

# Neonatal Chemical Sympathectomy Attenuates Fructose-Induced Hypertriglyceridemia and Hypertension in Rats

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## Abstract

Experiments were performed to determine the pathogenic contribution of the peripheral sympathetic nervous system to fructose-induced hypertriglyceridemia, hyperinsulinemia and hypertension in rats. Neonatal chemical sympathectomy was performed in neonatal Sprague-Dawley rats (1-week old) by administration of guanethidine (50 µg/g, i.p.) 5 times per week for consecutive 3 weeks and nerve-intact rats were served as controls. Both groups of rats were fed a fructose-enriched diet for 9 weeks. The systolic blood pressure (SBP) and body weight were measured weekly and arterial blood samples were taken weekly for determinations of plasma insulin, glucose and triglyceride levels. The results showed that fructose feeding for one week significantly increased SBP in intact rats and sympathectomized rats (116±1 to 119±1 mmHg and 116±1 to 120±1 mmHg, respectively). SBP further increased thereafter in both groups. However, the increased SBP levels were significantly higher in intact group than in sympathectomized group after 5 weeks of fructose feeding. Fructose feeding for one week concurrently produced hypertriglyceridemia that preceded the appearance of hyperinsulinemia in both groups. The elevated plasma triglyceride levels were significantly lower in sympathectomized rats than in intact rats after 3 weeks of fructose feeding, whereas the elevated plasma insulin concentrations were not different between groups throughout fructose feeding period. Plasma glucose concentrations of both groups were comparable and remained unchanged throughout the study. These data indicate that neonatal chemical sympathectomy attenuated, but did not prevent, fructose-induced elevations in blood pressure and plasma triglyceride levels, suggesting a partial dependency of fructose-induced hypertriglyceridemia and hypertension on the integrity of the peripheral sympathetic nervous system (SNS) in rats.

**Key Words:** fructose, hypertension, hypertriglyceridemia, hyperinsulinemia, , sympathetic nerves, guanethidine, chemical sympathectomy

## Introduction

Considerable correlational evidence indicates that insulin resistance, hyperinsulinemia and hypertriglyceridemia are characteristic for essential hypertensive patients and some genetic hypertensive rats (9, 24, 29, 31). Also, numerous studies have

demonstrated that high fructose feeding to normal Sprague-Dawley rats and mongrel dogs causes hypertriglyceridemia, hyperinsulinemia, insulin resistance and hypertension (15, 16, 18, 20, 22, 27, 34), although the hypertensive effect was not confirmed in other study (7). This non-obese, fructose-induced hypertensive rat model is frequently used for

elucidation of the relationships between insulin-associated metabolic disorders and cardiovascular dysfunctions. Although many investigators proposed that hyperinsulinemia and insulin resistance is causally related to the increases of blood pressure in hypertensive patients and chronic fructose-fed rats (31, 32, 35), the precise mechanism linked to insulin-related metabolic and vascular actions and hypertension is still not fully understood. Increased activation of sympathoadrenal system, in addition to angiotensin II, endothelin and endothelial and renal dysfunctions (12, 14, 16, 18, 20, 22), has been implicated in the pathogenesis of insulin- and fructose-associated hypertension (32). However, the potential contribution of the peripheral sympathetic nervous system (SNS) to fructose-induced hypertension is not yet determined. Bunnag et al. (8) showed that high fructose feeding impaired vascular responses to exogenous norepinephrine, a consequence probably resulting from adaptation to increased sympathetic activity in fructose-fed rats. Consistent with this notion is the observation that administrations of taurine and relmenidine (the antihypertensive and sympatholytic drugs) attenuated fructose-induced hypertension and insulin resistance in rats (3, 30). On the other hand, addition of clonidine to the drinking water inhibited fructose-induced hypertension, but not hyperinsulinemia and hypertriglyceridemia, suggesting the metabolic changes associated with fructose-induced hypertension are not resulted from an increased sympathetic nervous activity (15).

Recent studies suggested that an altered lipid profile, especially an elevated triglyceride level, is causally linked to the development of high blood pressure and increased vascular reactivity in fructose-induced hypertensive rats (10, 33). Rats fed high-fat or carbohydrate-enriched diet are characterized with hypertension and sympathetic hyperactivity (23, 39). It seems likely, therefore, that the peripheral SNS may play a crucial role in the pathogenesis of hypertriglyceridemia, hyperinsulinemia and hypertension associated with fructose feeding in rats. To test this hypothesis, we administrated guanethidine into newborn rats to produce permanent sympathectomy and then evaluated the development of fructose-induced hypertension in these sympathectomized rats in the present study. Guanethidine administration has been demonstrated to completely destroy peripheral SNS, but not affect adrenal glands and noradrenergic neurons in the brain (19). The aim of this study was to determine specifically the role of peripheral SNS in the development of fructose-induced hypertension and metabolic disorders in rats. Our data indicate that the presence of intact peripheral SNS is required for the full manifestation of hypertriglyceridemia and hypertension in rats fed

fructose-enriched diet.

## Materials and Methods

### *Animals, Diets and Experimental Preparations*

**Intact rats:** In control group, seven age-matched, male Sprague-Dawley rats with an initial weight of  $207 \pm 18$  g were housed individually with free access to standard rodent chow containing 60% vegetable starch, 11% fat and 29% protein and tap water before fructose treatment.

**Sympathectomized rats:** A separate group of seven male neonatal rats (1 week old) were used for chemical sympathectomy. Guanethidine ( $50 \mu\text{g/g}$ ) was administered intraperitoneally 5 times per week for consecutive 3 weeks. This procedure has been shown to produce permanent sympathectomy in peripheral sympathetic nervous system, but did not alter the noradrenergic neurons in central nervous system or destroy the adrenal glands (19). Before fructose treatment, the mean body weight of this group was  $147 \pm 8$  g. The experimental protocols were complied with the guidelines approved by the Animal Care and Use Committee of the institute.

### *Experimental Designs*

After the control period of 6 days, both groups of rats were fed a fructose-enriched diet containing of 60% fructose, 11% fat and 29% protein throughout the experiments. The systolic blood pressure (SBP) was measured at 9:00 AM every 3 days at the control period and every week during the experimental period by the tail-cuff method without external heating as described previously (16). The mean of 4 consecutive readings was used as the measurement of SBP of each rat for that day. The body weight was measured weekly and blood samples (1ml) by tail bleeding were taken every two weeks right after measurements of SBP. Plasma was separated, aliquoted, frozen and later measured for insulin, triglyceride and glucose levels. At the end of the experiments, the effectiveness of sympathectomy was tested by the pressor and cardiochronotropic responses to tyramine and phenylephrine before sacrificing the rats.

### *Chemical and Statistical Analyses*

The plasma insulin level was determined by radioimmunoassay (11) and triglyceride concentration was assayed enzymatically using commercial kits (Sigma Chem. Co., St. Louis, MI, USA) as previously described (38). Plasma glucose concentration was measured by a glucose analyzer (Model 23A, Yellow Spring Instrument Co., Inc. Yellow Spring, Ohio,

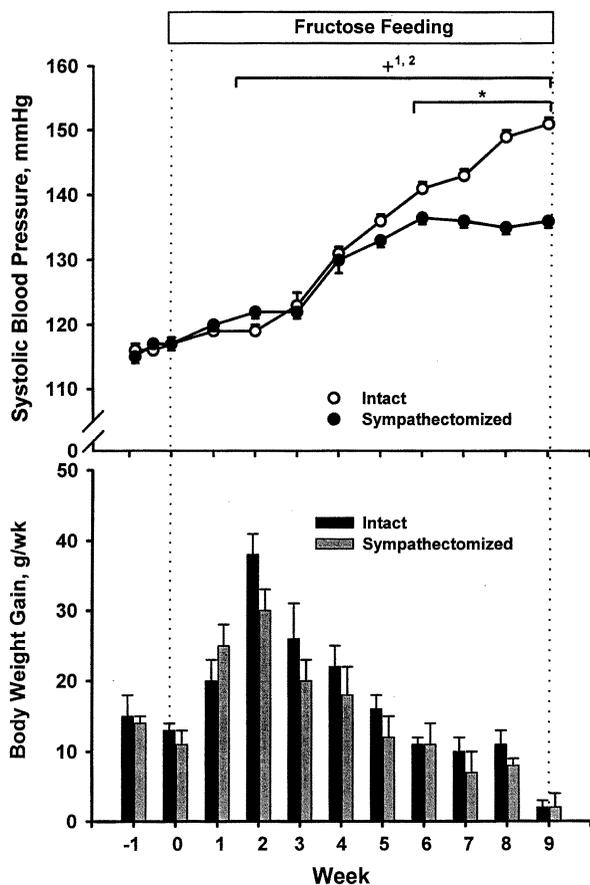


Fig. 1. Changes in blood pressure and body weight gain in fructose-fed rats with or without neonatal chemical sympathectomy. \*P<0.05 vs. intact rats at the corresponding time points. +<sup>1,2</sup>p<0.05 vs. the mean SBP in the control period of the intact (+<sup>1</sup>) and sympathectomized (+<sup>2</sup>) groups. Data are expressed as mean±SEM; n=7/group.

USA). The SYSTAT (SYSTAT, Evanston, IL) was used for statistical analysis. The time course data were analyzed with repeated-measures ANOVA with post hoc analysis by univariate F tests. Results were considered statistically significant at p<0.05. Data are presented as means±SEM.

### Results

#### Blood Pressure Response and Body Weight Gain

As shown in Figure 1, during the control period, the mean SBP of intact rats was similar to that of sympathectomized rats (116±1 vs. 116±1 mmHg). Fructose feeding for a week significantly increased SBP to 119±1 mmHg in intact rats and to 120±1 mmHg in sympathectomized rats. SBP further increased thereafter in both groups of rats. By the 5th week, the increased SBP level was significantly lower in the sympathectomized group than in intact

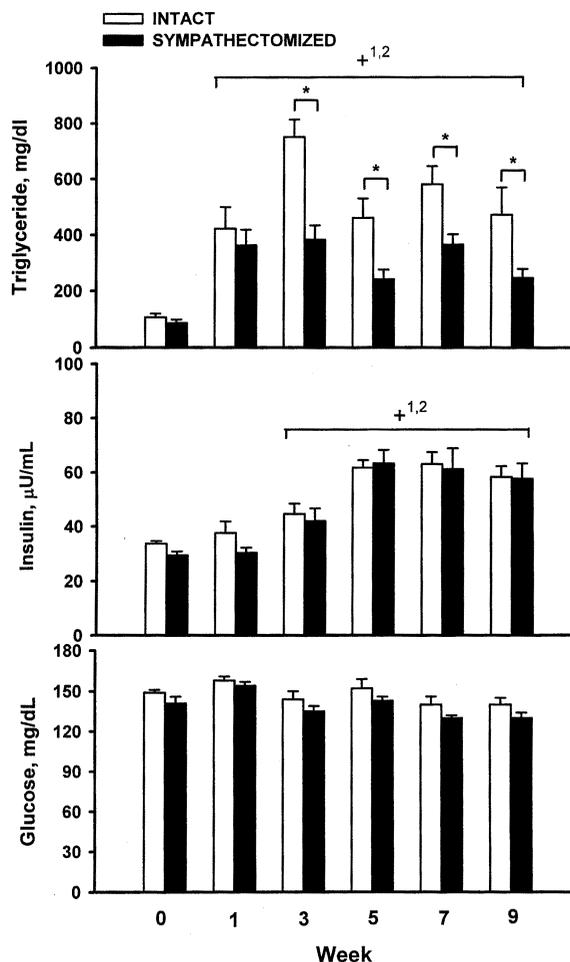


Fig. 2. Changes in plasma triglyceride, insulin and glucose levels in chronic fructose-fed rats with or without neonatal chemical sympathectomy. \*P<0.05 vs. intact rats at the corresponding time periods. +<sup>1,2</sup>p<0.05 vs. the control period of the intact (+<sup>1</sup>) and sympathectomized (+<sup>2</sup>) rats. Data are expressed as mean±SEM; n=7/group.

group (133±1 vs. 136±1 mmHg, p<0.05). The difference in blood pressure elevation augmented further and achieved 15±1 mmHg by the end of experiments. There were no significant differences in the body weight gains between groups of rats throughout the study, despite the mean initial weight of the sympathectomized group was 29% lower than that of the intact group (147±8 vs. 207±18 g, p<0.05).

#### Effects of Fructose Feeding on Plasma Triglyceride, Insulin and Glucose Concentrations

As revealed from Figure 2, the plasma triglyceride concentrations were significantly higher in the experimental periods on fructose diets than in the control periods on regular diets in both the intact and sympathectomized groups (538±88 vs. 107±13 mg/dl

for intact rats,  $p < 0.05$ , and  $320 \pm 35$  vs.  $87 \pm 12$  mg/dl for sympathectomized rats,  $p < 0.05$ ) (Fig. 2, upper). Although hypertriglyceridemia persisted throughout the fructose-feeding period in both groups, the elevated plasma triglyceride concentrations were significantly lower in sympathectomized rats than those in intact rats after 3 weeks of fructose treatment. Coincidentally, plasma insulin levels increased significantly after 3 weeks of fructose feeding in both groups and the elevated insulin concentrations were not different between intact and sympathectomized rats throughout the fructose treatment period (Fig. 2 middle). Plasma glucose concentrations of both groups were comparable and remained unchanged throughout the study (Fig. 2 bottom).

*Blood Pressure and Heart Rate Responses to Tyramine and Phenylephrine (Table 1)*

The effectiveness of chemical sympathectomy was tested by the pressor and tachycardiac responses to administrations of tyramine and phenylephrine in both intact and sympathectomized groups at the end of experiments. Tyramine administration significantly reduced the pressor and tachycardiac responses in sympathectomized rats as compared to the intact group. In contrast, the pressor response to phenylephrine was significantly enhanced in chronically sympathectomized group, suggesting a denervation-associated supersensitivity.

### Discussion

Hyperinsulinemia or insulin resistance and hypertriglyceridemia are highly related to the development of high blood pressure in essential hypertensive patients and genetic and fructose-fed hypertensive rats (9, 15, 24, 29, 31). Although the hyperactivity of SNS due to hyperinsulinemia has been implicated in the pathogenic processes (23, 32, 39), the mediating role of SNS in the hyperinsulinemia or fructose-induced metabolic disorders and hypertension is still uncertain. The present study demonstrated that neonatal chemical sympathectomy by repeated guanethidine administrations substantially attenuated, but did not prevent, the development of hypertriglyceridemia and hypertension in fructose-fed rats. On the other hand, fructose-induced hyperinsulinemia was not affected by chemical sympathectomy as shown in Fig. 2. Despite a significant increase in plasma insulin level after fructose feeding, the plasma glucose concentrations of intact and sympathectomized rats did not alter significantly from the control levels and were remained similar throughout the experiments. Our observations are consistent with previous studies (14, 16) and

**Table 1. Blood Pressure and Heart Rate Responses to Tyramine and Phenylephrine in Fructose-fed Rats with or without Sympathectomy**

Group	No.	Tyramine (0.1 g/kg)	Phenylephrine (1 g/kg)
$\Delta$ MAP (mmHg)			
Sympathectomized	7	$6 \pm 1^*$	$54 \pm 5^*$
Intact	7	$30 \pm 6$	$34 \pm 2$
$\Delta$ HR (beats/min)			
Sympathectomized	7	$30 \pm 10^*$	$11 \pm 5$
Intact	7	$63 \pm 13$	$-15 \pm 2$

Sympathectomized, fructose-fed rats with sympathectomy; Intact, fructose-fed rats without sympathectomy; MAP, the mean arterial pressure; HR, heart rate; \* $p < 0.05$  vs. intact rats;  $\Delta$ , the change in response to the treatment

further extend that insulin resistance is present in both intact and sympathectomized rats consumed fructose-enriched diet. Moreover, we found that the substantial improvement of hypertriglyceridemia in sympathectomized rats preceded blood pressure elevation. This suggests a pivotal role of an altered lipid metabolism for fructose-induced cardiovascular dysfunction. The difference in the elevated blood pressure levels between fructose-fed rats with and without guanethidine treatment is not due to guanethidine per se because the blood pressure of adult rats treated neonatally with guanethidine and fed regular chow did not change significantly (5, 14). We have shown that fructose-induced hypertension in rats was not due to obesity (14). Also, the less increase in blood pressure during the late phase of fructose feeding in sympathectomized rats can not be attributed to a lower initial body weight or a different body weight change from intact rats. This is because the guanethidine-treated rats appeared healthily and the growth rates reflected by the body weight gains were comparable in rats with and without chemical sympathectomy. Thus, these observations suggest that the full development of fructose-induced hypertriglyceridemia and hypertension is depended on the existence of an intact peripheral SNS.

It has been reported that fructose-induced hypertension is sympathoadrenal-dependent because adrenal medullectomy plus chemical sympathectomy with 6-hydroxydopamine blunted fructose feeding associated elevations in blood pressure and plasma insulin level (36). However, it must be emphasized that 6-hydroxydopamine administered centrally or peripherally has been demonstrated to increase plasma insulin, glucose and triglyceride levels in rats (2, 17). These metabolic effects of 6-hydroxydopamine will

inevitably complicate the interpretation of the experimental results obtained from fructose-fed rats. In the present study we chose neonatal treatment of rats with guanethidine. This procedure has been demonstrated to selectively destroy the postganglionic sympathetic fibers, but sparing central noradrenergic neurons and the adrenal medulla (19). Furthermore, neonatal sympathectomy with guanethidine per se has no significant effect on the body weight gain, food intake, food efficiency, body composition, and plasma triglyceride, insulin or glucose concentrations (26). Thus, guanethidine treatment seems unable to alter the lipid and glucose metabolisms. Under these circumstances, our present study demonstrated that guanethidine-induced sympathectomy diminished, but did not block, hypertriglyceridemia and blood pressure rise in chronic fructose-fed rats. In addition, fructose-induced hyperinsulinemia was persisted in the intact and sympathectomized rats, whereas the plasma glucose level and body weight gain were not different between groups. Interestingly, sympathectomy-associated reductions in plasma triglyceride levels were concurrently seen when plasma insulin levels were increased in guanethidine-treated rats. This coincidence seems to imply that the activated SNS secondary to fructose-induced hyperinsulinemia as shown previously (23, 39) might have been involved in the elevation of plasma triglyceride concentrations.

One might concern that the incomplete blockade of guanethidine-induced sympathectomy on fructose-induced elevations in blood pressure and plasma triglyceride and insulin levels might be related to the effectiveness of guanethidine sympathectomy. As shown in Table 1, administration of tyramine, a sympathomimetic agent, increased arterial pressure by  $30 \pm 6$  mmHg in nerve-intact rats but only  $6 \pm 1$  mmHg in guanethidine-treated rats. On the other hand, the pressor response to phenylephrine, a powerful  $\alpha_1$ -adrenoreceptor stimulant, was enhanced in sympathectomized rats. The profound reduction in the pressor response to tyramine and the denervated supersensitivity to phenylephrine suggest a successful denervation. The functional test might not be able to completely rule out the possibility that the minor pressor response to tyramine in sympathectomized rats could be due to incomplete sympathectomy. Alternatively, the pressor effect of tyramine might be mediated in part by a noepinephrine-independent mechanism as demonstrated by Bianchetti et al. (6). Nevertheless, it is unlikely that the failure of chemical sympathectomy to prevent fructose-induced blood pressure and triglyceride rise is due to sympathectomy-induced compensatory increase in the adrenal medullary function and the renin-angiotensin activity (21). This is because that an enhanced adrenal medullary function has been demonstrated to be

associated with reduced plasma triglyceride levels (25). Moreover, we did not find any significant differences in the basal blood pressure and plasma triglyceride levels between intact and sympathectomized rats.

The present study is consistent with previous studies showing that fructose-induced hypertriglyceridemia preceded the appearance of hyperinsulinemia and insulin resistance and hypertension in the fructose-fed rat model (13, 28). It has been shown that hypertriglyceridemia can increase the vascular sensitivity to vasoconstrictors and attenuate endothelium-dependent vasodilation (1, 4). Si et al. demonstrated that an enhancement of the glycolytic and/or lipid disorders, especially elevated plasma triglyceride concentrations, is causally related to the development of high blood pressure in fructose-fed rat model (33). On the other hand, administration of bezafibrate, an anti-hypertriglyceridemic drug, lowered blood pressure and plasma free fatty acid and triglyceride levels in fructose-induced hypertensive rats without significantly altering plasma insulin concentrations (33). Damiano et al. also reported that rats on fructose diet alone for 2 weeks developed hypertriglyceridemia and hypertension without hyperinsulinemia (10). Furthermore, rats treated with fructose plus glycerol exhibited hypertriglyceridemia, hyperinsulinemia and greater blood pressure elevation as compared to the rats on fructose diet alone. Collectively, these observations imply that an abnormal lipid profile, especially hypertriglyceridemia, plays a primary role in the development of high blood pressure in fructose-induced hypertensive rats. In the present study, we found that fructose feeding for a week caused significant increases in plasma triglyceride levels and blood pressure that preceded the rise of plasma insulin concentrations without substantially changing the plasma glucose levels in both groups. Thereafter, the plasma triglyceride level and blood pressure further increased. However, the magnitudes of increases in plasma triglyceride concentrations were significantly smaller in sympathectomized rats than in intact rats after the 3rd post-fructose week when the plasma insulin levels were coincidentally increased in both groups. An initially slight (4th-5th week) but later statistically significant (after the 6th post-fructose week) reduction in blood pressure elevation was observed in sympathectomized rats. The present results are consistent with the suggestion that chronic hypertriglyceridemia may play an important role in the development of fructose-induced hypertension.

The metabolic mechanism underlying fructose-induced hypertriglyceridemia is not well understood. Previous studies have indicated that overproduction rather than impaired peripheral clearance of hepatic

very-low-density-lipoprotein triacylglycerol (VLDL-TG) is involved (12, 40). Zavaroni et al. further suggested that fructose overconsumption could produce hypertriglyceridemia by directly stimulating hepatic VLDL-TG secretion and producing insulin resistance and hyperinsulinemia, and that the combined effect of these actions might determine the magnitude of fructose-induced hypertriglyceridemia (40). Our current data support this contention and further suggest that an activated peripheral SNS due to fructose-feeding may mediate the increase of plasma triglyceride levels. It needs, however, to further investigate in which metabolic pathway the SNS participates to produce hypertriglyceridemia after fructose feeding in rats (21).

In summary, we have demonstrated that neonatal chemical sympathectomy with guanethidine treatment attenuated, but did not prevent, fructose-induced elevations in plasma triglyceride concentrations and blood pressure. The amelioration of hypertriglyceridemia preceded the manifestation of lower blood pressure levels in fructose-fed, sympathectomized rats. Fructose feeding produced hyperinsulinemia but did not alter plasma glucose levels. The euglycemic hyperinsulinemia status was not affected by chemical sympathectomy. The present results suggest that the peripheral SNS participates in the mechanism of fructose-induced hypertriglyceridemia that might be causally related to the development of high blood pressure in fructose-induced hypertensive rats.

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