Familial Hypertension, Insulin, Sympathetic Activity, and Blood Pressure Elevation

Kazuko Masuo, Hiroshi Mikami, Toshio Ogihara, Michael L. Tuck

Abstract—This study evaluated the effects of a positive family history of hypertension (FH+) on the contributions of sympathetic nervous system (SNS) activity and insulin to blood pressure elevation (BPE). The study design was longitudinal and evaluated BP, body mass index (BMI), and fasting plasma insulin and norepinephrine (NE) levels for 10 years in 557 young, nonobese Japanese men who were normotensive at entry. FH+ was defined as hypertension in first-degree relatives as verified by historical records or direct determination. BPE was defined as a ≥10% rise in systolic and diastolic BP over entry levels during the 10-year period. In the total group FH+ was noted in 16%, and BPE occurred in 18% of normotensive subjects. When evaluated by FH, the prevalence of BPE was 33% in FH+ compared with 16% in FH− (P<0.05). BP levels were greater both at entry and at year 10 in the FH+ group. The absolute increment in plasma NE over 10 years was greater in the BPE group than in those without BPE (P<0.01). Of note, the rise in plasma NE levels in BPE individuals was identical in FH+ and FH− subjects. Plasma insulin increments were also greater in normotensive subjects with BPE than in normotensive subjects without BPE. However, compared with NE, development of hyperinsulinemia was more pronounced in the FH+ subjects. The results indicate that SNS hyperactivity may be a less genetically determined predictor of hypertension than is hyperinsulinemia. Because SNS changes in this initially normotensive population appeared more closely related to the development of hypertension than to hyperinsulinemia, environmental rather than genetic factors may be the main determinant of early BPE in nonobese normotensive subjects. (Hypertension. 1998;32:96-100.)

Key Words: family history ■ sympathetic nervous system ■ insulin ■ blood pressure

The association of hypertension with hyperinsulinemia and SNS hyperactivity is well established.1–7 What is less certain is whether increases in SNS activity and insulin precede or follow the development of hypertension. Increases in SNS activity and metabolic abnormalities may be closely aligned with the rise in BP. For example, in a cross-sectional study, our group found that SNS hyperactivity and abnormal blood glucose and insulin responses to glucose administration characterized the early phase of hypertension.6 In a 10-year longitudinal study, we also noted that increases in SNS activity preceded the hyperinsulinemia and rise in BP in subjects who were normotensive at entry.7 In the Normative Aging Study of 752 nondiabetic, middle-aged, male participants, it was also found that insulin levels and urinary NE excretion were related to BP levels.7 The study concluded that insulin levels and urinary NE excretion were independent predictors of hypertension. In analyzing the relationship of SNS activity and insulin to the development of coronary risk in hypertension, Julius et al10,11 commented on the “chicken-and-egg” question of whether SNS and insulin abnormalities precede the development of hypertension. Many short-term studies in humans have indicated that insulin administration is capable of altering SNS activity and vascular responses.12–19

Two important considerations in the role for insulin and SNS activity in BP are the effects of body weight and genetic influences. One method to study genetic influences of a trait (eg, BP) in humans is to select unaffected individuals with a family history of the trait. Several studies using this design have shown altered insulin sensitivity and hyperinsulinemia in normal-weight or obese normotensive offspring of hypertensive parents.20–30 However, most of the study protocols on genetic influences used a cross-sectional rather than a longitudinal design. Some studies noted that body weight was a factor in FH+.24,29,30

The present study extends previously reported data7 to examine, on a longitudinal basis, the influence of an FH+ on insulin, plasma NE, and rise in BP (ie, BPE) for 10 years in subjects who were normotensive at entry. The protocol measured BP, pulse, BMI, and plasma NE and insulin for 10 years in young (<50 years), nonobese (BMI <26.0 kg/m2), normotensive Japanese men. Data analysis compared these variables in those with and without BPE who were further subdivided into FH+ and FH− groups.

Methods

Subjects
A cohort of 1064 young normotensive Japanese men working in a factory in Osaka, Japan, were studied on an annual basis. Excluded
were 41 with obesity (BMI ≥26.0 kg/m²), 22 with diabetes mellitus (HbA1c >6.0%), 39 with a strong family history of diabetes, and 13 with heart disease. Additional exclusions were 241 subjects who were taking medications other than antihypertensive drugs, 3 subjects who had significant changes in BMI (≥1.0 kg/m²), and 158 subjects for whom a family history of hypertension was unknown. Consequently, 557 normotensive subjects were included in the study. At entry, individuals were young (mean±SD age, 39.1±2.1 years) and nonobese (BMI, 22.3±1.2 kg/m²). Normal BP was defined as the mean of three supine readings of ≤140/90 mm Hg. FH+ was defined as at least one parent’s having hypertension documented by previous medical records or by direct BP measurements in the parents. FH− was defined as both parents’ being normotensive. Informed consent was obtained from each subject as approved by the Ethics Committee of Osaka University Medical School.

Protocol
After subjects had fasted for 12 hours overnight, BP, pulse rate, and BMI were determined. After the subjects had rested for 30 minutes in the supine position in a quiet room, venous blood was taken for blood glucose, plasma insulin, and NE levels. Supine BP was measured three times and then averaged. BP and pulse rate were measured with an automated sphygmomanometer (TM-2711 or TM-2713, A&D), which was standardized against a mercury sphygmomanometer. Plasma NE was measured by the fluorometric method after separation by high-performance liquid chromatography. In this assay, the intra-assay CV was 2.1%, the interassay CV 3.6%, and sensitivity 0.01 to 20 ng/mL. Plasma immunoreactive insulin was measured by a standard radioimmunoassay method (insulin RIABEAD II, Dinabott). The intra-assay CV was 1.9%, the interassay CV 2.2%, and sensitivity 0.75 to 300 mU/mL. Blood glucose was measured by autoanalyzer (Hitachi-7050).

Statistical Analyses
Values are shown as mean ±SD. Changes in variables within each group and differences among groups were examined by two-way ANOVA. Dunnett’s test was used to determine whether the differences of the mean at 10 years from values at entry were significant among groups. The statistical analyses to compare prevalence of BPE and FH+ were performed by χ² test. Values of *P*<0.05 were considered significant.

Results
Of the total group, 87 of the 557 subjects (16%) were found to be FH+, and 103 of the 557 (18%) had a BPE during the study period. When analyzed by family history, the prevalence of BPE was 33% (29/87) in FH+ subjects versus 16% (74/470) in FH− subjects (*P*<0.05).

Figure 1 shows the mean ±SD systolic and diastolic levels of BP (top), mean age (middle), and mean BMI (bottom) at entry and at year 10 grouped by FH+ (right) and without (FH−, left) a family history of hypertension and with (≥10%) and without (<10%) BPE. Open and hatched bars indicate values at entry, and filled bars indicate values at year 10 compared with values in normotensives without a family history of hypertension. *P*<0.05 compared with values in normotensives without a family history of hypertension.

Mean BP levels at entry in FH+ was greater than FH− regardless of the BP change over time. In addition, in FH+, those with BPE had higher BP levels at entry and at year 10 compared with those without BPE. In FH− subjects, BP levels at entry were similar regardless of future BPE. Mean age did not differ in the four study groups at entry as well as at year 10 (Figure 1, middle). BMIs did not differ from each other at entry and year 10, nor did they change significantly in any study group (Figure 1, bottom).

Figure 2 shows mean fasting blood glucose (top), fasting plasma insulin (middle), and plasma NE (bottom) levels at entry and at year 10 in subjects subdivided by FH− (left) and FH+ (right). The groups were further subdivided by the presence (≥10%) or absence (<10%) of BPE. Fasting blood glucose levels were greater in FH+ than in FH− subjects (Figure 2, top). In FH+ who had a BPE, glucose levels were higher at year 10 compared with those at entry (*P*<0.05). Mean fasting plasma insulin levels increased significantly from entry to year 10 in the four study groups. These increments were greater in the BPE groups (Figure 2, middle). At entry and year 10, mean insulin levels were highest in the FH+ groups regardless of BPE (*P*<0.05). In general,
plasma insulin levels were highest in the group with combined FH+ and BPE. From entry to year 10, mean plasma NE levels increased significantly in all four study groups, but the rises were greater in the BPE groups. In the FH− group, entry plasma NE was significantly higher in the BPE group (P<0.05) but was not different in the FH+ group. At year 10, plasma NE levels were significantly higher in the BPE groups regardless of FH status (FH−, P<0.01; FH+, P<0.05; Figure 2, bottom).

Figure 3 shows that the increments and percent changes in insulin were higher in FH+ regardless of changes in BP over time. In the FH+ groups, insulin increments and percent changes were significantly greater in the BPE group (P<0.01 and P<0.01, respectively). Increments and percent changes in plasma NE were significantly higher in those with BPE whether FH+ or FH− (Figure 3). In the groups in which BP did not rise, there was no difference in NE increments between FH+ and FH− subjects. However, in the BPE groups, increments and percent changes in NE were greater in FH+ than FH−.

Discussion

In a previous study of the same cohort of 1064 subjects, we reported that sympathetic hyperactivity precedes hyperinsu-

linemia and BPE in young, nonobese Japanese men. The present report of the same population and study design examined the influence of FH+ on these variables. To study FH, 507 subjects were excluded, leaving 557 in whom the effects of FH could be examined without confounding variables. In this population, there was a 16% incidence of FH, as verified by medical records or direct BP measurements in their parents. Importantly, the occurrence of BPE over a 10-year period was much higher (33%) in the FH+ than in the FH− (16%) subjects. However, SNS hyperactivity, as indexed by plasma NE levels, contributed to BPE regardless of whether subjects were FH+ or FH−. Insulin was also associated with BPE, but compared with NE, the insulin increments were always greater in FH+ than in FH− groups. Thus, SNS hyperactivity may be a less genetically determined predictor of hypertension, whereas hyperinsulinemia is more genetically determined. These data also indicate that SNS activity may be more closely related to the early development of hypertension than to hyperinsulinemia and FH. These observations might imply that environmental rather than genetic factors play a greater role in the development of hypertension.

It should be noted that two important influences on BP, age and BMI, were matched at entry and remained comparable in each study group at year 10. Because BMI did not change, this study allows analysis of these neurogenic and metabolic variables on BP without the confounding effect of obesity. It can be concluded that obesity need not be a major prerequisite for BPE or for elevations in SNS and insulin. There is concern that plasma NE levels are merely a rough index of sympathetic nerve activity. However, in such a large population-based study as the present, more complex measures of SNS activity, such as microneurography and NE spillover, would not be feasible.

Several other studies have noted abnormal glucose and insulin metabolism in normotensive offspring of families with hypertension. Ferrari et al20 reported IR, greater insulin responses to glucose, and dyslipidemia in young normotensive males who were FH+. Beaty et al21 also found higher BP and IR in FH+ offspring. Neutel et al22 found higher insulin levels in normotensive individuals who were FH+. In that study as well as our present findings, FH+ also predicted other risk factors, such as higher levels of NE, renin, and cholesterol. Facchini et al23 noted greater insulin responses and IR in 38 normotensive subjects who were FH+. Ishibashi24 found higher insulin levels in 152 FH+ school-age girls compared with 131 FH− girls and noted an increased body weight in the FH+ girls. Ionic risk factors may also be important because FH+ with IR have abnormal erythrocyte Na+ transport25 and higher platelet calcium levels.26 One study included only lean normotensive subjects, suggesting, as in our study, that body weight may not be the major factor in the occurrence of metabolic abnormalities in FH+ subjects.27 The Heureka study of 11 001 participants reported that plasma insulin was correlated with BP in FH+ subjects only.27 One study noted higher levels of insulin and C peptide in both normotensive and essential hypertension subjects who were FH+.28 A recent study from Mexico City concluded that IR in FH+ subjects was more closely related to obesity than
In general, most of these family studies offer strong evidence that young normotensive subjects who are FH+ are at increased risk for BPE. These data also imply that hyperinsulinemia and IR precede the changes in BP. The majority of these studies were cross-sectional in data analysis. The present study differs from these reports because it presents the influence of FH on BPE and insulin with a longitudinal design and links the effects of SNS activity with the other variables.

We have also recently reported higher fasting and glucose-stimulated insulin and NE levels in FH+ compared with FH− subjects in three study groups: (1) normotensive subjects, (2) borderline hypertensives, and (3) established hypertensive subjects. A positive family history of hypertension was defined as both parents having hypertension. This cross-sectional study concluded that FH+ could be an important determinant of SNS activity and insulin in all three BP-level groups but could differ in contribution, depending on the stage of BPE. Thus, in normotensive subjects, increased SNS seemed to be the major finding, whereas in borderline hypertensives, increases in SNS and insulin were noted concurrently. Our previous work has also shown that normotensive subjects with hyperinsulinemia have greater plasma NE levels than those with normal insulin levels.

It is now well documented that vascular smooth muscle and the endothelium are insulin-sensitive tissues. Rowe et al first showed that infusion of large doses of insulin increased plasma NE levels and BP in normal subjects. Anderson et al using doses that were more physiological, found that insulin increased plasma NE but did not alter BP and reduced total peripheral resistance, suggesting an acute vasodilator effect. These studies suggest that if insulin affects BPE, it might do so through concomitant influences, such as genetic, metabolic, and neurogenic influences. Lembo et al noted abnormal SNS overactivity evoked by insulin in the skeletal muscle of subjects with essential hypertension. In addition, both adrenergic and cholinergic blockade altered the effect of insulin on calf blood flow. Of interest, infusion of insulin in subjects with established IR produced vasoconstriction rather than vasodilation. Baron demonstrated that the dose-dependent effects of insulin to increased leg blood flow are markedly impaired in obesity and type 2 diabetes mellitus. These studies support the present findings that in young, normotensive, nonobese men, the greater rise in insulin levels over 10 years in the BPE groups could be contributing to their rise in BP.

It has been argued whether the initial event in BPE is hyperactivity of the SNS, which then leads to increased insulin and BP levels, or whether higher BP activates these systems. Julius et al have proposed that prolonged stimulation of the SNS leads to elevated BP and plasma insulin levels. This “chicken-and-egg” question can only be resolved in longitudinal studies such as the present report, wherein NE, insulin, and BP levels can be examined over time in normotensive subjects. In support of the findings of Julius et al, we reported that in initially normotensive subjects who had a BPE over 10 years, SNS hyperactivity preceded the emergence of hyperinsulinemia. The present study links hyperinsulinemia and SNS hyperactivity to a family history of hypertension and BPE by use of a longitudinal design. The normotensive subjects with FH+ had greater BP, fasting insulin, and NE levels at any time compared with FH− subjects. Furthermore, in FH− subjects, plasma NE levels at entry and the increments in plasma NE during 10 years were

Figure 3. Absolute (left) and percent (right) increments during the 10-year period in plasma insulin (top) and plasma NE (bottom) levels. Open bars indicate values in subjects without BPE (< +10%), and hatched bar indicate values in subjects with BPE (≥ +10%).
greater in subjects with BPE than in those without BPE. Also, higher BP levels were recorded at entry in FH+ subjects with BPE. In contrast to NE and BP values, fasting plasma insulin levels at entry, increments in insulin, and percent increments in insulin over 10 years were similar between subjects with and without BPE in FH− subjects; however, in FH+ subjects, these measures were greater in subjects with BPE than in those without BPE.

In summary, SNS hyperactivity is more closely related to BPE than are insulin levels or FH+ in normotensive subjects. FH+ appears to be more closely related to increases in insulin. SNS hyperactivity appears to play a greater role in the development of hypertension in an normotensive population compared with insulin or genetic influences.

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References

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