Enhanced sympathetic reactivity associates with insulin resistance in the young Zucker rat

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First published March 30, 2006; doi:10.1152/ajpregu.00644.2005.—Somatosympathetic reflexes were studied in young hyperinsulinemic, insulin-resistant (Zucker fatty) rats (ZFR) and a related control (Zucker lean) strain (ZLR). Glucose metabolism was characterized by minimal model analysis of intravenous glucose tolerance test data. Seven-week-old ZFR (n = 18) and ZLR (n = 17) were studied under pentobarbital anesthesia. Mean body weight and plasma glucose and insulin concentration were significantly greater (P < 0.05) in ZFR than in ZLR, whereas basal values of mean arterial pressure (MAP) and heart rate (HR) were not significantly different. Increments of MAP (∆MAP) and HR (∆HR) elicited by electrical stimulation of the sciatic nerve (5-s trains of 100 pulses, 0.5-ms pulse duration, 100- to 400-μA pulse intensity) were significantly higher (ANOVA, P < 0.05) in ZFR at each level of stimulus intensity. Regression analysis showed a linear increase in ∆MAP and ∆HR with increasing sciatic nerve stimulus intensity. Pressor responses to phenylephrine after ganglionic blockade demonstrated that vascular reactivity to adrenergic stimulation is not increased in ZFR compared with ZLR. Thus this factor does not contribute to enhancement of somatosympathetic reflexes observed in this strain. Insulin sensitivity in ZFR was one-fourth (P < 0.05) that in ZLR. These results suggest that stronger sympathetic nervous reactivity in ZFR is associated with a severe insulin-resistant state before the onset of hypertension and support the hypothesis that insulin-mediated stimulation of the sympathetic nervous system is involved in the development of cardiovascular diseases related to alterations of glucose metabolism.

sympathetic nervous activity; minimal model analysis; glucose kinetics; hypertension

HYPERINSULINEMIA AND INSULIN resistance are considered important risk factors for development of hypertension (2, 39), and a number of studies have shown a significant association between hypertension and insulin resistance in obese and nonobese individuals (12, 15, 27, 28, 46). However, the pathophysiological relation among hyperinsulinemia, insulin resistance, and hypertension remains poorly understood.

Some experimental reports suggest that an increase in sympathetic nervous system activity (SNA) may play a role in the association between insulin resistance and elevated blood pressure (39). This association might be due to a primary increase in sympathetic activity (22). Although an increase in sympathetic activity can cause hypertension and insulin resistance, studies performed on animal models indicate that the insulin resistance induced by a high-lipid diet occurs before the onset of hypertension (20), suggesting the primacy of the insulin-mediated stimulation of the sympathetic nervous system. If this is true, a suitable animal model to investigate the mechanisms underlying insulin resistance and its associated pathologies is the obese Zucker rat, homozygous for the fa allele (fafa), in which a mutation of the leptin receptor-coding gene impairs the ability of leptin to suppress food intake. Homozygous Zucker rats are insulin resistant, hyperinsulinemic, and obese. Previous studies on the link between alterations of blood pressure and SNA in the presence of insulin resistance in this strain have yielded contradictory results (1, 10, 19, 24, 30, 35, 36, 47, 50) that might be caused, in part, by limitations of the assessment of the degree of alterations of glucose kinetics.

We showed previously in the spontaneously hypertensive rat (SHR) and its related control strain (33, 34) that a suitable characterization of the dynamics of glucose kinetics is obtained from the intravenous glucose tolerance test (IVGTT) interpreted with the minimal model (4, 16). On the other hand, an important index of SNA is provided by somatosympathetic reflexes, which are coordinated autonomic responses to activation of somatic afferents mediated by changes in sympathetic activity that cause a cardiovascular reaction to changes in the physical state of the body (14, 40). On the basis of these considerations, the aim of the present investigation was to improve our knowledge of the existence of a relation between changes in sympathetic activity and alterations of glucose kinetics in the young hyperinsulinemic, insulin-resistant homozygous Zucker rat and its related heterozygous control strain by analysis of reflex cardiovascular responses to stimulation of the sciatic nerve and characterization of glucose metabolism by minimal model interpretation of IVGTT data. Furthermore, in additional experiments, pressor and tachycardic responses to phenylephrine, a selective α1-adrenoceptor agonist, were analyzed after ganglionic blockade to investigate whether alterations in vascular reactivity to adrenergic activation could contribute to cardiovascular responses to somatic nerve stimulation.

MATERIALS AND METHODS

Seven-week-old male homozygous (fafa, ZFR, n = 18) and heterozygous Zucker rats (fa+/−, ZLR, n = 17) were housed in controlled conditions of temperature (21 ± 1°C), humidity (60 ± 10%), and lighting (0800–2000) and fed a standard rat chow contain-
ing 0.3% sodium, with tap water ad libitum. The experiments were performed at 0800, after a 12-h overnight fast. The animals were anesthetized with pentobarbital sodium (50 mg/kg ip plus maintenance doses if necessary; Sigma Chemical, St. Louis, MO). Changes in heart rate (HR) and arterial pressure (AP) and the state of the pupils were monitored to assess the adequacy of the anesthesia. The experiments were performed in accordance with Italian National Guidelines on Animal Experimentation (Decreto Legislativo 27/1/1992, no. 116, Attuazione della Direttiva no 86/609/CEE in materia di protezione degli animali utilizzati a fini sperimentali o ad altri fini scientifici). The study was approved by the Ethical Committee of the University of Genoa and by the Italian Ministry of Health. Rectal temperature was controlled and maintained at 37.5 ± 0.5°C by a heating pad. The trachea and right femoral artery and vein were cannulated. The arterial cannula, which was connected to a pressure transducer (Spectramed Statham P23XL, Viggo-Spectramed, Oxnard, CA), provided a recording of AP through a preamplifier (model 7P1A4, Grass Instruments, Quincy, MA). HR was monitored using a tachograph (model 7P4, Grass Instruments) triggered by lead II of the electrocardiogram (ECG). The venous cannula was used for drug injection. AP, ECG, and HR were digitally recorded by an analog-to-digital converter (Power1401, Cambridge Electronic Design, Cambridge, UK), stored on a personal computer, and analyzed by laboratory software (Spikew2, Cambridge Electronic Design). The rats were killed at the end of the experiments by an overdose of pentobarbital sodium.

**Nerve stimulation.** The left sciatic nerve was isolated and dissected. The central end of the crushed nerve was placed on two stainless steel bipolar hook electrodes for stimulation and recording, respectively, spaced 10 mm apart, and then covered with a silicone sealant for peripheral nerves (Kwik-Cast, World Precision Instruments, Sarasota, FL). The distal stimulating electrode was connected to a constant-current isolated stimulator (model DS2A, Digitimer, Welwyn Garden City, UK), which was controlled by a computer sequencer via the analog-to-digital converter. The proximal recording electrode was connected through a preamplifier (model P15, Grass Instruments) to an amplifier (model 4660, Ortec, Oak Ridge, TN). The output signal of the amplifier was digitized via the analog-to-digital converter and recorded and analyzed by Spike2 software. In 12 ZFR and 11 ZLR, cardiovascular responses to stimulation of the sciatic nerve were elicited by electrical stimulation of the nerve with 5-8 trains of 100 pulses (0.5-ms pulse duration, 100-, 200-, 300-, and 400-μA pulse intensity). In two other ZFR and two other ZLR, cardiovascular responses to electrical stimulation of the sciatic nerve were studied before and after intravenous administration of atropine (1 mg/kg).

**Vascular reactivity to adrenergic stimulation.** In four more ZFR and four more ZLR, vascular reactivity to selective stimulation of α₁-adrenoceptors, the major receptor subtype for adrenergic actions on vasculature, was investigated. These rats were pretreated with the autonomic ganglionic antagonist mecamylamine (4 mg/kg iv). Then on vasculature, was investigated. These rats were pretreated with the products S₁-V and S₂-V yield whole body indexes, which have the same units [dl-kg⁻¹min⁻¹/l(MU/ml) and dl-kg⁻¹min⁻¹, respectively] as the analogous clamp indexes (5, 6).

Starting time for the IVGTT protocol was 1 h after completion of the sciatic nerve stimulation protocol to allow for recovery from the stress response. Two basal blood samples (200 μl) were taken from the arterial catheter at 5 and 2 min before the glucose injection. A glucose bolus of 400 mg/kg was injected over 1 min into the femoral vein (time 0). Nine additional blood samples were collected at 1, 2, 3, 5, 8, 15, 25, 40, and 70 min after the injection. Plasma volume was replaced by controlled normal saline infusion. Minimal model equations, which are described in detail elsewhere (33), were used to describe glycemia data, with insulinemia data used as model input. SAAM II software (SAAM Institute, University of Washington, Seattle, WA) was used to estimate the model parameters with a nonlinear estimation technique (3) by fitting to measured glycemia data. Insulin data (model input) were assumed to be without error. The errors associated with total glucose measurement were assumed to be random variables normally distributed, with zero mean and a constant 1.5% coefficient of variation from reality. Weights were chosen optimally equal to the inverse of the measurement errors (11).

Precision of parameter estimates was expressed as percent coefficient of variation, CV% = (SDp/p) × 100, where SDp is the parameter standard deviation derived from the inverse of the Fisher information matrix and p is the related parameter estimate (11).

**Assays.** Blood was promptly centrifuged and glucose immediately measured with the glucose oxidase method using an automated glucose analyzer. The remaining plasma was stored at −80°C for insulin determination. Insulin was measured with a commercially available rat insulin ELISA kit (Mercodia, Uppsala, Sweden). Sensitivity of the insulin assay is 0.07 g/l with an inter- and intraprecision of 3.3 ± 0.1 and 1.8 ± 0.3%, respectively.

**Data analysis.** Baseline values of MAP and HR were calculated over 30 s before peripheral nerve stimulation. Maximum changes in MAP (ΔMAP) and HR (ΔHR) were computed as the difference between the peak values of the responses to nerve stimulation and the related baseline values. A one-way analysis of variance with repeated measures was used to evaluate the significance of ΔMAP and ΔHR elicited by nerve stimulation. Mann-Whitney’s U-test was used for further statistical comparisons (43). P < 0.05 was taken to indicate significance. Values are means ± SE.

**RESULTS**

Body weight, basal cardiovascular parameters, and plasma glucose and insulin concentrations in ZFR and ZLR are shown in Table 1. Mean body weight and plasma glucose and insulin

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<td>Plasma insulin, μU/ml</td>
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Values are means ± SE. ZFR, zucker fatty rat; ZLR, zucker lean rat. *Significantly higher than in ZLR.
concentrations were significantly greater \( (P < 0.05, \text{by Mann-Whitney's } U \text{-test}) \) in ZFR than in ZLR, whereas no significant difference between the two groups was found in basal values of MAP and HR.

**Somatosympathetic reflexes.** Electrical stimulation of the sciatic nerve (5-s trains, 20 Hz, 0.5-ms pulse duration with 100-, 200-, 300-, and 400-\( \mu \text{A} \) intensity) in 12 ZFR and 11 ZLR yielded a significant \( (P < 0.05, \text{by ANOVA}) \) increase in MAP (\( \Delta \text{MAP} \)) and HR (\( \Delta \text{HR} \)) in both groups. Figure 1 shows the cardiovascular effects of sciatic nerve stimulation in one ZFR and one ZLR. On average, the magnitude of \( \Delta \text{MAP} \) (Fig. 2) and \( \Delta \text{HR} \) (Fig. 3) elicited by each of our four pulse intensities (PI) of the electrical stimulation of the sciatic nerve was significantly higher in the ZFR than in the ZLR. In both groups, pressor and tachycardic responses showed a tendency to increase with increasing stimulus intensity. Time to maximum \( \Delta \text{MAP} \) and \( \Delta \text{HR} \) was 3–5 s, according to the magnitude of the response. For the ZFR, regression analysis of \( \Delta \text{MAP} \) vs. PI values (Fig. 4) yielded a straight line with a positive slope of 0.033 (CI = 0.015 + 0.050) beats\( \cdot \)min\(^{-1} \cdot \mu \text{A}^{-1} \), \( \Delta \text{HR} \) intercept at zero PI of 13.1 (CI = 8.4 + 17.8) beats/min, and correlation coefficient of 0.52 \( (P < 0.001) \). For the ZLR, linear regression yielded an almost parallel straight line with a slope of 0.026 (CI = 0.013 + 0.038) beats\( \cdot \)min\(^{-1} \cdot \mu \text{A}^{-1} \), a significantly lower \( \Delta \text{HR} \) intercept of 4.4 (CI = 0.8 + 7.9) beats/min, and correlation coefficient of 0.55 \( (P < 0.001) \).

In two more ZFR and two more ZLR, somatosympathetic reflexes were tested before and after intravenous administration...
of atropine (1 mg/kg) to investigate the role of the parasympathetic nervous system in pressor and tachycardic responses to electrical stimulation of the sciatic nerve. In both groups, no statistically significant difference was observed in cardiovascular responses to sciatic nerve stimulation before and after elimination of parasympathetic activity.

Vascular reactivity to adrenergic stimulation after ganglionic blockade. Ganglionic blockade, performed by intravenous administration of mecamylamine (4 mg/kg), caused a decrease in MAP in ZFR that was not significantly different from that observed in ZLR: 59.5 ± 2.3 and 55.0 ± 2.1 mmHg, respectively. Basal values of MAP after ganglionic blockade were not significantly different between ZFR and ZLR: 59.5 ± 2.4 and 55.0 ± 2.1 mmHg, respectively.

Randomized doses of PE, after ganglionic blockade, induced dose-dependent increases in MAP (Fig. 6) and HR (Fig. 7) in ZFR and ZLR. Pressor and tachycardic responses to PE, analyzed by doses, were larger in ZFR than in ZLR, but these differences failed to reach statistical significance. Similarly, increases in HR induced by PE, presumably due to direct activation of cardiac \( \alpha_1 \)-adrenoreceptors, in ZFR were not significantly different from those in ZLR.

Assessment of glucose metabolism. Mean estimates of SI, SG, and V from ZFR (n = 6) and ZLR (n = 6) are presented in Table 2. Mean CV% over all 12 cases were 14.6 ± 3.6% for SI, 28.5 ± 5.9% for SG, and 5.2 ± 1.0% for V. Significantly lower (P < 0.05) SI values were found in ZFR than in ZLR, whereas no significant difference between the two groups was found in SG or V.

\[ S_V = 21.2 \pm 3.9 \times 10^{-4} \text{dl} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} / (\mu\text{U} \cdot \text{ml}^{-1}) \] in ZLR and significantly reduced (P < 0.05) to 5.73 \pm 1.70 \times 10^{-4} \text{dl} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} / (\mu\text{U} \cdot \text{ml}^{-1}) in ZFR. No significant differ-
ference was found in S Gur V, which averaged $12.6 \pm 1.9 \times 10^{-2}$ and $11.4 \pm 1.6 \times 10^{-2}$ dl-kg$^{-1}$-min$^{-1}$ in ZLR and ZFR, respectively.

**DISCUSSION**

Stimulation of somatic afferent nerves provides coordinated autonomic responses mediated by changes in sympathetic activity (42). It is well known that, in the rat sciatic nerve, stimulation induces a pressor and tachycardic reflex, the somatosympathetic reflex, which is mediated by activation of sympathoexcitatory bulbospinal neurons located within the rostral ventrolateral medulla. These neurons provide excitatory inputs to spinal intermediolateral neurons, which regulate sympathetic drive to the heart and vessels (9, 13).

A novel finding of the present study was the evidence of a marked enhancement in cardiovascular responses to electrical stimulation of the sciatic nerve in our ZFR compared with ZLR. This enhancement of somatosympathetic reflexes in the young ZFR was associated with no significant difference in basal blood pressure between the two groups (Table 1). Rather, an association is evident with an insulin-resistant state in the ZFR compared with the ZLR, which is characterized by significantly higher values of steady-state (fasting) insulinemia and glycemia and a significant reduction in S Gur (Tables 1 and 2).

The enhanced pressor and tachycardic responses to somatic nerve stimulation in the ZFR could depend on an increased sympathetic nervous activity and/or alterations in vascular reactivity to adrenergic stimulation. Indeed, a vascular dysfunction in the ZFR might be associated with the insulin-resistant state. Insulin resistance has been reported to result in a number of changes that could promote a direct vascular dysfunction with increased vascular reactivity to adrenergic stimulation, impaired endothelium-dependent relaxation, and increased intracellular calcium, leading to enhanced vasoconstriction (23). To investigate the relative contributions of sympathetic activity and vascular reactivity to the enhancement of reflex cardiovascular responses to sciatic nerve stimulation in the ZFR, we tested pressor responses to randomized serial doses of PE, a selective agonist of $\alpha_1$-adrenoceptors, the major receptor subtype for adrenergic actions on vasculature. Vascular adrenergic reactivity was studied after ganglionic blockade to eliminate potentially confounding endogenous sympathetic vasomotor tone and baroreceptor reflexes. Under our experimental conditions, ganglionic-blocked ZFR did not show significantly greater pressor responses to intravenous administration of PE. This indicates that the enhanced pressor responses to sciatic nerve stimulation are not affected by alterations in vascular reactivity and suggests that, in the 7-wk-old ZFR, the enhanced somatosympathetic reflexes reflect an increased reactivity of the sympathetic nervous system.

The present findings are in agreement with those of a recent report by Schreihofer et al. (45), who demonstrate that the reactivity of the total vascular system to adrenergic stimulation is not augmented in obese Zucker rats. They also suggest that normal adrenergic vascular reactivity in obese Zucker rats may reflect a combination of different vascular reactivities across beds, compared with lean Zucker rats. Particularly, a redistribution of $\alpha$-adrenergic vascular reactivity is observed, in which mesenteric reactivity is reduced and hindquarter reactivity is increased.

Schreihofer et al. (45) also observed that basal MAP was significantly higher in older (15-wk-old) obese Zucker rats than in lean Zucker rats and that elimination of autonomic tone, by ganglionic blockade, induced a greater reduction in MAP in the ZFR. They suggest that MAP differences in obese Zucker rats reflect dysfunction in sympathetic control. In our study, there was no significant difference in basal values of MAP between 7-wk-old ZFR and ZLR. Accordingly, we found that the decrease in MAP after ganglionic blockade is not significantly larger in ZFR than in ZLR. Thus we infer that young hyperinsulinemic, insulin-resistant ZFR show an increased reactivity of the sympathetic nervous system before the onset of enhanced basal sympathetic activity and elevated blood pressure.

In our ZFR and ZLR, we investigated the magnitude of $\Delta$MAP and $\Delta$HR induced by sciatic nerve stimulation and found increases that were correlated with PI of the stimulation. Four levels of PI (100, 200, 300, and 400 $\mu$A) were used, and, on average, at each level, a significantly higher cardiovascular response characterized the ZFR than the ZLR (Figs. 2 and 3). This is consistent with the increased efferent SNA in response to the nerve stimulation. Regression analysis of individual $\Delta$MAP values reported in Fig. 4 shows, in ZFR, a significantly steeper increase of $\Delta$MAP with increasing PI as judged from the estimated slope coefficients and related 95% CI (see RESULTS). The divergent straight lines that characterize ZFR and ZLR showed no significant difference in extrapolated $\Delta$MAP intercept at zero PI (see estimates and related CI in RESULTS), which appears consistent with the lack of baseline differences in cardiovascular parameters of the two groups (Table 1). Our experimental observation of no significant increase of vascular reactivity in ZFR suggests that the divergence of $\Delta$MAP vs. PI

![Graph](https://via.placeholder.com/150)

**Table 2. Estimates of glucose metabolism indexes**

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<th>ZFR</th>
<th>ZLR</th>
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<tr>
<td>$S_G$, $10^{-3}$ min$^{-1}$(mU.ml$^{-1}$)</td>
<td>$1.45\pm0.56^*$</td>
<td>$6.52\pm1.35$</td>
</tr>
<tr>
<td>$S_G$, $10^{-2}$ min$^{-1}$</td>
<td>$2.93\pm0.72$</td>
<td>$3.92\pm0.68$</td>
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<tr>
<td>$V$, dl/kg</td>
<td>$4.63\pm0.67$</td>
<td>$3.36\pm0.25$</td>
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Values are means $\pm$ SE ($n=6$). $S_G$, index of insulin sensitivity; $S_G$, index of glucose effectiveness; $V$, plasma glucose distribution volume. *Significantly lower than ZLR.
straight lines reflects the additional contributions of other factors, such as alterations of cardiac output, as a result of increased HR and stroke volume. Because there is no difference in ΔHR-to-PI ratio between the two groups (Fig. 5), an enhancement of cardiac contractility in ZFR might explain the increased ΔMAP-to-PI ratio in Fig. 4.

The relation between insulin and sympathetic activity has been recently stressed, and central and peripheral mechanisms have been hypothesized to account for it (31, 44). This has been considered possible, because insulin can cross the blood-brain barrier (26, 37), and insulin receptors in discrete regions of the brain are involved in regulation of central autonomic activity (51). Moreover, we previously demonstrated that insulin inhibits the spontaneous discharge of barosensitive neurons within the nucleus tractus solitarii of rats, suggesting that insulin can increase SNA via a central neural mechanism and may play a role in the central regulation of cardiovascular function (41).

In previous reports, the relation between hypertension and alterations of glucose kinetics has been investigated in SHR, which are generally considered the best available experimental model of essential hypertension (48). However, these studies yielded contradictory results. Some studies showed a reduction of glucose tolerance and insulin action (18, 21, 29, 38). On the contrary, in other studies, an increased insulin sensitivity (17, 49) or no evidence of insulin resistance (7, 8, 17) has been observed in SHR. To clarify these contradictions, more recently, we applied the minimal model of glucose kinetics to insulinemia and glycemia data obtained from IVGTT to test whether high blood pressure causes reductions of Si and SG indexes in the SHR similar to those observed in hypertensive humans (32). These studies demonstrated that insulin resistance is not a primary metabolic defect in this genetic model of hypertension (33, 34). On this basis, the SHR cannot be considered a suitable experimental model to study the relation between insulin resistance, hyperinsulinemia, and associated cardiovascular diseases.

The Zucker rat may be a more appropriate experimental model to study the mechanisms underlying impaired glucose metabolism and its associated cardiovascular pathologies. However, also in this strain, previous studies reported contradictory results in evaluation of arterial pressure control and SNA. Zucker rats have been described as being both hypertensive and normotensive. Several studies indicate that ZFR are hypertensive compared with phenotypically normal heterozygous Zucker rats (1, 10, 24, 50), whereas other studies show a normotensive state of ZFR (30, 35, 36). Several studies (10, 19, 45, 47) indicate higher levels of SNA in homozygous Zucker rats than in phenotypically normal heterozygous Zucker rats (jun−/−), and it has been suggested that alterations in sympathetic function in obese Zucker rats can be tissue specific (30). In contrast to these findings, other studies demonstrated in this experimental animal model an organ-specific decrease in SNA (25). Two determinants of blood pressure values have been suggested to explain the discrepancy in the literature regarding MAP in Zucker rats: age and plasma glucose concentration of the Zucker rats used in the experiments. Experimental observations of the present study confirm that young (7-wk-old) rats are normotensive. Plasma glucose concentration may change considerably in Zucker rats, and only a few studies have used hyperglycemic Zucker rats, which appear to be a more appropriate model for non-insulin-dependent diabetes.

In the present study, minimal model analysis of IVGTT data shows that mean Si in ZFR is one-fourth (P < 0.05) that in ZLR (Table 2). Thus the insulin-resistant state in the former strain exists at 7 wk of age and is mainly determined by a defect in insulin action. Indeed, the absence of significant differences in SG values between the two groups indicates that insulin-independent glucose disposal remains unaltered in the two strains. That no significant alteration in MAP was observed between our ZFR and ZLR suggests that insulin resistance is not necessarily associated with high blood pressure. Moreover, our observation that, in young ZFR, insulin resistance and enhanced somatosympathetic reflexes occur before the onset of hypertension supports the hypothesis of insulin-mediated stimulation of the reactivity of the sympathetic nervous system.

In conclusion, our results provide new information on the relation between alterations of glucose kinetics and impaired sympathetic control. Specifically, this study demonstrates that somatosympathetic reflexes are enhanced in 7-wk-old insulin-resistant ZFR, suggesting the existence of an enhanced sympathetic nervous reactivity in this strain that associates with insulin resistance before the onset of hypertension. This finding reinforces the hypothesis that insulin-mediated stimulation of the sympathetic nervous system is involved in development of cardiovascular diseases related to alterations of glucose metabolism.

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