Effects of Aging on the Insulin Actions for the Glucose Metabolism and Renal Function in Normotensives and Essential Hypertensives


It has been suggested that hyperinsulinemia compensating insulin resistance in glucose metabolism may be a pathogenic factor in essential hypertension. On the other hand, age-associated increases in the prevalence of glucose intolerance and hypertension are also well established. The aim of this study is to clarify the influence of aging on insulin sensitivity in glucose metabolism and on renal sodium handling under hyperinsulinemia, which may relate to high blood pressure in insulin-resistant subjects. Fifty-two normotensive subjects and 61 patients with essential hypertension were evaluated in this study. The subjects of these groups were divided into young (<40 years old) and middle-elderly (≥40 years old): young normotensives (Y-NT, n = 22); middle-elderly normotensives (ME-NT, n = 30); young hypertensives (Y-HT, n = 9); and middle-elderly hypertensives (ME-HT, n = 52). Using the euglycemic hyperinsulinemic glucose clamp, insulin sensitivity was assessed as M value. Just before the start and the termination of the glucose clamp, creatinine clearance (Ccr) and urinary excretion of sodium (UNaV) were measured. In addition, renal plasma flow assessed as para-aminohippuric acid clearance was also measured at the same time in several subjects; 8 Y-NT, 8 ME-NT, 3 Y-HT, and 10 ME-HT. The M value was significantly lower in ME-NT, Y-HT, and ME-HT, compared to Y-NT, although blood sugar and immunoreactive insulin levels were similar in all four groups. In normotensive subjects, there was a significant, negative correlation between age and M value. However, this correlation was not observed in hypertensive patients. UNaV decreased in ME-NT, Y-HT, and ME-HT, but not in Y-NT under hyperinsulinemia by the glucose clamp, whereas Ccr showed no significant change in any group. In all subjects, the change of UNaV (∆UNaV) correlated significantly and positively with the M value. Renal plasma flow significantly increased under hyperinsulinemia by the glucose clamp in only Y-HT, but not in the other groups. There was a significant, positive correlation between ∆UNaV and the change of renal plasma flow under hyperinsulinemia by the glucose clamp. These results suggested that both the impairments of the insulin sensitivity and insulin-induced vasodilation at the renal artery with aging may partially contribute to age-related elevation of blood pressure through renal sodium retention by compensating hyperinsulinemia. On the other hand, it seems reasonable to assume that these abnormalities, which can contribute to high blood pressure in essential hypertension, already may exist at lower ages in essential hypertensive patients. Am J Hypertens 1998;11:1056–1064 © 1998 American Journal of Hypertension, Ltd.

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EFFECTS OF AGING ON INSULIN ACTIONS IN HYPERTENSIVES

It has been revealed that insulin resistance and hyperinsulinemia are linked with essential hypertension. Hyperinsulinemia that compensates for insulin resistance is suggested to play some role in the onset and maintenance of hypertension by augmenting sodium reabsorption in renal tubules and pressor system activities.

It is also confirmed that prevalence of glucose intolerance and hypertension increase with age. Moreover, insulin resistance has been thought of as a common pathophysiologic factor in glucose intolerance and hypertension. An age-related reduction of insulin sensitivity was reported in healthy volunteers and in subjects with impaired glucose tolerance. However, the effect of aging on insulin sensitivity has hardly been studied in essential hypertensive patients.

On the other hand, as mentioned, the sodium-retaining action in hyperinsulinemia may be one of the pressor mechanisms in essential hypertensive patients with insulin resistance. However, using the glucose clamp, we noted that young healthy subjects did not show the sodium retention under hyperinsulinemia that was observed in insulin-resistant obese subjects or hypertensive patients under the same conditions.

We speculated that this inconsistency could be attributed to differences among the subjects in the changes of renal blood flow under hyperinsulinemia attributable to insulin-mediated vasodilation. However, there is also a complete absence of reports on the effect of aging on insulin-mediated renal sodium handling and renal hemodynamics in normotensive subjects or hypertensive patients using the euglycemic hyperinsulinemic glucose clamp.

**METHODS**

**Subjects** Fifty-two normotensive subjects and 61 patients with essential hypertension were evaluated in this study (Table 1). Both the normotensives and hypertensive subjects were divided into young (<40 years old) and middle-elderly (≥40 years old) groups; these groups were referred to as young normotensives (Y-NT), middle-elderly normotensives (ME-NT), young hypertensives (Y-HT), and middle-elderly hypertensives (ME-HT). The subjects were hospitalized and given a diet containing 120 mEq/day of sodium and 75 mEq/day of potassium. Drugs that affect insulin sensitivity and renal function were discontinued at least 2 weeks before the study in subjects receiving medical treatment. All subjects were screened for complications such as endocrine or metabolic disturbances, cerebrovascular or cardiovascular disease, and renal disease by routine physiologic and laboratory examinations; none showed any evidence of complications. The study was approved by the ethical committee of Sapporo Medical University, and informed consent was obtained from each subject.

**Methods** Study 2 Several subjects, 8 Y-NT, 8 ME-NT, 3 Y-HT, and 10 ME-HT, were also evaluated for the effect of...
hyperinsulinemia on renal plasma flow. At 8 AM on the morning of the study, these subjects drank 500 mL of water. At 8:30 AM an initial dose of 10% para-aminohippuric acid (10% PAH; 8.0 mg/kg) was injected for 5 min, subsequently the PAH was continuously infused at a constant rate of 12 mg/min\textsuperscript{19,20} to maintain the plasma PAH level at about 2 mg/dL. Throughout the study, at 10 am each subject drank water equivalent to the 2-h urine volume obtained between 8 to 10 am, and the glucose clamp was started. PAH clearances were measured using blood samples taken 30 min before the start and termination of the glucose clamp, and urine taken for 30 min before the start and termination of the glucose clamp. Blood and urine samples were obtained in the same way as mentioned in study 1 for measurements of Ccr and UNaV.

**Analytical Methods** The immunoreactive insulin level was measured by radioimmunoassays of Insulin RIA bead (Dainabot, Tokyo, Japan). PAH concentration was analyzed spectrophotometrically.

**Statistical Analysis** All data are expressed as mean ± SEM. The two-tailed Student’s t test for paired samples was used to compare changes before and during the glucose clamp within each group. One-way analysis of variance for multiple comparisons (Scheffe’s method) was used to compare the four groups. For relationships between pairs of variables, linear regression analysis was used. A level of \( P < .05 \) was considered statistically significant.

**RESULTS**

**Study 1** The four groups were matched for body mass index (Table 1). As shown in Table 1, mean blood pressure in the hypertensive patients was significantly higher than in the normotensive subjects. ME-NT had slightly but significantly higher mean blood pressure than Y-NT. There was no difference in mean blood pressure between Y-HT and ME-HT. The four groups had similar Ccr levels, fasting BS levels, and fasting IRI levels. Insulin sensitivity (M value) in ME-NT, Y-HT, and ME-HT was significantly lower than in Y-NT (Figure 1). There were no differences in M value among ME-NT, Y-HT, and ME-HT. A significant, negative correlation (\( n = 52, r = -0.48, P < .01 \)) was observed between age and M value in normotensives (Figure 2A). However, there was no significant correlation between age and M value in hypertensives (Figure 2B).

Under hyperinsulinemia by the glucose clamp, \( U_{NaV} \) was reduced in ME-NT, Y-HT, and ME-HT. There were no differences in M value among ME-NT, Y-HT, and ME-HT. A significant, negative correlation (\( n = 52, r = -0.48, P < .01 \)) was observed between age and M value in normotensives (Figure 2A). However, there was no significant correlation between age and M value in hypertensives (Figure 2B).

**FIGURE 1.** Comparison of insulin sensitivity (M value) among young (<40 years old) normotensives (Y-NT), middle-elderly (≥40 years old) normotensives (ME-NT), young hypertensives (Y-HT), and middle-elderly hypertensives (ME-HT).
showed no change during the glucose clamp (from 103.4 ± 13.9 to 101.5 ± 18.0 μEq/min). The changes of UNaV (ΔUNaV) of ME-NT, Y-HT, and ME-HT showed lower tendencies than that of Y-NT (Table 1). Before the glucose clamp, the baseline level of UNaV and Ccr were similar among the four groups. In addition, there were no significant changes in Ccr during the glucose clamp in all groups (Y-NT, from 136.9 ± 10.6 to 126.9 ± 9.7 mL/min; and ME-NT, from 117.8 ± 12.1 to 91.9 ± 7.0 mL/min; Y-HT, from 93.8 ± 11.8 to 100.5 ± 15.6 mL/min; ME-HT, from 105.2 ± 7.6 to 97.5 ± 4.2 mL/min). A significant positive correlation (n = 113, r = 0.224, P < 0.05) was observed between M value and ΔUNaV in all subjects (Figure 2C).

Study 2 Clinical characteristics of four subgroups (8 Y-NT, 8 ME-NT, 3 Y-HT, 10 ME-HT) are shown in Table 2. The four groups had similar body mass index, fasting BS, fasting IRI, Ccr, and UNaV levels before the glucose clamp. The M value of ME-HT was significantly lower than that of Y-NT and that of ME-NT and Y-HT also showed a lower tendency. Under hyperinsulinemia by the glucose clamp, the UNaV level of ME-HT significantly decreased (from 220.9 ± 29.2 to 136.3 ± 12.4 μEq/min, P < 0.05), and that of ME-NT and Y-HT showed a decreasing tendency (ME-NT, from 201.5 ± 32.6 to 152.5 ± 20.2 μEq/min; Y-HT, from 180.6 ± 33.2 to 144.1 ± 42.2 μEq/min). In contrast that of Y-NT tended to increase under hyperinsu-
levels did not change during the glucose clamp in any group. The changes of RPF during the glucose clamp (∆RPF) of ME-NT, Y-HT, and ME-HT were significantly lower than that of Y-NT (Y-NT, 306.6 ± 80.2; ME-NT, 31.3 ± 13.8; Y-HT, −72.4 ± 54.5; ME-HT, −64.3 ± 61.1 mL/min) (Figure 3B). There was significant correlation between ∆RPF and ∆UNaV (r = 0.49, P < .01). Moreover, there was significant correlation between M value and ∆RPF (r = 0.47, P < .05) (Figure 4).

DISCUSSION

In this study, using the euglycemic hyperinsulinemic glucose clamp, we clarified the effects of aging on the glucose disposal rate under hyperinsulinemia (the insulin sensitivity) and the action of hyperinsulinemia on renal function, in young (<40 years old) normotensives, middle-elderly (≥40 years old) normotensives, young hypertensives, and middle-elderly hypertensives.

Several studies have confirmed that insulin sensitivity declines with age in normotensive subjects.12–16 Our result is consistent with those reports, and in addition we found that there was no discernible influence of aging on the insulin sensitivity in essential hypertensives in this study. An age-related decline of glucose tolerance has been known for several decades.10 This phenomenon has been attributed to both a decreasing capacity to secrete insulin from the pancreas and a decline in insulin sensitivity. The insulin resistance observed in elderly subjects can be held at least partially responsible for the age-related increase in the prevalence of glucose intolerance or hypertension. The exact mechanism responsible for this diminished insulin sensitivity in the elderly remains unclear. The following factors have been implicated in this phenomenon: 1) a decrease in muscle volume due to reduced daily activity21; 2) a decrease in insulin and glucose delivery by attenuated capillary vessels in the musculature22; 3) an increase in visceral fat13; 4) abnormalities in receptor binding or number14; 5) defects in postreceptor signal transduction15,16; and 6) abnormalities in intracellular concentration of calcium and magnesium.23

One of the important findings in this study is the lack of an age-dependent decline in the insulin sensitivity of essential hypertensives. Although there was an empiric limitation due to the relatively small number of Y-HT, the M value in this group was significantly lower, compared with that of Y-NT (Y-NT, 74.6 ± 52.3; ME-NT, −64.5 ± 34.1; Y-HT, −36.6 ± 10.8; ME-HT, −84.6 ± 24.2 μEq/min). In addition, renal plasma flow (RPF) assessed as PAH clearance, significantly increased under hyperinsulinemia in only Y-NT (from 464.4 ± 51.8 to 771.0 ± 40.8 mL/min, P < .01). In other groups, RPF did not change during the glucose clamp (ME-NT, from 564.4 ± 52.3 to 595.7 ± 53.9 mL/min; Y-HT, from 526.5 ± 77.4 to 454.1 ± 23.1 mL/min; and ME-HT, from 553.9 ± 68.0 to 489.6 ± 61.4 mL/min). The basal RPF levels before the glucose clamp were similar among the four groups, and Ccr
hypertension had insulin resistance. From these facts, it seems unlikely that aging affects the insulin sensitivity of hypertensives, as they are in an insulin-resistant state well before they overtly manifest hypertension. Rather than being a result of high blood pressure, insulin resistance may actually contribute to the genesis of essential hypertension. However, the M value of ME-NT did not differ from those of Y-HT or ME-HT (Figure 1), which suggests that insulin resistance could not induce hypertension by itself alone and some other genetic predisposition may be necessary for the onset of essential hypertension. As common mechanisms for insulin resistance between aging and hypertension, the following possibilities can be suggested: 1) an intracellular excess of calcium ion or a decrease in magnesium ion; and 2) structural vascular change, namely vascular rarefaction and sclerosis in musculature.

Turning now to the effect of aging on renal sodium metabolism under hyperinsulinemia, several studies have reported that hyperinsulinemia may induce renal sodium retention, which can relate to elevation of blood pressure in hypertensive patients with insulin resistance. In this study, sodium retention was observed in ME-NT, Y-HT, and ME-HT under hyperinsulinemia by the glucose clamp. In Y-NT, however, sodium excretion was not reduced under hyperinsulinemia, and this result was different from the results of other studies. We are not certain why the difference in the results between other studies and our study with respect to the effect of hyperinsulinemia on sodium excretion in young normotensive subjects. Age and body mass index of the subjects are nearly similar between those studies and ours. Four mechanisms whereby hyperinsulinemia can have an influence on renal sodium metabolism have been suggested: 1) insulin can directly enhance sodium reabsorption in the proximal or distal tubules of the kidney; 2) insulin increases the sympathetic nervous system and the renin-angiotensin system activity and thereby could indirectly induce sodium retention; 3) insulin and glucose independently induce the increase in intracellular sodium, which can contribute to the sodium retention and decrease in renal sodium excretion; and 4) insulin may increase renal blood flow due to insulin-induced vasodilation, which decreases sodium reabsorption at tubules of the kidney. Therefore, sodium metabolism under hyperinsulinemia might be controlled by the counterbalance between the sodium-retaining action and the natriuretic action. It is inconceivable that the actions of insulin on renal tubules, intracellular sodium metabolism, and the sympathetic nervous system and renin-angiotensin system are attenuated only in Y-NT.
plasma glucose level was clamped at 80 mg/dL during the glucose clamp in all subjects of each group, therefore the effects of the difference in plasma glucose level on renal sodium metabolism may be negligible. Furthermore, we have already reported that hyperinsulinemia by the glucose clamp increases plasma norepinephrine levels and plasma renin activity in Y-NT as was also observed in middle-aged normotensives and hypertensives. Therefore, the difference in responses of renal sodium excretion to hyperinsulinemia between Y-NT and other groups cannot be explained by mechanisms 1, 2, and 3. Another contributing factor to renal sodium metabolism by hyperinsulinemia is the vasodilating action of insulin, which may increase renal blood flow and attenuate sodium reabsorption at the proximal tubules in the kidney. On the other hand, Feldman and Bierbrier reported that the potency of insulin as a vasodilator was impaired in hypertensive patients or obese subjects who may have insulin resistance. If this holds true in the renal artery, it could contribute to sodium retention under hyperinsulinemia in ME-NT, Y-HT, and ME-HT who showed insulin resistance. The positive correlation between M value and $\Delta U_{NaV}$ under hyperinsulinemia observed in all subjects (Figure 2C) is suggestive of the relevance between impaired insulin-induced dilation at the renal artery and insulin resistance.

We then investigated the effect of hyperinsulinemia on renal plasma flow in 8 Y-NT, 8 ME-NT, 3 Y-HT, and 10 ME-HT. As in study 1, they had similar body mass index, fasting BS, fasting IRI, and Cr levels. The M value was significantly lower in only ME-HT, and those of ME-NT or Y-HT tended to be lower, compared with that of Y-NT. As shown in Figure 3, there were sharp contrasts in the changes of $U_{NaV}$ or RPF under hyperinsulinemia between Y-NT and the other groups. Furthermore, $\Delta U_{NaV}$ positively correlated with $\Delta$RPF (Figure 4A), which indicates that the change in RPF may play an important role in renal sodium metabolism under hyperinsulinemia. In addition, there was significantly positive correlation between M value and $\Delta$RPF (Figure 4B). Attenuated insulin-mediated skeletal muscle blood flow is thought to contribute to insulin resistance in glucose metabolism through a decrease in the delivery of glucose or insulin to the muscle. Our results implicate that insulin-induced vasodilation at the renal artery may also be impaired in subjects with insulin resistance. With regard to the change of renal blood flow under hyperinsulinemia, the results have been controversial. Some studies reported that hyperinsulinemia increased renal blood flow, others reported that renal blood flow showed no change under hyperinsulinemia. However, those reports examined the renal blood flow under hyperinsulinemia without distinction of age or insulin sensitivity. In our study, renal plasma flow significantly increased under hyperinsulinemia only in Y-NT, but not in ME-NT, Y-HT, and ME-HT who have insulin resistance. In addition, in studies with young normotensive subjects, only one study measured RPF before and under hyperinsulinemia by the glucose clamp, and RPF did not significantly change under hyperinsulinemia. Therefore, sodium retention under hyperinsulinemia might be observed even in young normotensive subjects in that study. However, we cannot explain why renal plasma flow did not increase in that study. On the other hand, several studies have reported that insulin resistance and compensatory hyperinsulinemia can play an important role in the pathogenesis of salt-sensitive hypertension. Weir noted that insulin resistance can be associated with renal hemodynamic abnormality, namely an impairment in renal blood flow in response to high salt diet, which may contribute to salt-sensitive hypertension. Our results are partially in agreement with those studies with respect to renal hemodynamic abnormality in insulin-resistant subjects. It has been reported that insulin has both vasodilator and vasoconstrictor (sympathetic) actions. We can speculate that accumulation of intracellular calcium or structural vascular change (capillary rarefaction and sclerosis), which can be observed in elderly subjects and patients with hypertension, may contribute to insulin resistance and impairment of insulin-induced vasodilation. This abnormality can relate to renal sodium retention under hyperinsulinemia in subjects with insulin resistance. However, details of the mechanism remains unclear.

In summary, 1) insulin sensitivity declines with age in normotensive subjects, 2) in essential hypertensive patients, insulin sensitivity may be already reduced at a lower age and is independent of aging, 3) the renal sodium-retaining action of hyperinsulinemia is observed in subjects with insulin resistance such as middle-aged hypertensives and hypertensives, but not in young normotensives, and 4) hyperinsulinemia can increase renal plasma flow due to insulin-induced vasodilation only in young normotensives, and this may exceed the sodium-retaining action of hyperinsulinemia.

These results suggest that both the impairments of insulin sensitivity in glucose metabolism and insulin-induced vasodilation at the renal artery may partially contribute to age-related elevation of blood pressure through renal sodium retention by hyperinsulinemia. On the other hand, it seems reasonable to assume that these abnormalities, which can contribute to high blood pressure in essential hypertension, already may exist at lower ages in essential hypertensive patients.
REFERENCES


