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Sympathectomy prevents fructose-induced hyperinsulinemia and hypertension

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Abstract

The fructose-induced hypertensive rat is a widely used model to study the inter-relationship between hyperinsulinemia, insulin resistance and high blood pressure. Evidence suggests that hyperinsulinemia and insulin resistance may be pathogenic in the development of high blood pressure in this model. To determine the contribution of the sympathetic nervous system towards fructose-induced hypertension, the present study examined the effects of chemical sympathectomy (adrenal medullectomy, followed by weekly 6-hydroxydopamine injections) on plasma insulin levels and systolic blood pressure in control and fructose-induced hypertensive rats. Sympathectomy abrogated the development of *both* hyperinsulinemia and hypertension in fructose hypertensive rats without affecting these parameters in control rats. These data uncover, for the first time, the primacy of the sympathetic nervous system as a mediator of both elevated plasma insulin levels and high blood pressure in rats fed a high fructose diet.

Keywords: Hypertension; Hyperinsulinemia; Insulin resistance

1. Introduction

In the past several years, there has been growing interest in the hypothesis that resistance to the metabolic effect of insulin (insulin resistance) and compensatory hyperinsulinemia may contribute towards increased blood pressure and essential hypertension (Bhanot and McNeill, 1996). This observation is strengthened by studies demonstrating the antihypertensive effects of drugs that are known to counter insulin resistance and decrease plasma insulin levels (Bhanot and McNeill, 1996). The fructose-induced hypertensive rat is a diet induced model of hypertension, wherein feeding normal Sprague–Dawley rats a fructose-enriched diet, results in marked insulin resistance, hyperinsulinemia and elevated blood pressure (Verma et al., 1995; Bhanot and McNeill, 1996). This model is extensively employed to study the inter-relationship between these metabolic defects and hypertension independent of obesity or genetic contributions. Despite the suggestion that hyperinsulinemia/insulin resistance may lead to hypertension through changes in insulin's cardiovascular actions (Baron, 1993), the contribution of the sympathetic nervous system towards fructose-induced hypertension remains undetermined. To this aim, we examined the effects of chemical sympathectomy on the development of hyperinsulinemia and elevated blood pressure in rats fed a high fructose diet. The data indicate that the presence of a functional sympathetic nervous system is required for the final expression of both hyperinsulinemia and elevated blood pressure in fructose-induced hypertensive rats.

2. Materials and methods

Male Sprague–Dawley rats were procured at 5 weeks of age (University of British Columbia Animal Care Unit) and were divided into the following experimental groups: control ($n = 16$), control-sympathectomized ($n = 7$), fructose ($n = 16$) and fructose-sympathectomized ($n = 8$). At week 6 (weeks signify the age of rats), systolic blood pressure, plasma glucose and plasma insulin (5 h fasted)

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were measured. At week 7, adrenal medullectomy (under pentobarbital anesthesia) was performed in the control-sympathectomized and fructose-sympathectomized groups, following which these groups received weekly intraperitoneal injections of 6-hydroxy dopamine (50 mg/kg dissolved in 0.5 ml of 0.9% sodium chloride saline containing 0.5 mg ascorbic acid) for the remainder of the experiment. Starting at week 9, the rats in the fructose and fructose-sympathectomized groups were started on a 66% fructose diet as described previously (Verma et al., 1995). The sodium content of the diet was reasonably similar to that of the standard rat chow (standard chow: 4 g/kg; fructose diet: 4.2 g/kg). Weekly measurements of plasma insulin, glucose and systolic blood pressure were conducted in the four groups. Systolic blood pressure was measured in conscious rats using the indirect tail cuff method without external preheating (Verma et al., 1995). The animals were preconditioned to the experimental protocol before the actual measurements were conducted. Plasma insulin levels were assayed using a double antibody radioimmunoassay using a kit from Linco Research (St. Louis, MO).

3. Experimental

Evidence of successful sympathectomy: At week 17, rats from the four experimental groups were killed with an overdose of pentobarbital and the tail artery was carefully dissected out, cleaned of adherent connective tissue and cut into rings. Two rings from each rat were suspended in an isolated tissue bath containing modified Krebs–Ringer bicarbonate solution maintained at 37°C and oxygenated with a mixture of 95% oxygen and 5% carbon dioxide. Each ring was placed under a resting tension of 2 g. Following equilibration for 90 min, isometric responses to 10^{-5} M tyramine were examined. The inability of tyramine to elicit a contractile response was used to indicate successful sympathectomy.

4. Results

Adrenal medullectomy followed by weekly 6-hydroxy dopamine injections resulted in successful sympathectomy as shown by a lack of tail arterial responses to 10^{-5} M tyramine in the control-sympathectomized and fructose-sympathectomized groups (Fig. 1a). Fig. 1b and c depict the effects of fructose feeding and sympathectomy on plasma insulin levels and blood pressure. The fructose group was hyperinsulinemic and hypertensive when compared to the control group. Importantly, sympathectomy prevented the development of fructose-induced hyperinsulinemia and hypertension without affecting these parameters in the control-sympathectomized group.

Insulin-induced stimulation of the sympathetic nervous system has been long proposed to present a link between

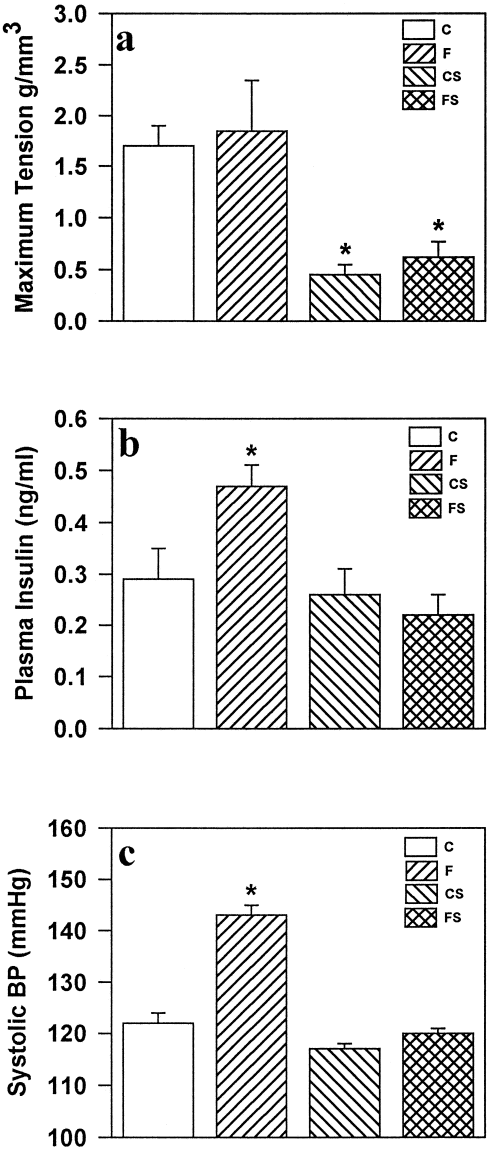

Fig. 1. Maximum tension developed in the presence of 10^{-5} M tyramine in tail arteries from control ©, fructose-induced hypertensive (F), control-sympathectomized (CS) and fructose-sympathectomized (FS) groups elicited using the isolated tissue bath procedure and measurement of isometric responses. Inability of tyramine to elicit contractile responses (with subsequent tension development) in CS and FS groups is evidence of successful sympathectomy. Plasma insulin levels and systolic blood pressure in the four experimental groups. $^{*}P < 0.05$. Sympathectomy prevented fructose-induced hyperinsulinemia and hypertension.

hyperinsulinemia and hypertension (Muntzel et al., 1995). Indeed, insulin may evoke sympathoexcitatory effects via a direct action on the central nervous system, via changes in norepinephrine metabolism or through a baroreflex action secondary to hemodynamic changes (Muntzel et al., 1995). However, an equally compelling case has been made for elevated sympathetic activity as the primary defect, modulating both insulin resistance (and consequently hyperinsulinemia) and elevations in blood pressure. In support of this view, are studies demonstrating the induction of in-

sulin resistance through β-adrenoceptor stimulation, possibly by increasing the proportion of insulin resistant fast twitch fibers in skeletal muscle (Zeman et al., 1988). An additional mechanism through which sympathetic activation may lead to insulin resistance is by vasoconstriction of skeletal muscle vasculature (Muntzel et al., 1995). This, in turn, may lead to decreases in glucose delivery to skeletal muscle and the development of insulin resistance. Thus, the question as to whether hyperinsulinemia/insulin resistance precedes sympathetic activation or is a secondary manifestation of increased sympathetic activity remains unclear; a question that was addressed in this study. Results from this study demonstrate that chemical sympathectomy completely prevents the development of hyperinsulinemia and hypertension in fructose-induced hypertensive rats without affecting these parameters in control-sympathectomized rats (Fig. 1b and c). These data indicate that the presence of a functional sympathetic system is required for the development of both elevated plasma insulin levels and blood pressure in rats fed a high fructose diet.

Although there appears to be general agreement in the literature regarding the dependence of insulin-induced hypertension (in rats) on a functional sympathetic nervous system the question as to which comes first (sympathetic over-activity or insulin resistance) has been debated. The balance of published work (in rats) favors a paradigm in which elevated sympathetic activity leads to insulin resistance. Compensatory hyperinsulinemia that ensues in the face of insulin resistance, serves as a continual stimulus for sympathetic activation, further reinforcing the insulin resistant state. Thus, it is plausible that sympathetic hyperactivity is an early and integral part of fructose-induced hypertension and that the metabolic consequences are secondary to sympathetic nervous system-induced insulin resistance. In support of this view are data demonstrating that chronic moxonidine treatment attenuates the development of both hyperinsulinemia and hypertension in fructose-induced hypertensive rats (Rosen et al., 1997). As moxondine is a centrally acting imidazoline-1 receptor agonist (which reduces sympathetic discharge), the authors conclude that the improvement in insulin sensitivity and attenuation of hyperinsulinemia in fructose hypertensive rats was secondary to a reduction in sympathetic outflow, a view that is supported by our sympathectomy data.

The sympathetic nervous system is exquisitely sensitive to dietary intake (Fournier et al., 1986). Food restriction/fasting decrease sympathetic activity and lowers plasma insulin levels and blood pressure. Likewise, sucrose feeding enhances sympathetic activity and raises blood pressure (Fournier et al., 1986). Although enhanced sympathetic activity has not been previously demonstrated in fructose-induced hypertensive rats, the available data (on sucrose-fed and other diet-fed models) strongly suggests a similar mechanism.

We have previously demonstrated an important role for endothelin-1 in the development of fructose-induced hypertension. Fructose-induced hypertensive rats are characterized by an elevated total mesenteric vascular endothelin-1 content and an altered arterial reactivity to endothelin-1 (Verma et al., 1995). Furthermore, chronic endothelin receptor blockade prevents the development of fructose-induced hypertension without affecting plasma insulin levels (Verma et al., 1995). Based on the data from this study, if we assume that the sympathetic nervous system is the primary modulator of hyperinsulinemia and hypertension, then it can be speculated that the sympathetic system (through mechanism/s unknown) may lead to an increase in blood vessel endothelin-1 levels. In other words, one effect of sympathectomy may be to block endothelin release. Although speculative at this time, studies demonstrating a suppression of endothelin release following long-term guanethidine sympathectomy support such a theory (Milner et al., 1996).

5. Conclusion

In conclusion, sympathectomy prevents the development of fructose-induced hyperinsulinemia and hypertension in rats. This suggests that sympathoexcitation may play an early and integral role in the final expression of elevated plasma insulin levels and blood pressure in rats fed a high fructose diet.

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