 1991.
2. **Bogardus, C., E. Ravussin, D. C. Robbins, R. R. Wolfe, E. S. Horton, and E. A. H. Sims.** Effects of physical training and diet therapy on carbohydrate metabolism in patients with glucose intolerance and non-insulin-dependent diabetes mellitus. *Diabetes* 33: 311–318, 1984.
3. **Cohen, P., N. Barzilai, A. Lerman, H. Harel, P. Szylman, and E. Karnieli.** Insulin effects on glucose and potassium metabolism *in vivo*: evidence for selective insulin resistance in humans. *J. Clin. Endocrinol. Metab.* 73: 564–568, 1991.
4. **DeFronzo, R. A., C. R. Cooke, R. Andres, G. R. Faloona, and P. J. Davis.** The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. *J. Clin. Invest.* 55: 845–855, 1975.
5. **DeFronzo, R. A., D. Simonson, and E. Ferrannini.** Hepatic and peripheral insulin resistance: a common feature of type 2 (non-insulin-dependent) and type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 23: 313–319, 1982.
6. **DeFronzo, R. A., J. D. Tobin, and R. Andres.** Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am. J. Physiol.* 237 (*Endocrinol. Metab. Gastrointest. Physiol.* 6): E213–E223, 1979.
7. **Diebert, D. C., and R. A. DeFronzo.** Epinephrine-induced insulin resistance in man. *J. Clin. Invest.* 65: 717–721, 1980.
8. **Emmanuel, R. L., J. P. Cain, and G. H. Williams.** Double antibody radioimmunoassay of renin activity and angiotensin II in human peripheral plasma. *J. Lab. Clin. Med.* 81: 632–640, 1973.
9. **Ferrannini, E., E. J. Barrett, S. Bevilacqua, and R. A. DeFronzo.** Effect of fatty acids on glucose production and utilization in man. *J. Clin. Invest.* 72: 1737–1747, 1983.
10. **Ferrannini, E., G. Buzzigoli, R. Bonadonna, M. A. Giorico, M. Oleggini, L. Graziadei, R. Pedrinelli, L. Brandi, and S. Bevilacqua.** Insulin resistance in essential hypertension. *N. Engl. J. Med.* 317: 350–357, 1987.
11. **Goodfriend, T. L., D. L. Ball, M. H. Weinberger, T. J. Moore, A. B. Weder, and B. M. Egan.** Salt loads raise plasma fatty acids and lower insulin. *Hypertension* 17: 958–964, 1991.
12. **Groop, L. C., R. C. Bonadonna, D. C. Simonson, A. S. Petrides, M. Shank, and R. A. DeFronzo.** Effect of insulin on oxidative and nonoxidative pathways of free fatty acid metabolism in human obesity. *Am. J. Physiol.* 263 (*Endocrinol. Metab.* 26): E79–E84, 1992.
13. **Helderman, J. H., D. Elahi, D. K. Andersen, G. S. Raizes, J. D. Tobin, D. Shocken, and R. Andres.** Prevention of the glucose intolerance of thiazide diuretics by maintenance of body potassium. *Diabetes* 32: 106–111, 1983.
14. **Iwaoka, T., T. Umeda, M. Ohno, J. Inoue, S. Naomi, T. Sato, and I. Kawakami.** The effect of low and high NaCl diets on oral glucose tolerance. *Klin. Wochenschr.* 66: 724–728, 1988.
15. **Jarett, R. J., H. Keen, M. McCartney, J. H. Fuller, P. J. S. Hamilton, D. D. Reid, and G. Rose.** Glucose tolerance and blood pressure in two population samples: their relation to diabetes mellitus and hypertension. *Int. J. Epidemiol.* 7: 15–24, 1978.
16. **McGuire, E. A. H., J. H. Helderman, J. D. Tobin, R. Andres, and M. Berman.** Effects of arterial versus venous sampling on analysis of glucose kinetics in man. *J. Appl. Physiol.* 41: 565–573, 1976.
17. **Pagano, G., P. Cavallo-Perin, M. Cassader, A. Bruno, A. Ozzello, P. Masciola, A. M. Dall'Omo, and B. Imbimbo.** An in vivo and in vitro study of the mechanism of prednisone-inducedinsulin resistance in healthy subjects. *J. Clin. Invest.* 72: 1814–1820, 1983.
18. **Peuler, J. D., and G. Johnson.** Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine, and dopamine. *Life Sci.* 21: 625–631, 1977.
19. **Pollare, T., H. Lithell, and C. Berne.** A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N. Engl. J. Med.* 321: 868–873, 1989.
20. **Randle, P. J., P. B. Garland, C. N. Hales, and E. A. Newsholme.** The glucose fatty-acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1: 785–789, 1963.
21. **Randle, P. J., E. A. Newsholme, and P. B. Garland.** Regulation of glucose uptake by muscle: effects of fatty acids, ketone bodies and pyruvate, and of alloxan-diabetes and starvation, on the metabolic fate of glucose in rat heart and diaphragm muscles. *Biochem. J.* 93: 652–665, 1964.
22. **Reaven, G. M.** Role of insulin resistance in human disease. *Diabetes* 37: 1595–1607, 1988.
23. **Rizza, R. A., L. J. Mandarino, and J. E. Gerich.** Effects of growth hormone on insulin action in man: mechanisms of insulin resistance, impaired suppression of glucose production, and impaired stimulation of glucose utilization. *Diabetes* 31: 663–669, 1982.
24. **Rizza, R. A., L. J. Mandarino, and J. E. Gerich.** Cortisol-induced insulin resistance in man: impaired suppression of glucose production and stimulation of glucose utilization due to a post-receptor defect of insulin action. *J. Clin. Endocrinol. Metab.* 54: 131–138, 1982.
25. **Rowe, J. W., J. D. Tobin, R. M. Rosa, and R. Andres.** Effect of experimental potassium deficiency on glucose and insulin metabolism. *Metab. Clin. Invest.* 29: 498–502, 1980.
26. **Rowe, J. W., J. B. Young, K. L. Minaker, A. L. Stevens, J. Pallotta, and L. Landsberg.** Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man. *Diabetes* 30: 219–225, 1981.
27. **Saccà, L., C. Vigorito, M. Cicala, B. Ungaro, and R. S. Sherwin.** Mechanisms of epinephrine-induced glucose intolerance in normal humans. *J. Clin. Invest.* 69: 284–293, 1982.
28. **Sandyk, R.** Dopamine and insulin interact to modulate in vitro glucose transport in rat adipocytes. *Int. J. Neurosci.* 43: 9–14, 1988.
29. **Sharma, A. M., K. Ruland, K. P. Spies, and A. Distler.** Salt sensitivity in young normotensive subjects is associated with a hyperinsulinemic response to oral glucose. *J. Hypertens.* 9: 329–335, 1991.
30. **Sharma, A. M., S. Schattenfroh, A. Kribben, and A. Distler.** Reliability of salt-sensitivity testing in normotensive subjects. *Klin. Wochenschr.* 67: 632–634, 1989.
31. **Simonson, D. C.** Etiology and prevalence of hypertension in diabetic patients. *Diabetes Care* 11: 821–827, 1988.
32. **Soeldner, J. S., and D. Slone.** Critical variables in the radioimmunoassay of serum insulin using the double antibody technique. *Diabetes* 14: 771–779, 1965.
33. **Swislocki, A. L. M., B. B. Hoffman, and G. M. Reaven.** Insulin resistance, glucose intolerance and hyperinsulinemia in patients with hypertension. *Am. J. Hypertens.* 2: 419–423, 1989.
34. **Williams, G. H., and N. K. Hollenberg.** Pathophysiology of essential hypertension. In: *Cardiology*, edited by W. W. Parmley and K. Chatterjee. Philadelphia, PA: Lippincott, 1990, p. 1–18.