Sex-Specific Effects of an Insulin Secretagogue in Stroke-Prone Hypertensive Rats

Jacob D. Peuler, Barbara A.B. Johnson, Susan M. Phare, James R. Sowers

Glyburide, an insulin secretagogue and an insulin-sensitizing agent, lowers blood pressure in normal male and female dogs when administered acutely. Because insulin resistance may contribute to spontaneous hypertension in rats, we sought to determine if long-term administration of glyburide (5 mg/kg per day by diet, age 5 weeks to 5 months) would lower blood pressure in male and female stroke-prone spontaneously hypertensive rats. Arterial (aortic) rings from these rats were incubated with insulin in vitro (100 mU/mL) 1 hour before and during phenylephrine-induced contraction to determine if long-term glyburide administration improves vascular sensitivity to the intrinsic vasodilator action of insulin. Glyburide, however, significantly increased blood pressures and ratios of heart weight to body weight in 5-month-old female rats (+20 mm Hg diastolic, $P < .05$), with no significant change noted in male rats (+4 mm Hg diastolic). Glyburide increased plasma insulin levels (twofold, $P < .04$) in female but not in male rats. Glyburide did not affect plasma glucose or catecholamine levels. After incubation with insulin, aortic rings from glyburide-treated female rats demonstrated more than 40% greater contractile responsiveness to phenylephrine compared with aortic rings from control female rats ($P < .04$). This insulin-dependent increase in phenylephrine-induced contraction consisted of a reversal in the in vitro action of insulin, from attenuation to accentuation of such contraction ($P < .05$). This change was not seen in male rats. Neither gender, glyburide, nor insulin influenced acetylcholine-induced relaxation of phenylephrine-induced contraction. Insulin in vitro slightly increased nitroprusside-induced relaxation ($P < .05$) of aortic rings from female but not from male rats, and glyburide administration abolished this increase. Thus, long-term glyburide administration aggravates hypertension selectively in female stroke-prone spontaneously hypertensive rats. This aggravation may be due to a sustained increase in circulating insulin accompanied by emergence of a paradoxical vasoconstrictor sensitivity to insulin in vascular smooth muscle. *Hypertension* 1993;22:214-220

**KEY WORDS** • vascular resistance • insulin • sulfonylurea compounds • catecholamines • glucose • gender

There is considerable evidence that the insulin resistance and hyperinsulinemia of diabetes also exists in essential hypertension and in various genetic models of hypertension such as Zucker obese, Dahl salt-sensitive, and spontaneously hypertensive rats (SHR).2-4 Recently, two separate classes of antidiabetic, insulin-sensitizing agents (biguanides and thiazolidinediones) were reported to attenuate hypertension in these animal models.5-7 Glyburide (a second-generation sulfonylurea antidiabetic agent) has been reported to decrease blood pressure when administered acutely to normal male and female dogs.8,9 Sulfonylurea agents are insulin secretagogues but have also been reported to sensitize peripheral tissues to insulin actions.10,11 We sought to determine if long-term administration of glyburide would lower blood pressure in the combined form of salt-sensitive and spontaneous hypertension bred into the stroke-prone spontaneously hypertensive rat (SHRSP). This rat and its hypertensive parent (SHR) were originally derived from normal Wistar rats.

Various mechanisms have been proposed to explain the possible contribution of insulin resistance to hypertension. The hyperinsulinemia that often accompanies insulin resistance may elevate blood pressure by stimulating sodium retention and sympathetic neural activity. Insulin can also alter vascular smooth muscle responsiveness to endogenous vasoactive substances, and this action is relatively more complex. For example, insulin in vitro is capable of both attenuating12-16 and accentuating13,15,17,18 adrenergically mediated contractile responses of arterial tissues and can do so in vessels of various sizes ranging from aortas to arterioles. At present, little is known about those factors that mediate opposing vasodilator and vasoconstrictor effects of insulin in arterial tissues except that both require sufficient time to appear (1 to 2 hours in vitro) due to dependence on protein synthesis.14,17 Both can be demonstrated with either low (physiological) or high (pharmacological) levels of insulin,13,15,18 and the vasoconstrictor effect appears more frequently in female than in male Wistar rats.13 Recently, the hypertensive, insulin-resistant and hyperinsulinemc Zucker obese rat demonstrated diminished ability of insulin in vitro to atten-
ulate aortic contractile responses to phenylephrine when compared with normal Zucker lean rats. Otherwise, little is known about either intrinsic arterial vascular sensitivity to insulin in hypertension or modulation of that sensitivity by insulin-sensitizing or insulin-secretory agents. Therefore, we sought to determine if glyburide alters vascular sensitivity to insulin in either male or female SHRSP consistent with its effects on blood pressure.

Methods

Thirty male and 30 female SHRSP were obtained from a colony at the University of Michigan, Ann Arbor, Mich. They were randomly segregated into two groups per gender (15 animals per group) at age 5 weeks and fed the following synthetic diets (Purina, Richmond, Ind) ad libitum with free access to water until age 5 months: a control diet high in salt (6% NaCl) or a glyburide diet (control diet mixed with glibenclamide, approximately 5 mg/kg per day). High salt was fed because hypertension in SHRSP is salt sensitive, and salt sensitivity has been associated with insulin resistance in humans. The glyburide (U-26452) was supplied by The Upjohn Co, Kalamazoo, Mich. Body weight and food intake were monitored at regular intervals to permit experimental adjustment of glyburide concentration in the food. From age 5 to 7 weeks, these adjustments were performed twice weekly with powdered food. From age 7 weeks to 5 months, they were performed weekly with admixtures of food pellets containing different glyburide concentrations. Others have administered glyburide in food admixtures at 10 mg/kg per day to both male and female rats for up to 1 year without toxic effects.

All other measurements were performed with rats at age 5 months. In accordance with institutional guidelines, each rat was instrumented with vascular catheters while anesthetized with methohexital sodium (40 mg/kg intraperitoneal, IP), as described previously. A thin nonthrombogenic (PTFE) abdominal aortic catheter was inserted through the ventral tail artery and a polyethylene catheter into the right femoral vein. Three days later, arterial pressure was monitored for several hours during the day (9 AM to 5 PM) in awake, unrestrained rats. Rats were not allowed food during this 8-hour interval. At 5 PM, an arterial blood sample (approximately 0.8 mL) was obtained for later analysis of plasma glucose by oxidation (Glucose Analyzer, Yellow Springs Instrument Co, Yellow Springs, Ohio), catecholamines by radioenzymatic assay (Amersham Corp, Arlington Heights, Ill), and insulin by radioimmunoassay (INCSTAR, Stillwater, Minn).

After another 1 to 2 days, each rat was anesthetized with sodium pentobarbital (40 mg/kg IV) and killed. The heart was removed and weighed, and the thoracic aorta was removed and placed in an ice-chilled buffer containing the following (mol/L): NaCl, 130; NaHCO₃, 15.0; KCl, 4.7; KH₂PO₄, 1.2; CaCl₂, 1.6; MgSO₄, 1.2; Na₂EDTA, 0.03; and glucose, 5.6. The aorta was cut into four 2-mm rings that were individually suspended by isometric force transducers (Gould Instruments, Cleveland, Ohio) from two muscle baths (two rings per bath) containing the same buffer warmed to 37°C and aerated with 95% O₂-5% CO₂ to achieve a stable pH of 7.4. All aortic rings were stretched mechanically to a baseline tension of 2.5 g (± less than 0.1 g per group), which in preliminary experiments optimized tension induced by phenylephrine. After 30 minutes, human insulin (100 mU/mL; Novolin R, Novo Nordisk Pharmaceuticals, Inc, Princeton, NJ) was added to one bath and vehicle (0.0002% phenol) to the second bath. One hour later, the aortic rings in both baths were contracted with phenylephrine administered cumulatively from 10⁻⁸ to 10⁻⁵ mol/L. The dose-response data were evaluated by regression analysis with a multiparameter logistic equation to obtain best estimates of maximal tension and the half-maximal effective dose (ED₅₀) for phenylephrine. Then acetylcholine was added (4×10⁻⁶ mol/L) followed 10 minutes later by nitroprusside (10⁻⁵ mol/L) to assess maximal endothelium-dependent and -independent relaxations, respectively. These data were expressed as percent relaxation of the maximum phenylephrine-induced tension.

All data are summarized as mean±SEM for each group, transformed if necessary to achieve homogeneity of variance and then subjected to two-factor analysis of variance and multiple mean comparisons. Differences between factor levels and corresponding individual group means were considered statistically significant if the error probability was less than .05.

Results

Five glyburide-fed and four control rats of each sex died spontaneously between ages 2 and 5 months. Death was either sudden or preceded by clinical signs of stroke. For a few rats (two glyburide-fed females, one control female, and one glyburide-fed male), such signs appeared within a few days before scheduled removal of vascular tissues for contractility studies.

Body weights were similar among all rats on initiation of experimental diets at age 5 weeks (mean±SEM, 15 rats each: 81±3 and 80±2 g, glyburide-fed and control female rats; 87±4 and 86±3 g, glyburide-fed and control male rats). By age 5 months, body weights were substantially less in female compared with male rats and were not affected by glyburide (Table 1). Ad libitum food intake was often slightly less in female compared with male rats. This was seen as early as 1 week (P<.01) after initiation of experimental diets (mean±SEM, 15 rats each: 10.2±0.2 and 10.9±0.4 g per rat per day, glyburide-fed and control female rats; 12.3±0.4 and 13.3±0.3 g per rat per day, glyburide-fed and control male rats).

Diastolic blood pressure and heart weight (independent of body weight) were both significantly increased by glyburide in female but not in male rats at age 5 months (Table 1). Increases were observed in systolic and mean arterial pressures in the same female rats, but these increases were slightly less in magnitude and did not achieve statistical significance (P=.2). Plasma insulin concentration in control male rats was twice that seen in control female rats (Table 2). This difference was abolished by glyburide, which increased plasma insulin by twofold in females but did not affect plasma insulin in males (Table 2). Plasma glucose and catecholamines were not influenced by glyburide in either sex.

The insulin pretreatment of aortic rings in vitro did not affect their baseline tension during the 1 hour before phenylephrine administration. There was an overall trend for aortic rings isolated from glyburide-fed
TABLE 1. Direct Arterial Pressures, Heart Weight, and Body Weight in Stroke-Prone Spontaneously Hypertensive Rats After Long-term Oral Glyburide Administration

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Female rats</th>
<th>Male rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Glyburide</td>
</tr>
<tr>
<td>Arterial pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>243 ±7</td>
<td>259 ±6</td>
</tr>
<tr>
<td>Mean (mm Hg)</td>
<td>187 ±7</td>
<td>200 ±7</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>147 ±6</td>
<td>167 ±7*</td>
</tr>
<tr>
<td>Heart weight (mg)</td>
<td>1043 ±26</td>
<td>1163 ±38*</td>
</tr>
<tr>
<td>Heart weight-body weight ratio</td>
<td>594 ±20</td>
<td>660 ±28*</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>177 ±6</td>
<td>177 ±4</td>
</tr>
</tbody>
</table>

Values are mean ± SEM of 8 to 10 rats per group.

*P < .05 vs control rats.
†P < .05 vs female rats.

rats to demonstrate increased contractile tension in response to the phenylephrine when compared with rings isolated from control rats (Figs 1 and 2). However, this increase in tension achieved statistical significance (P < .05) only for those rings isolated from females and then only if they were treated with insulin in vitro 1 hour before and during administration of the phenylephrine (Fig 1). At phenylephrine concentrations ranging from 10^-7 to 10^-2 mol/L, the insulin-treated aortic rings from glyburide-fed females averaged more than 40% greater tension than those from control females (P < .04). Other non-insulin-treated aortic rings from the same female rats averaged only 10% greater tension (due to glyburide) over the same range of phenylephrine concentrations (P ≥ .5). Aortic rings from glyburide-fed males averaged 30% and 34% greater phenylephrine-induced tension when compared with aortic rings from control males, with and without insulin treatment, respectively (Fig 2). These increases in male rats achieved a level of only borderline significance (P ≤ .1) and only at a limited number of phenylephrine concentrations.

The insulin dependence of the glyburide-related increase in phenylephrine-induced tension seen in aortic rings from female rats (Fig 1) consisted of a reversal of the in vitro action of insulin, from attenuation to accentuation of such tension. This reversal is illustrated in Fig 3, which shows changes produced by the in vitro insulin in maximum phenylephrine-induced tensions as seen at 10^-5 mol/L phenylephrine. This reversal was also seen at lower phenylephrine concentrations (10^-7 to 4 x 10^-6 mol/L). In other words, although the presence of insulin in vitro appeared to attenuate phenylephrine-induced contractions in aortic rings from control female rats, it actually accentuated such contractions in aortic rings from glyburide-fed female rats. This reversal was not seen in male rats (Fig 3). Indeed, insulin exerted no effect at all on phenylephrine-induced tension in aortic rings from male rats (Fig 3). Two-way analysis of variance on data illustrated in Fig 3 revealed a significant interaction between gender and glyburide (P < .05) on the ability of insulin to alter phenylephrine-induced tension in vitro.

Maximum phenylephrine-induced tension values as determined by regression analysis were identical to those seen at 10^-5 mol/L phenylephrine (data not shown). Half-maximal effective doses (ED_m) for phenylephrine-induced aortic ring tension as determined by regression analysis were not significantly influenced by gender, glyburide, or insulin. An overall tendency for glyburide to decrease these ED_m values was seen, but it was not significant (data not shown).

No statistically significant differences in maximal acetylcholine-dependent relaxations of phenylephrine-induced tensions were apparent (Table 3). However, there were significant differences in maximal nitroprusside-dependent relaxations of phenylephrine-induced tensions (Table 3). In aortic rings from female rats, insulin in vitro slightly increased this relaxation, and

TABLE 2. Circulating Insulin, Glucose, and Catecholamines in Stroke-Prone Spontaneously Hypertensive Rats After Long-term Oral Glyburide Administration

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Female rats</th>
<th>Male rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Glyburide</td>
</tr>
<tr>
<td>Plasma insulin (µU/mL)</td>
<td>32 ±7 (9)</td>
<td>62 ±13 (8)*</td>
</tr>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>105 ±5 (9)</td>
<td>116 ±14 (8)</td>
</tr>
<tr>
<td>Plasma norepinephrine (pg/mL)</td>
<td>253 ±38 (9)</td>
<td>299 ±31 (8)</td>
</tr>
<tr>
<td>Plasma epinephrine (pg/mL)</td>
<td>212 ±43 (9)</td>
<td>260 ±43 (8)</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Number of rats per group shown in parentheses.

*P < .05 vs control rats.
†P < .05 vs female rats.
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Glyburide abolished the effect. In aortic rings from male rats, glyburide attenuated nitroprusside-dependent relaxation independent of the presence of insulin in vitro.

Discussion

There are three noteworthy findings from the present study. First, long-term glyburide administration did not, as we hypothesized, decrease blood pressure in SHRSP. Rather, it significantly increased diastolic blood pressure selectively in SHRSP of the female gender. Second, glyburide induced a twofold increase in circulating insulin in female SHRSP. Third, glyburide induced an insulin-dependent increase in adrenergically mediated contraction of arterial tissue isolated from female but not from male SHRSP.

We had hypothesized that long-term glyburide administration would decrease blood pressure chronically in SHRSP because it does so acutely in normal dogs and because other hypoglycemic agents decrease blood pressure chronically in other genetic rat models of hypertension, including SHR. We do not know if transient acute changes in blood pressure occurred in our SHRSP. However, glyburide clearly did not decrease blood pressure chronically in either male or female SHRSP. Rather, glyburide appeared to cause a sustained increase in blood pressure in female SHRSP. After nearly 4 months of glyburide administration, diastolic blood pressures in awake resting rats and ratios of heart weight to body weight were both increased significantly in female SHRSP. These measures also tended to be increased in male SHRSP, but these tendencies were not statistically significant. Thus, the blood pressure effect of glyburide contrasts with a new class of agents (the thiazolidinediones) that reduce blood pressure in other hypertensive rats, including female Zucker obese rats, in which plasma insulin levels are also markedly reduced along with the blood pressure. Interestingly, others recently reported a specific association between increases in diastolic (but not systolic) blood pressures and prehypertensive fasting insulin levels in hypertensive women.

The specific increase in blood pressure produced by glyburide in female SHRSP was accompanied by equally specific increases in the circulating level of insulin and intrinsic vascular contractile responses to adrenergic stimulation in the presence of insulin in vitro. Together, these increases provide a reasonable explanation for the observed increase in blood pressure. The increase in circulating insulin in female SHRSP could also stimulate sympathetic neural activity and sodium retention, both of which could potentially contribute to the increase in blood pressure. However, there are several reasons to question whether these changes actually occurred or could sustain an increase in blood pressure.

In other species, plasma catecholamines are increased after 2 hours but not after 7 days of insulin infusion. We measured plasma catecholamines and found levels similar to those reported previously for SHRSP. We observed plasma epinephrine levels that appeared to be unusually high for resting animals. But in SHRSP, such elevated epinephrine levels are
induced by high salt intake, which is thought to stimulate their sympathetic nervous system activity centrally and is known to impair their catecholamine reuptake into sympathetic terminals peripherally.\textsuperscript{20,34,35} Most importantly, we did not observe a specific insulin- or glyburide-related increase in either epinephrine or norepinephrine in either female or male SHRSP. Recently, we found a difference in blood pressure between hypertensive Zucker obese rats and normal Zucker lean rats that remained intact after ganglionic blockade of sympathetic neural traffic.\textsuperscript{20,34,35} Most importantly, we did not observe a specific insulin- or glyburide-related increase in either epinephrine or norepinephrine in either female or male SHRSP. Recently, we found a difference in blood pressure between hypertensive Zucker obese rats and normal Zucker lean rats that remained intact after ganglionic blockade of sympathetic neural traffic.\textsuperscript{20,34,35} Even acute increases in actual sympathetic neural traffic produced by intravenous insulin are not associated with increases in blood pressure in humans\textsuperscript{27,28} except when accompanied by increased vascular resistance.\textsuperscript{26} Similarly, there is no convincing evidence that sodium retention associated with hyperinsulinemia could itself cause hypertension. Rather, there are several examples of insulin-induced changes in sodium balance that appear to be independent of changes in blood pressure.\textsuperscript{29-31,33,37} Finally, it is noteworthy that glyburide can exert a direct diuretic action\textsuperscript{38} that could partially counterbalance the sodium-retaining effect of insulin.

Plasma glucose levels were not reduced by glyburide in either female or male SHRSP after nearly 4 months of administration. We did not measure plasma glucose initially, but others have reported "escape" from early hypoglycemic effects of glyburide in normal rats of both sexes and in diabetes-prone rats after similar long-term administrations.\textsuperscript{22,39} However, even if such escape occurred in our SHRSP, it does not readily explain the long-term sex-specific hyperinsulinemic and hypertensive effects of glyburide.

As previously observed by Levy et al\textsuperscript{40} in normal adult male and female Sprague-Dawley rats, we found that baseline (control) levels of plasma insulin were twice as high in adult male compared with adult female SHRSP. As also seen in adult Sprague-Dawley rats,\textsuperscript{40} this difference coincides with a substantial difference in adult body weight between male and female SHRSP at the time insulin levels were measured. Glyburide abolished this difference in insulin levels by increasing plasma insulin only in adult female SHRSP. In Sprague-Dawley rats, the sex-related difference in circulating baseline insulin as seen in adults is not seen in young (6-week-old) animals.\textsuperscript{40} Thus, by initiating long-term glyburide treatment at a young age (5 weeks), we may have disrupted development of a normal difference between mature male and female SHRSP in terms of the rate of insulin secretion. However, the development of a normal difference in body weight between our male and female SHRSP was not affected by glyburide. In addition, without actual measures of plasma insulin at age 5 weeks in SHRSP, we cannot fully substantiate this notion.

A second possible explanation for the sex-specific hyperinsulinemic response to glyburide could be an inherent difference in long-term sensitivity of pancreatic beta cells to the insulin-secretory action of glyburide. Sulfonylureas can produce long-term increases in circulating insulin.\textsuperscript{10} Furthermore, long-term decreases in circulating insulin after a single neonatal injection of streptozocin (which impairs beta cell function) also differ between male and female rats despite similar increases in plasma glucose.\textsuperscript{40} A third explanation is that glyburide could paradoxically decrease rather than increase sensitivity of certain peripheral tissues (eg, liver and skeletal muscle) to metabolic effects of insulin.

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Measurement} & \textbf{Female rats} & & \textbf{Male rats} & \\
& \textbf{Control} & \textbf{Glyburide} & \textbf{Control} & \textbf{Glyburide} \\
\hline
Maximum relaxation by acetylcholine (\%) & & & & \\
Without insulin & 28±4 & 31±3 & 36±5 & 27±3 \\
With insulin\textsuperscript{*} & 30±3 & 29±3 & 34±4 & 28±3 \\
Change by insulin & +2±2 & -2±1 & -2±2 & +1±2 \\
\hline
Maximum relaxation by nitroprusside (\%) & & & & \\
Without insulin & 103±4 & 105±4 & 128±11 & 103±5\textdagger \\
With insulin\textsuperscript{*} & 113±4 & 105±4 & 128±8 & 106±8\textdagger \\
Change by insulin & +10±4\textdagger & -2±4 & 0±5 & +3±4 \\
\hline
\end{tabular}
\caption{Endothelium-Dependent and -Independent Relaxation of Phenylephrine-Induced Aortic-Ring Tension in Stroke-Prone Spontaneously Hypertensive Rats After Long-term Oral Glyburide Administration}
\end{table}

Values are mean±SEM of 9 to 10 rats per group.
\textsuperscript{*}Rings incubated with 100 mU/mL insulin.
\textsuperscript{\dagger}P<.05 vs control rats.
\textsuperscript{\ddagger}P<.05 vs zero change (paired t).
actions of insulin in female but not in male SHRSP. Indeed, long-term oral glyburide administration slightly increased the plasma level of glucose in our female rats. Additional experiments at multiple ages will be necessary to determine which of these or other mechanisms are responsible for the sex-specific hyperinsulinemic response to glyburide.

The most provocative findings from the present study relate to effects of long-term glyburide administration in vivo on arterial contractile responses to adrenergic and nitric oxide forms of stimulation in vitro. These effects were most likely related to smooth muscle and not endothelium, as they involved phenylephrine and nitroprusside but not acetylcholine. Furthermore, because the action of at least two smooth muscle cell receptors was involved, the influence of long-term glyburide therapy in vivo most likely engages postreceptor smooth muscle cell mechanisms. The same argument would apply to the insulin dependence of the vascular effects of glyburide as seen in female SHRSP. Glyburide effected a change in direction of insulin action, from vasodilatation to vasoconstriction, rather than simply a change in magnitude of either action.

This reversal in the ability of insulin in vitro to modulate intrinsic vascular reactivity has not been reported previously. Others have seen vasoconstrictor sensitivity to insulin in several tissues including rat aorta but not its induction by long-term antidiabetic drug administration nor its specific association with long-term increases in blood pressure and circulating insulin. One other laboratory has reported an influence of gender on the in vitro vascular effects of insulin seen without antidiabetic drug administration. Alexander and Oake reported that exposure of tail arterial tissues from normal male Wistar rats to either physiological or pharmacological levels of insulin attenuated all individual vasoconstrictor responses to norepinephrine by more than 40% on the average. In the same study, similar exposure to insulin of tail arterial tissues from female Wistar rats attenuated more but accentuated some individual vasoconstrictor responses to norepinephrine with a net insignificant effect of only 12% attenuation. Alexander and Oake suggested that these mixed effects of insulin on arterial tissues from individual female rats related to hormonal changes associated with estrus. We speculate that by chronically elevating circulating insulin in female SHRSP, glyburide unmasked increased expression of a preexisting interaction between female sex hormones and insulin that is capable of accentuating adrenergically mediated constriction and blunting nitric oxide–related relaxation of vascular smooth muscle.

As yet, such interaction has received little if any experimental attention, particularly in the context of hypertensive vascular disease. However, chronic hyperinsulinemia has emerged from epidemiological studies as an important risk factor in arterial diseases of the heart, lower limbs, and brain. Several of these studies suggest a role for insulin in sex-related differences in the incidence of ischemic vascular disease and related mortality, as well as the notable absence of these differences among diabetic men and women. Paradoxically, one of these studies demonstrated that long-term insulin therapy was associated with markedly greater cardiovascular-related mortality in diabetic women compared with diabetic men. Other studies suggest that a high ratio of estrogen to testosterone combined with hyperinsulinemia may predispose even men to premature ischemic vascular disease. The SHRSP is widely recognized as a relevant model for the study of naturally occurring cardiovascular-related mortality and its contributing factors. Our study clearly raises the possibility that vascular interactions of female sex hormones and high circulating insulin may aggravate hypertension in this model. If these or other vascular interactions of the same hormones increase risk of cardiovascular-related mortality in humans, then the SHRSP will be a useful model with which to further investigate mechanisms related to such phenomena.

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