Insulin Sensitivity and Sodium Excretion in Normotensive Offspring and Hypertensive Patients

Daniel Kopf, Isabel Mühlen, Gerd Kröning, Ilka Sendzik, Babette Huschke, and Hendrik Lehnert

Insulin resistance and hyperinsulinemia have been suggested to precede and promote hypertension, possibly by impairing sodium balance. We examined insulin sensitivity and the influence of acute hyperinsulinemia on sodium excretion after acute sodium loading in hypertension-prone individuals. Insulin sensitivity and sodium excretion in response to a 1,000-mL isotonic saline bolus were examined in 24 strictly normotensive offspring of at least 1 hypertensive parent, 19 controls without a family history of hypertension, and 8 untreated, young hypertensive patients. After the saline bolus, urinary sodium excretion was measured at baseline and during a 2-hour euglycemic, hyperinsulinemic clamp, and insulin sensitivity was determined. Insulin, pressor hormones, and atrial natriuretic peptide (ANP), were measured by radioimmunoassay (RIA) or high-performance liquid chromatography (HPLC). Results are given as means ± SEM. Offspring and controls were well matched in age (23.7 ± 0.5; 24.6 ± 0.5 years, respectively), blood pressure (113.0 ± 2.9/68.5 ± 1.9; 110.6 ± 2.5/71.7 ± 2.2 mm Hg, respectively), bone mass index (BMI), plasma glucose, and lipid parameters. Insulin sensitivity index did not significantly differ between offspring and controls (0.102 ± 0.012; 0.112 ± 0.018 μmol/min/kg/body weight [BW]/pmol, respectively), but was markedly reduced in hypertensives (0.045 ± 0.006, $P < .001$). In response to sodium loading, natriuresis increased significantly ($P < .05$) in both offspring and controls to a similar extent, despite the presence of hyperinsulinemia, but failed to increase in hypertensives. In normotensive offspring of hypertensive patients who have not yet developed any features of the metabolic syndrome, insulin sensitivity is not impaired. Acute hyperinsulinemia impairs the ability to excrete an acute sodium load in hypertensive patients, but not in offspring of hypertensives with normal insulin sensitivity.
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PRIMARY HYPERTENSION HAS been shown to be closely linked to insulin-resistant glucose metabolism and hyperinsulinemia.[1] Some studies in normotensive offspring of hypertensive patients, who are under increased risk of developing hypertension, have suggested that insulin resistance precedes hypertension, thus supporting the notion that insulin resistance may be a primary factor contributing to the development of hypertension in at least one subset of hypertensive patients.[2-4] However, this observation was not uniformly confirmed in more recent studies[5,6] (for review, see Allemann and Weidmann[7] and Kopf et al[8]).

While subjects in these studies were all normotensive by World Health Organization (WHO) definition, blood pressure was slightly, but significantly, higher in offspring of hypertensive individuals in some studies.[2,6] Not all studies matched subjects for other metabolic parameters linked to insulin resistance. We hypothesized that small differences in these parameters might influence the results concerning insulin sensitivity.

Several pathophysiologic pathways have been proposed to connect insulin resistance with hypertension. However, their individual contribution has not been clearly defined. One possible link between insulin resistance and hypertension is the sodium-retaining effect of insulin.[9-11]

Our experiments were designed to investigate insulin sensitivity and insulin effects on renal sodium handling early in the pathogenesis of primary hypertension. We performed our experiments in young, normotensive offspring with at least 1 hypertensive parent. To avoid possibly confounding metabolic factors, subjects with hyperlipidemia, obesity, or diabetes were not included. Subjects having no familiy history of hypertension or diabetes and young hypertensive subjects served as controls.

We pretreated our subjects with an intravenous (IV) bolus of isotonic saline to unmask a possible latent tendency towards sodium retention in hypertension-prone subjects. This sodium bolus also served to suppress the renin-angiotensin system, one of the most powerful regulators of natriuresis, thus minimizing the influence of a possible confounding factor.

To study the specific effects of insulin on sodium excretion and to measure insulin sensitivity, we measured sodium excretion at baseline and under the conditions of an euglycemic, hyperinsulinemic clamp. In addition, some endocrine and neuronal factors that affect renal sodium handling were assessed.

We wanted to shed more light on the following questions: (1) are young, normotensive offspring of hypertensive patients with no evidence of the metabolic syndrome less insulin-sensitive than controls? (2) What is the role of insulin-induced changes in sodium excretion early in the pathogenesis of hypertension?

A secondary goal was to identifiy counterregulatory mechanisms, which may maintain sodium and blood pressure homeostasis in subjects who are insulin-resistant and hyperinsulinemic, but still normotensive.

SUBJECTS AND METHODS

Study Subjects

Twenty-four healthy, young volunteers with at least 1 hypertensive parent served as study subjects ("normotensive, positive family his-

From the Department of Endocrinology and Metabolism and the Institute of Clinical Chemistry, Otto-von-Guericke-University, Magdeburg, Germany.

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Address reprint requests to Hendrik Lehnert, MD, Department of Endocrinology and Metabolism, Otto von Guericke University, Leipziger Str 44, 39120 Magdeburg, Germany.

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tory"). Nineteen normotensive individuals with no family history of hypertension ("normotensive, negative family history") and 8 untreated hypertensive patients ("hypertensive patients") served as control groups. Subjects were recruited among medical students and hypertensive patients of the University of Magdeburg. To qualify for the study, subjects had to be between 18 and 30 years of age, free of any known medical disorder, and not taking any regular or current medication (with the exception of oral contraceptives). To keep offspring and normotensive control groups comparable, care was taken not to include subjects with hypertension (systolic blood pressure equal or greater than 140 mm Hg, diastolic blood pressure equal or greater than 90 mm Hg after at least 30 minutes of rest in a sitting position), obesity (body mass index [BMI] greater than 30 kg/m^2), fasting hyperglycemia or hyperlipidemia (fasting capillary blood glucose level greater than 5.5 mmol/L [100 mg/dL], serum total cholesterol greater than 5.2 mmol/L, and serum total triglycerides greater than 2.2 mmol/L). An additional exclusion criterion was hypokalemia below 3.8 mmol/L on the day of the study. Pregnant women or nursing mothers were also excluded. For standardization, all female subjects were studied during the second half of their menstrual cycle. This time interval was chosen because some were taking oral contraceptives containing gestagens.

Family history was ascertained by at least 3 independent blood pressure readings in each parent. These were obtained by detailed questionnaires, which were completed by primary care physicians of both of the subjects' parents. Parents were required to see their physicians before the study. Information obtained from primary care physicians included a current blood pressure reading, previous blood pressure readings on at least 2 different occasions, blood pressure readings before initiation of antihypertensive treatment, where applicable, a past medical history, current medication including antihypertensive medication, current weight, height, and blood tests (glucose, uric acid, total triglycerides, and cholesterol). If neccessary, data were completed or confirmed by personally contacting parents or their physicians. Diagnosis of essential hypertension was made according to current WHO criteria. Subjects were not enrolled into the study unless family information was complete.

Because hypertensive patients were slightly older on average than both normotensive groups, we formed a subgroup of normotensive subjects with negative family history for hypertension by selecting those 11 subjects who were 25 years of age or older. For direct comparison of hypertensive patients with normotensive subjects, this subgroup was used.

Informed consent was obtained from all subjects before the study. This project was approved by the local Ethics Committee.

Analytical Procedures

Electrolytes, glucose, creatinine, urea, uric acid, complete blood count, and lipid parameters were determined in the Department of Clinical Chemistry, either with daily routine or in the emergency laboratory facilities (potassium, glucose). Tests were performed on automated analyzers (Hitachi, Boehringer Mannheim, Mannheim, Germany). Venous or capillary glucose was measured amperometrically with the glucose oxidase reaction.

Plasma samples for hormone assays were collected in precooled tubes and placed on ice immediately and stored at -70°C. All hormones except for catecholamines were analyzed using commercially available radioimmunoassay (RIA) test kits. Assays were performed in duplicate. For insulin, the Insulin CT kit (CIS Diagnostik, Dreieich, Germany) was applied. According to information obtained from the manufacturer, this assay has a cross-reactivity of 40% with human split-32,33-proinsulin and 60% with intact human proinsulin. C-Peptide was analyzed on an automated analyzer (Immulite; Hermann Biermann GmbH, Bad Nauheim, Germany). Active renin was measured by a sandwich technique RIA test kit with 2 monoclonal antibodies (ERIA Diagnostics Pasteur, Marnes-La-Coquette/France). Normal range in supine position is 5 to 25 pg/mL. Aldosterone was assayed using the Aldosteron-RIA Coat-A-Count Kit supplied by Hermann Biermann GmbH, with a normal range of 28 to 440 pmol/L in supine position. Blood for atrial natriuretic peptide (ANP) assays was collected in tubes containig EDTA and aprotinine (Trasylol; Bayer AG, Leverkusen, Germany). ANP concentration was determined with a RIA kit provided by Nichols Institute (Bad Nauheim, Germany).

Plasma and urinary adrenaline and noradrenaline were measured by high-performance liquid chromatography (HPLC) and subsequent electrochemical detection. All laboratory analyses were performed according to good laboratory practice.

Euglycemic, Hyperinsulinemic Clamp

Clamp studies were performed using a biostator (Miles Laboratories, Indianapolis, IN and MTB, Amstetten, Germany). Procedures were performed as described by Fogt et al.[12] Briefly, venipuncture and placement of indwelling flexible venous catheters was necessary at 3 different sites: 1 catheter in an antecubital vein of each arm and in a hand vein on 1 side. The catheter in the hand vein was inserted in retrograde direction and was connected to the biostator via a double lumen catheter. Blood was arterialized by heating this hand. This catheter provided the Biostator with a blood buffer mixture for continuous blood glucose monitoring. Blood glucose was analyzed by a glucose oxidase membrane and electrochemical detection. Glucose, insulin, and saline were infused into the cubital vein of the contralateral arm. During clamp, insulin (H-Insulin Hoechst; Hoechst AG, Frankfurt, Germany) was given at a constant rate of 1 mU/kg/body weight (BW)/min. Forty percent glucose solution was given as required to maintain baseline blood glucose concentration. The cannula in the ipsilateral antecubital vein served for blood withdrawals during various times of the study as described below.

Calculations

Insulin sensitivity index was calculated as the amount of glucose infused during the second hour of the clamp (insulin steady state) divided by time and BW and increment in insulin concentration. Data are given as μmol glucose * kg^{-1} BW * min^{-1}/pmol/L insulin. If blood glucose concentration at the end of the second hour differed from the beginning of the second hour, the amount of glucose infused was corrected for changes in actual glucose concentrations as described by DeFronzo et al.[13]

Study Protocol

Study subjects were required to fast for at least 10 hours before the procedures. They were, however, allowed to drink water. Patients were placed in a supine position and kept in this position throughout the procedures. At this time point, all necessary venipunctures were performed, and the cannula in the hand vein was connected to the biostator for equilibration of glucose measurement devices. At approximately 8:15 AM, blood was withdrawn for determination of plasma glucose and electrolytes (sample A). Subsequently, a bolus of 1,000 mL isotonic saline was given IV. A timetable of infusions, blood samples, and urine collections is given in Fig 1.

At 9:00 AM, 45 minutes after venipunctures, blood pressure was measured by sphygmomanometry. Blood was withdrawn (sample B) for determination of plasma glucose, electrolytes, creatinine, blood urea nitrogen, complete blood count, blood lipids, and hormones (insulin, C-peptide, renin, aldosterone, ANP, adrenaline, and noradrenaline). Subjects were asked to void on a bedpan while remaining in a supine position. Throughout the experiment, IV saline was given in an amount to substitute fluid loss by voiding.

At the end of this hour (10:00 AM), blood was withdrawn (sample C),

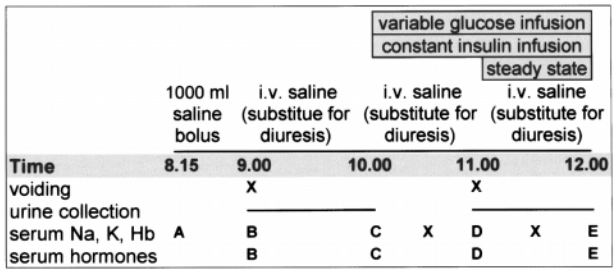

Fig 1. Experimental protocol (letters denote time points of sampling). For further details, see Methods.

and patients were asked to void again. The same parameters were determined as in sample B except for uric acid and white blood cell count. Quantitative excretion of electrolytes, adrenaline, and noradrenaline during the past hour (baseline collection period) was determined.

Thereafter, the euglycemic hyperinsulinemic clamp was started as described above. After 1 hour, at 11:00 AM when an insulin steady state was achieved, blood sampling was repeated (sample D, same parameters as in sample C). Subjects voided again, and the urine was discarded. The clamp was continued during the last hour of the study (11:00 AM to 12:00 AM), which served as the urine collection period under hyperinsulinemia. At the end of this period, blood and quantitative urine sampling was repeated (sample E, parameters as in sample C). At this time, insulin infusion was stopped, while glucose infusion was continued as needed to prevent hypoglycemia.

Statistics

All data are given as arithmetic means ± SEM. Nonparametric tests were applied throughout the study. Wilcoxon test for unpaired samples was used for comparisons between groups. Comparisons within groups were performed by 1-way analysis of variance (ANOVA) for repeated measures and subsequent *t* tests or by *t* test for paired samples, as appropriate. Statistical significance was accepted at $P < .05$. At a group size of n = 19, a difference of 0.82 standard deviations (SD) was detected with a power of 80%. Spearman's rank correlation test was used to calculate correlation coefficients. Stepwise multivariate linear regression analysis was performed with $P < .05$ for inclusion and $P < .10$ for exclusion of variables.

RESULTS

Baseline Characteristics

Twenty-four subjects had a positive family history, and 19 patients had a negative familiy history for hypertension. Baseline characteristics are given in Table 1. Subjects of both normotensive groups did not differ significantly in any of the parameters analyzed. Most importantly, offspring of hypertensive families did not have increased blood pressure compared with controls. In addition, both groups were comparable in metabolic and anthropometric parameters.

Hypertensive patients did not differ significantly from the corresponding normotensive subjects in terms of age. However, they had a higher systolic and diastolic blood pressure, BMI, and waist-to-hip (WHR) ratio, while differences in fasting plasma insulin did not reach statistical significance (Table 2).

Insulin and Insulin Sensitivity

Insulin concentration reached a steady state after 1 hour of insulin infusion as indicated by virtually identical levels of insulin after 1 and 2 hours of the clamp procedure (Fig 2 shows the data for the normotensive groups).

Insulin sensitivity index was markedly reduced in hypertensive subjects compared with the corresponding normotensive subgroup (Fig 3, $P < .001$). In contrast, in both normotensive groups, insulin sensitivity index was almost identical between offspring of hypertensive and normotensive subjects (Fig 3). In keeping with this finding, fasting insulin and C-peptide concentrations did not differ significantly between both groups (Table 1).

Insulin sensitivity index correlated well with plasma fasting insulin ($r = -.457$; $P < .01$). In addition, the insulin-induced glucose disposal rate correlated well with fasting triglycerides and various other lipid parameters ($P < .01$; data not shown, described in Ambrosch et al[16]).

Blood Pressure

Diastolic, not systolic blood pressure, decreased slightly, but significantly ($P < .05$) after infusion of insulin in normotensive

Table 1. Baseline Characteristics of Normotensive Subjects With Positive Versus Negative Family History

	Normotensive, Positive Family History	Normotensive, Negative Family History	Statistical Analysis
No.	24	19	NS
Age (yr)	23.7 ± 0.5	24.6 ± 0.5	NS
Gender (male/female)	13/11	10/9	NS
Females on oral contraceptives	6	6	
Systolic blood pressure (mm Hg)	113.0 ± 2.9	110.6 ± 2.5	NS
Diastolic blood pressure (mm Hg)	68.5 ± 1.9	71.7 ± 2.2	NS
BMI (kg/m^2)	22.4 ± 0.5	22.8 ± 0.5	NS
WHR	0.793 ± 0.016	0.790 ± 0.018	NS
Triglycerides (mg/dL)	92 ± 6	108 ± 10	NS
Total cholesterol (mg/dL)	165 ± 10	181 ± 13	NS
HDL cholesterol (mg/dL)	59.3 ± 4.8	56.9 ± 4.9	NS
Free fatty acids (mmol/L)	0.55 ± 0.06	0.44 ± 0.05	NS
Fasting C-peptide (pmol/L)	533 ± 40	503 ± 71	NS
Fasting insulin (pmol/L)	123.5 ± 24.6	118.9 ± 22.0	NS

NOTE. NS, not significant at $P < .05$.

Table 2. Baseline Characteristics of Hypertensive Patients Versus Normotensive Subjects With Negative Family History (subgroup)

	Hypertensive Patients	Normotensive, Negative Family History (subgroup)	Statistical Analysis
No.	8	11	
Age (yr)	30.5 ± 3.3	26.3 ± 0.3	NS
Gender (male/female)	6/2	6/5	
Systolic blood pressure (mm Hg)	155 ± 5	112 ± 4	$P < .001$
Diastolic blood pressure (mm Hg)	96 ± 3	74 ± 3	$P < .001$
BMI (kg/m^2)	27.7 ± 2.3	22.8 ± 0.5	$P < .05$
WHR	0.893 ± 0.022	0.779 ± 0.027	$P < .01$
Fasting insulin (pmol/L)	145.7 ± 27.3	101.0 ± 26.2	NS

NOTE. NS at $P < .05$.

subjects with a negative family history (Fig 4). Blood pressure did not change in the course of the study in the other groups.

Sodium Excretion

In each normotensive group, urinary sodium excretion was significantly higher during the second sampling period (clamp) than during the baseline period (Fig 5, $P < .05$). Urinary sodium excretion did not differ between both normotensive groups, either under baseline conditions or under conditions of hyperinsulinemia. In contrast, hypertensive patients failed to increase sodium excretion during the second sampling period in a statistically significant manner. There was a significant difference in increase of urinary sodium excretion between hypertensive patients and the corresponding subgroup of normotensive subjects ($P < .05$).

Total saline infusion was not significantly different between groups (1,588 ± 75 mL in normotensive subjects with a positive family history, 1,731 ± 96 in normotensive subjects with a negative family history, 1,774 ± 198 in hypertensive patients) nor were there any significant differences in urine volumes during the collection periods (baseline, 273 ± 41, 247 ± 36, 257 ± 52, respectively; hyperinsulinemia, 107 ± 18, 149 ± 22, 157 ± 43, respectively).

Sodium excretion did not correlate with baseline or clamp insulin levels or with insulin sensitivity index.

Pressor Hormones and ANP

Compared with baseline, urinary excretion of noradrenaline increased during hyperinsulinemia statistically significant ($P < .01$) in all groups to a similar extent (Table 3).

Baseline renin and aldosterone concentrations (blood sample C) were suppressed to the lower normal range after administration of the saline bolus. For both hormones and ANP, there were no statistically significant differences between groups and no significant changes in the course of the experiment.

Multivariate Regression Analysis

Stepwise multivariate regression analysis was performed including insulin sensitivity index, insulin, renin, aldosterone, and ANP. The only predictors of the increase in sodium excretion were the ANP concentrations measured during hyperinsulinemia ($r^2 = .400$; $P = .009$) and the relative increase in renin concentrations (.591; $P = .028$).

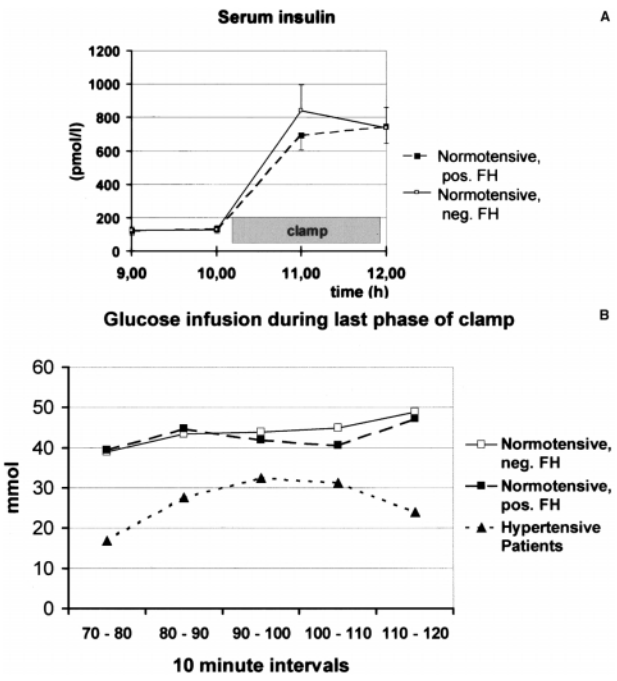

Fig 2. (A) Insulin levels in the course of the study in normotensive subjects with and without a family history of hypertension. (B) Mean amount of glucose infused during the last four 10-minute intervals of the clamp phase.

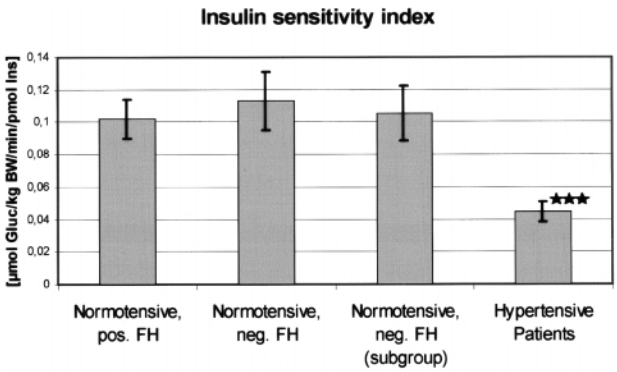

Fig 3. Insulin sensitivity index in normotensive subjects with and without a family history of hypertension and in hypertensive subjects (* $P < .001$).**

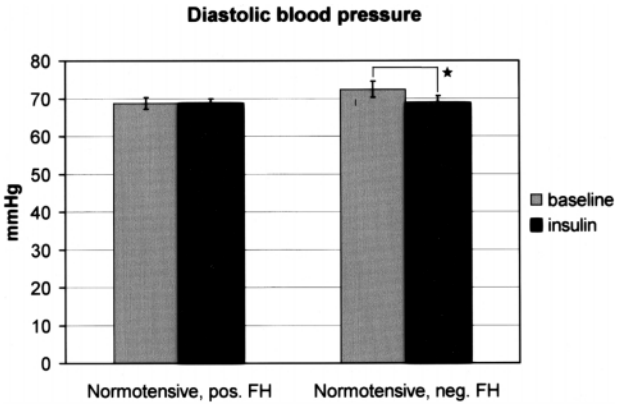

Fig 4. Blood pressure in the course of the study in normotensive subjects with and without a family history of hypertension (* *P* < .05 *v* baseline).

DISCUSSION

In summary, our data suggest that insulin sensitivity is not markedly impaired in young, normotensive offspring of hypertensive parents, if subjects are comparable concerning clinical features of the metabolic syndrome. We confirmed the finding that insulin sensitivity is significantly reduced in patients with manifest hypertension. In addition, we demonstrated that under the conditions of sodium loading and simultaneous hyperinsulinemia, renal sodium excretion is blunted or delayed in hypertensive patients. By the same techniques, we could not find any differences in renal sodium handling and endocrine sodium and blood pressure regulation between subjects with a positive versus negative family history of hypertension.

The present report bears various novel aspects with regard to its study design. First, while applying a 3 group design, normotensive offspring of hypertensive patients are not only compared with normotensive subjects with a negative family history, but also with a group of young, untreated hypertensive patients. Second, study subjects were well characterized and comparable not only with respect to blood pressure, but also with respect to metabolic features, such as BW, lipids, and glucose. Finally, we sought to unmask latent sodium retention by pretreatment with a saline bolus.

Our first important finding was that insulin sensitivity did not differ between subjects with or without a family history of hypertension in our study population. While this result appears to be at odds with some previous reports,[2-4] support comes from more recent studies.[5,6,15]

Both differences in applied techniques and in subject selection may account for these discrepancies. Most of the studies used the hyperinsulinemic clamp technique, while 1 study[4] used the frequent sampling intravenous glucose tolerance test to assess insulin sensitivity. The importance of the applied technique is well illustrated by the study of Endre et al,[15] who found a significant difference in insulin sensitivity when calculated as insulin sensitivity index, but not when calculated as glucose disposal rate.

The validity of insulin sensitivity measurement in this study is confirmed by correlations with various lipid parameters. The influence of insulin sensitivity on lipid metabolism, particularly on low-density lipoprotein (LDL) composition, in the same study subjects has been reported elsewhere.[16]

Another factor, which in our opinion is even more important, is subject selection. In the study of Beatty et al,[2] blood pressure was already slightly, but significantly, higher in offspring of hypertensive parents than in controls. Thus, insulin resistance in their study may either be the primary factor leading to hypertension or may be part of the early sequelae of hypertension. In contrast, the subjects studied in the present report, as well as the population investigated by Hausberg et al,[5] were exactly matched concerning blood pressure and a number of metabolic parameters.

We studied a larger sample size than 2 previous studies, which have found significant differences in insulin sensitivity.[2,3] Differences in insulin sensitivity between groups in those studies amounted to more than the 1.5-fold SD. Our study was sufficiently powered to detect much smaller differences.

These findings suggest that insulin resistance and hypertension are very closely linked even in early stages. Thus, it may be very difficult to find a period when blood pressure is still completely normal, but insulin sensitivity is already significantly reduced.

The complex heredity and heterogeneity of hypertension may also contribute to conflicting results in offspring of hypertensive patients. The influence of insulin sensitivity on blood pressure may differ between various subsets of hypertensive patients. In addition, we cannot exclude that we may have

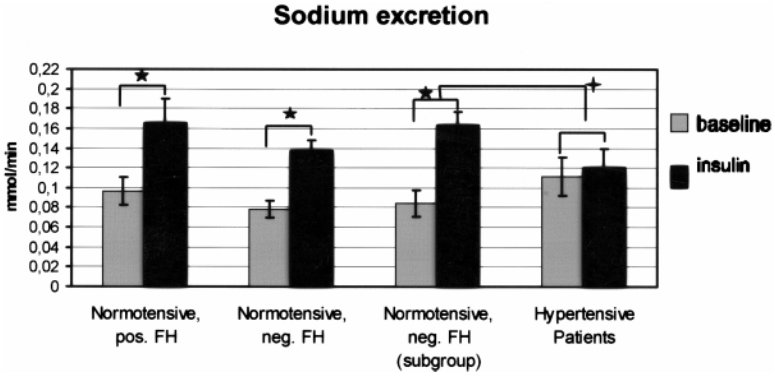

Fig 5. Sodium excretion at baseline and during hyperinsulinemia ("clamp") in subjects with or without a family history of hypertension and in hypertensive subjects (* *P* < .05 *v* baseline; + *P* < .05 for difference in sodium excretion in hypertensive patients *v* normotensive subjects).

Table 3. Plasma Hormone Levels at Baseline (blood sample C, 10:00 AM) and Under Hyperinsulinemia (blood sample E, 12:00 AM)

	Normotensive, Positive Family History	Normotensive, Negative Family History	Hypertensive Patients
Plasma renin, C (pg/mL)	5.47 ± 0.96	6.16 ± 3.26	6.13 ± 2.00
Plasma renin, E	6.35 ± 0.89	5.40 ± 2.18	6.43 ± 1.77
Plasma aldosterone, C (pmol/L)	144 ± 21	174 ± 30	102 ± 28
Plasma aldosterone, E	152 ± 23	147 ± 25	170 ± 50
Plasma ANP, C (pg/mL)	4.23 ± 0.34	4.77 ± 0.39	5.22 ± 1.14
Plasma ANP, E	4.62 ± 0.44	4.35 ± 0.43	3.63 ± 0.49
Urinary noradrenaline excretion, baseline (μg/h)	13.0 ± 1.3	10.7 ± 1.8	11.9 ± 0.4
Urinary noradrenaline excretion, clamp	21.1 ± 3.0*	18.1 ± 5.2*	17.9 ± 4.8*

* Significant increase *v* baseline urinary noradrenalin excretion, $P < .01$.

selected offspring who will not proceed to develop hypertension themselves by excluding offspring with any evidence of metabolic abnormalities.

As a consequence of sodium and volume loading, insulin sensitivity may have been altered in our experiment, for example, by suppressing sympathetic nerve activity or renin and redirecting blood flow to skeletal muscle. There is, however, no reason to believe that this suppression is less effective in offspring of normotensive than in offspring of hypertensive subjects, thus blunting a possible difference in insulin sensitivity.

In response to sodium loading, sodium excretion increased in the second sampling period in both normotensive groups, despite the presence of hyperinsulinemia. In contrast, hypertensive subjects were not able to increase sodium excretion in the presence of hyperinsulinemia. The sodium-retaining effects of hyperinsulinemia are well described. The classic work by DeFronzo et al,[9] as well as several other groups,[15,17,18] found a significant decrease in renal sodium excretion during insulin infusion. Our study shows a difference between hypertensive and normotensive subjects in the ability to handle an acute sodium load under the conditions of hyperinsulinemia.

The fact that sodium excretion in normotensive individuals increased during the second sampling period, despite hyperinsulinemia, is explained by sodium loading immediately before baseline sodium excretion was measured. In previous studies, a similar bolus of isotonic saline without insulin has led to a continuous increase in sodium excretion over the first 3 hours after the infusion[19,20] and to a rapid suppression of plasma renin activity.[19] Thus, insulin-induced sodium retention was overridden by the natriuretic response to sodium loading in the second part of our study.

Sodium loading may also be the reason why a decrease in blood pressure under acute hyperinsulinemia was observed only in the group of normotensive subjects without a family history of hypertension. Obviously, the acute vasodilating effect of insulin was blunted in offspring of hypertensive patients. This finding is in favor of the hypothesis of impaired sensitivity to the vasodilating effects of insulin in hypertension.[11,14]

Both in our study and in the study by Endre et al,[15] sodium excretion during the clamp did not differ between normotensive groups. However, in the latter study, a significant difference between groups in the changes of norepinephrine and aldosterone from baseline to hyperinsulinemia was found. In our experiments, catecholamines increased to a similar extent in all groups during hyperinsulinemia. An increase of catecholamines under insulin is expected, because insulin is known to increase sympathetic nerve activity.[11] While the insulin levels achieved during clamp were almost identical between groups in our study, these levels were slightly different in the study of Endre et al, which may explain different levels of sympathetic activation, and, as a consequence, different degrees of stimulation of the renin-angiotensin-aldosterone system.

The secondary goal of our study was to characterize mechanisms compensating for insulin-induced sodium retention in still normotensive, but insulin-resistant subjects. However, our finding that strictly normotensive offspring of hypertensive parents were not insulin-resistant or hyperinsulinemic limited the ability of our study to address this issue.

Nevertheless, we found absolutely parallel behavior of all determined hormones over the course of the study without any differences between groups, even including manifest hypertensive patients. Moreover, when a multifactorial analysis was performed across all groups, no significant interactions between insulin and sodium-regulating hormones was identified. This suggests that other endocrine or paracrine systems, which were not investigated here, significantly contribute to the regulation of renal sodium handling in the presence of hyperinsulinemia. Such candidates may include endothelin or the renal kinin-kallikrein system.[21,22] A study design including these candidates, as well as separate investigations of different parts of the nephron, may be helpful in addressing this question.[23,24]

An important limitation of our study is the short time course. In the present report, we conducted short-term experiments studying effects over a time period of a few hours, while the development of insulin resistance and hypertension extends over many years. In addition, the time course of insulin action may differ between hypertensive and normotensive patients.[25]

The present study has been conducted in nonobese offspring. We did not distinguish between offspring of obese and nonobese parents. Hypertension of obesity may be a subset of essential hypertension, in which renal sodium handling appears to be even more crucial.[25,26] In line with these observations, we found significant differences in insulin sensitivity and sodium handling in the manifest hypertensive patients, who also had a significantly higher mean BMI and WHR. Thus, overweight may be one important determinant of progression to insulin resistance and hypertension in hypertension-prone subjects. It is conceivable that a study limited to offspring of obese hyper-

tensives would yield more clear-cut results concerning the mechanisms.

In conclusion, our study suggests that the development of insulin resistance, hypertension, and metabolic abnormalities occurs in parallel rather than in sequence. In hypertensive subjects, the ability to excrete a sodium load is impaired under acute hyperinsulinemia, while in normotensive offspring with normal insulin sensitivity, this ability is maintained. The interaction of insulin sensitivity, sodium handling, and blood pressure may be different in various subgroups of essential hypertension and may involve others than the classic regulators of renal sodium handling, such as the sympathetic nervous system, the renin-angiotensin system, or ANP.

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