

# Attenuation of Hypertriglyceridemia-induced Pressor Effect in Rats with Fructose-induced Insulin Resistance

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## Abstract

This study was designed to compare the pressor response to hypertriglyceridemia under basal glucose and insulin condition as well as the decay pattern of this lipid-induced pressor effect in normal (NRs) and fructose-induced insulin resistant rats (FIRs). The rats were on a fructose-enriched or a regular chow diet for 8 wks and then were further divided into two subgroups (n = 8/group) with lipofundin (a 20% triglyceride emulsion) or saline infusion during the following clamp study. The acute clamp experiment contained a 30-min basal period, followed by a 120-min test period and a 90-min off period. After the basal period, somatostatin (1.3 µg/kg/min) combined with regular insulin (0.6 mU/kg/min) and variable glucose infusion were given to keep insulin and glucose levels basal throughout the experiment. The baseline triglyceride levels were about 6 folds higher in FIRs than those in NRs. During the test period, the lipofundin infusion (1.2 ml/kg/hr) increased plasma triglyceride levels by  $368 \pm 39$  and  $489 \pm 38$  mg/dL from baseline in NRs and FIRs, respectively. The elevated triglyceride level was dropped promptly while the lipofundin infusion was discontinued in the following off period. FIRs have higher mean arterial blood pressure (MAP) levels than those in NRs. During the test period, the hypertriglyceridemia-induced press responses were markedly delayed and attenuated in FIRs compared with those in NRs. Accordingly, the value of  $\Delta\text{MAP}/\Delta\text{TG}$  served as an index of the hypertriglyceridemia-induced increase in BP was significantly lower in FIRs than in NRs. This hypertriglyceridemia-induced pressor effect was sustained to the end of study even after removal of the lipid infusion for 60 min in NRs and FIRs. In rats without lipofundin infusion, MAP and plasma triglyceride levels failed to change throughout the study. The present results suggest that the prolonged pressor response induced by acute hypertriglyceridemia is attenuated in rats with fructose-induced insulin resistance.

**Key Words:** hyperlipidemia, hypertriglyceridemia, pressor response, fructose-fed rats, insulin resistance

## Introduction

Epidemiologic and clinical evidence document

a close association among hypertension, insulin resistance and dyslipidemia (hypertriglyceridemia and lower levels of high-density lipoprotein cholesterol)

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and they also are the predominant features of metabolic syndrome (17, 22, 29). However, the interactions among these pathological conditions are only partly understood. Recent study conducted in humans demonstrated an independent association between baseline lipids and hypertension, excluding men with diabetes and obesity (11). In addition, hypertriglyceridemia has been demonstrated to induce an endothelial dysfunction through the production of an oxidative stress (1, 2, 4). This process may cause endothelial damage and the loss of physiological vasomotor activity, that results from endothelial damage, may eventually become manifested as increased blood pressure (BP). However, a specific and direct role of hypertriglyceridemia, independent of the concomitant hyperinsulinemia in pathogenesis of insulin-resistant associated hypertension is still not well defined (6).

On the other hand, although the dyslipidemia associated with insulin resistance has been postulated to contribute to elevated blood pressure (BP) (4, 11), much of our knowledge about the chronic cardiovascular actions of lipid is based on the extrapolations from the acute studies or on the correlations and associations between lipids and various cardiovascular changes rather than experimentally established, direct cause and effect relationship.

Hyperinsulinemia/insulin resistance, hypertriglyceridemia and hypertension have been documented in the fructose-induced hypertensive rat model (9, 15). Although the precise mechanism has not been fully understood, it has been proposed that hypertension in fructose-fed rats is causally related to the development of metabolic abnormalities such as hypertriglyceridemia (20, 26) and hyperinsulinemia/insulin resistance (9, 17). Thus, the fructose-induced hypertensive rat is an appropriate animal model for evaluating the contribution of elevated triglyceride levels to the pathogenesis of hypertension under insulin resistant condition.

The aim of the present study was to compare the pressor response to acute hypertriglyceridemia created by infusing a triglyceride emulsion in rats with normal and fructose-induced insulin resistance under basal glucose and insulin condition. We are also interested in evaluating whether the decay patterns of the hypertriglyceridemia-induced pressor responses are different between normal and fructose-fed rats.

## Materials and Methods

### *Animals and Surgical Procedures*

Male Sprague-Dawley rats (5-6 weeks old) were purchased from the National Laboratory Animal Breeding and Research Center (Taipei, Taiwan). The rats were housed in regular cages in an animal room

with a constant temperature of  $22 \pm 1^\circ\text{C}$  and a fixed 12 h light-dark cycle. All animals were handled and housed according to the guidelines of the Committee of the Care of Laboratory Animals of this institute.

The rats were randomly assigned into four groups ( $n = 8/\text{group}$ ): rats in group C and  $C_{TG}$  were fed regular chow diet ( $n = 8/\text{group}$ ). Rats in group F and  $F_{TG}$  were fed a 60% fructose-enriched diet (TD89247; Teklad Primer Labs, Madison, WI, USA). After 8 weeks on their respective diets, rats were catheterized with micro-renathane implantation tubing (0.040 in. O.D.  $\times$  0.025 in. I.D. and 0.033 in. O.D.  $\times$  0.014 in. I.D.) in the left femoral artery for BP measurement and blood sampling as well as right femoral vein for solution infusion. The proximal ends of these implanted cannulations were sealed off and placed in subcutaneous pockets under scapular area of rats. After recovery for 3 to 4 days, the rats were studied only if they had restored pre-operation body weight. On the morning of acute study, the proximal ends of the catheters were exteriorized and cleared. Thus, the intravenous and intra-arterial accesses were established. The following clamp experiments were performed on rats under unanesthetized and unrestrained conditions.

### *Experimental Designs*

There was a 30-min basal period, followed by a 120-min test period and a 90-min off period. After the basal period, constant infusions of the following solutions were begun, and these infusions were continued throughout experiment. Somatostatin (1.3  $\mu\text{g}/\text{kg}/\text{min}$ , BACHEM, AG, San Carlo, CA, USA) was infused to suppress endogenous insulin and glucagon secretion. Regular insulin (0.6 mU/kg/min, Actrapid, Novo Nordisk A/S, Denmark) was replaced in all groups to maintain a similar basal insulin level. In addition, a primed, continuous peripheral infusion of 50% dextrose was begun at time 0 in order to quickly clamp the blood glucose at the basal level. A primed-continuous infusion (primed 0.2 ml, continuous infusion with 1.2 ml/kg/hr) of lipofundin (a triglyceride emulsion, 20% MCT/LCT, B Braun, Melsungen, Germany) was given in group  $C_{TG}$  and  $F_{TG}$  respectively during the test period to create a comparable and significantly high triglyceride level. Plasma triglyceride levels during the test period were increased by  $368 \pm 39$  and  $489 \pm 38$  mg/dl as compared to their baseline values in  $C_{TG}$  and  $F_{TG}$  groups, respectively. The same infusion rate of saline instead of lipofundin was given into group C and F. Previous studies have shown that acute administration of a triglyceride emulsion alone could create a prominent hypertriglyceridemia but only increased relatively small amount of plasma nonesterified fatty acids (NEFAs) (10, 28). During the following off period, lipofundin or saline infusion

was stopped in all groups. Blood samples of 0.05 ml were obtained from the femoral artery every 10-15 min for measuring the whole blood glucose concentrations to allow maintenance of steady-state basal arterial glucose levels. Larger blood samples (0.4 ml) for data acquisition were obtained from the femoral artery at time 0, 60, 90, 120, 150, 180 and 210 min. The total blood withdrawn was not more than the amount (7 ml/kg) shown previously to provoke stress and insulin resistance in glucose clamp studies in anesthetized rats (25). Indeed, the present result showed that hematocrit levels did not significantly change throughout the whole experiments in all rats.

### Blood Pressure Measurements

Direct blood pressure measurements were performed in the experimental rats under conscious state by connecting the femoral artery catheter to a polygraph (Gould RS3400 4-ch recorder, Gould Inc., Oxnard, CA, USA) *via* a pressure transducer (Spectramed P23XL, Spectramed Inc., Oxnard, CA, USA) for arterial pressure and heart rate monitoring.

### Chemical Analysis

Whole blood glucose levels were assayed by the glucose oxidase method with a YSI glucose analyzer (YSI 2300 Plus, Yellow Springs Instruments, Yellow Springs, OH, USA). Plasma triglyceride levels were determined by using appropriate enzymatic colorimetric method (Roche Mira plus, Roche Diagnostic systems, Inc, Basel, Switzerland). Plasma insulin levels were measured by solid phase two-site enzyme immunoassay technique using a commercial available kit provided by ALPCO (rat insulin ELISA kit, Mercodia AB, Uppsala, Sweden).

### Calculation

$\Delta\text{MAP}/\Delta\text{TG}$  represents the increase in mean arterial blood pressure (MAP) divided by the increase in plasma triglyceride (TG) level and was served as an index of triglyceride-induced increase in BP. The increase in MAP or TG was defined by the difference of mean MAP or TG level between groups with and without lipofundin infusion in each corresponding period.

### Statistical Analysis

Statistical analysis was performed according to the repeated measurements of one-way analysis of variance (ANOVA) followed by Bonferroni test. A probability of  $P < 0.05$  was taken to indicate a significant difference between means. Values are expressed as mean  $\pm$  SEM.

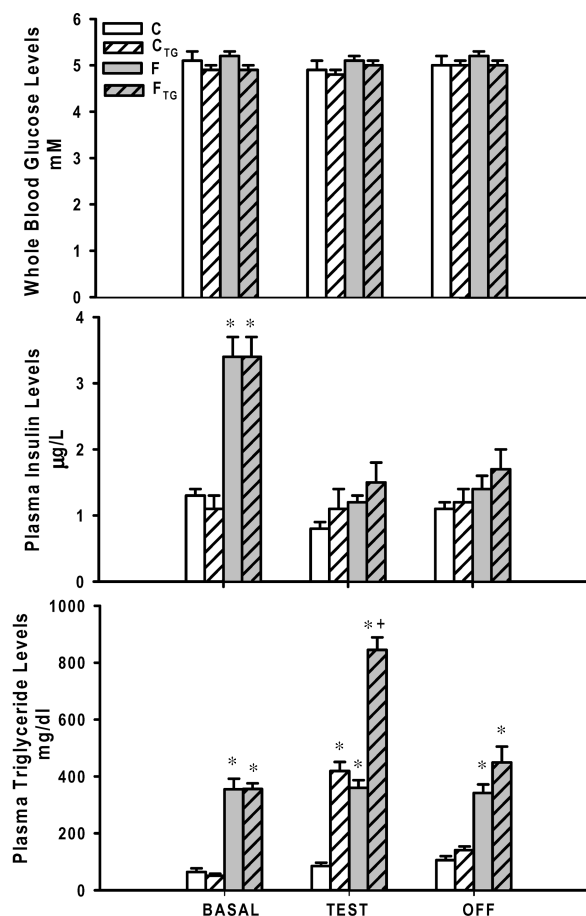


Fig. 1. Changes in whole blood glucose, plasma insulin and triglyceride concentrations. BASAL, basal period; TEST, test period with lipofundin or saline infusion; OFF, off period in which lipofundin or saline infusion was discontinued. C, control rats with saline infusion during the test period; C<sub>TG</sub>, control rats with lipofundin infusion during the test period; F, fructose-fed rats with saline infusion during the test period; F<sub>TG</sub>, fructose-fed rats with lipofundin infusion during the test period. N = 8/group. \*,  $P < 0.05$  vs. the value from the corresponding time point of C; +,  $P < 0.05$  vs. the value from the corresponding time point of F.

## Results

### Body Weight, Whole Blood Glucose, Plasma Insulin and Triglyceride Concentrations

Pre-experimental body weight was not significantly different among all groups ( $490 \pm 8$ ,  $487 \pm 6$ ,  $502 \pm 8$ ,  $499 \pm 9$  g in C, C<sub>TG</sub>, F, F<sub>TG</sub>, respectively). As shown in Fig. 1, whole blood glucose levels remained basal and similar throughout the experiment. The baseline plasma insulin levels were significantly higher in fructose-fed groups (F, F<sub>TG</sub>) than those in control groups (C, C<sub>TG</sub>) ( $P < 0.05$ ). During the test and off periods,

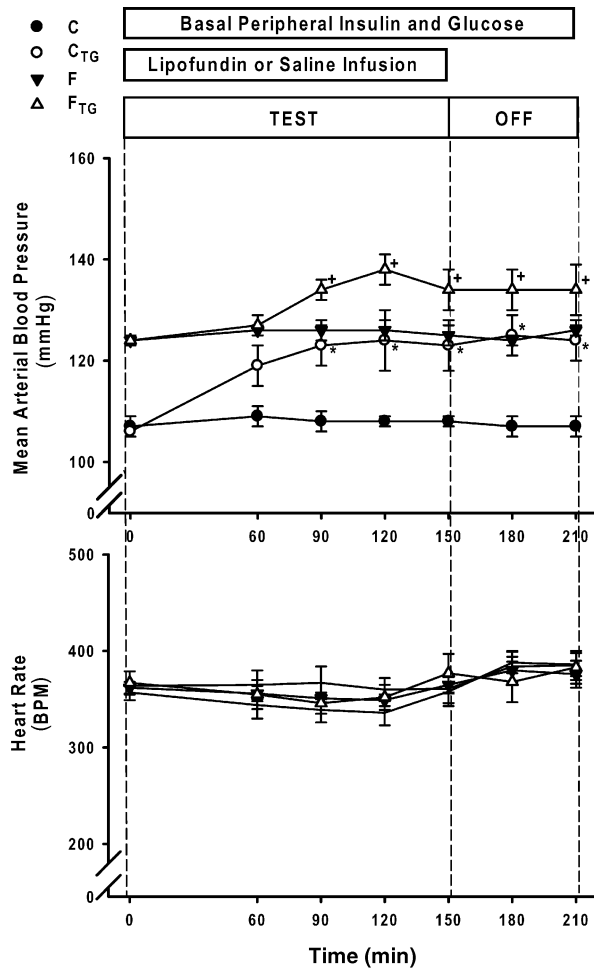


Fig. 2. Changes in the mean arterial blood pressure and heart rate. For abbreviations see Figure 1.  $N = 8/\text{group}$ . \*,  $P < 0.05$  vs. the value from the corresponding time point of C; +,  $P < 0.05$  vs. the value from the corresponding time point of F.

somatostatin combined with low-dose insulin infusion created a steady and similar basal insulin levels in all groups. The baseline triglyceride levels were about six-fold higher in fructose-fed rats than those in control rats. During the test period, the lipofundin infusion increased plasma triglyceride levels by  $368 \pm 39$  and  $489 \pm 38$  mg/dl from baseline in  $C_{TG}$  and  $F_{TG}$ , respectively. During the following off period, the elevated plasma triglyceride level was dropped promptly and returned to basal level after 60 min in both groups ( $C_{TG}$ ,  $F_{TG}$ , data not shown). Plasma glucose, insulin and triglyceride levels did not significantly change throughout the experiment in rats without lipofundin infusion.

#### MAP, Heart Rate and $\Delta\text{MAP}/\Delta\text{TG}$

Figure 2 (upper panel) showed that fructose-fed

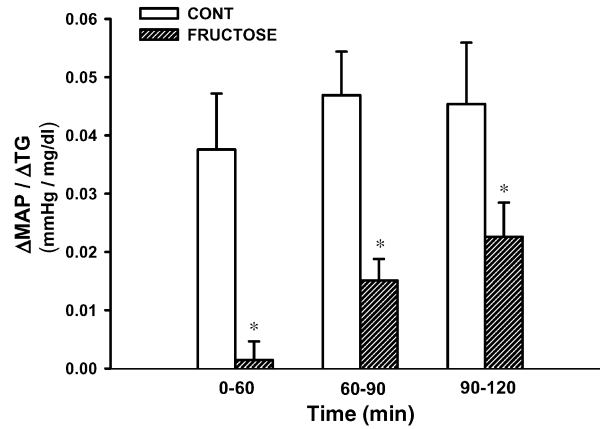


Fig. 3. Changes in the ratio of  $\Delta\text{MAP}/\Delta\text{TG}$  served as an index of the effect of triglyceride-induced increase in BP.  $\Delta\text{MAP}$ , the difference of MAP between groups with and without lipofundin infusion in each corresponding period;  $\Delta\text{TG}$ , the difference of plasma triglyceride levels between groups with and without lipofundin infusion in each corresponding period. CONT, control groups; FRUCTOSE, fructose-fed groups.  $N = 8/\text{group}$ . \*,  $P < 0.05$  vs. CONT in the corresponding period.

rats have significantly higher baseline MAP levels than those in control rats. From the basal to test period, the lipofundin-induced pressor responses were markedly delayed and attenuated in fructose-fed rats (from  $124 \pm 1$  to  $133 \pm 1$  mmHg) compared with those in control rats (from  $106 \pm 1$  to  $122 \pm 4$  mmHg). Accordingly, the ratio of  $\Delta\text{MAP}/\Delta\text{TG}$  served as an index of triglyceride-induced increase in BP was significantly decreased in fructose-fed rats (Fig. 3). Nevertheless, this lipid-induced pressor effect was sustained to the end of study in the following off period in both groups.

No significant difference was found in heart rate among all groups throughout the experiment (Figure 2, lower panel).

## Discussion

Hypertriglyceridemia associated with insulin resistance has been postulated to involve in the pathogenesis of hypertension and cardiovascular diseases. However, the contribution and characteristics of hypertriglyceridemia in regulation of BP under insulin resistant condition remains undefined. In this study, we compared quantitatively the hypertriglyceridemia-induced pressor responses in normal and fructose-induced insulin resistant rats. Our results demonstrate that the hypertriglyceridemia-induced prolonged pressor effect showed in normal rats was blunted in fructose-fed rats. Nevertheless, the prolonged pressor responses induced by lipofundin sustained both in normal and fructose-fed rats. These observations

suggest that this long lasting pressor response triggered by acute hypertriglyceridemia was attenuated under the development of insulin resistance in rats.

Previous studies showed that bezafibrate, an anti-hypertriglyceridemic drug, could attenuate the elevated BP in fructose-induced hypertensive rats (26) and hypertensive patients with hypertriglyceridemia (16). Moreover, troglitazone, a peroxysome proliferator-activated receptor agonist, was shown to normalize the elevated plasma triglyceride concentration and systolic blood pressure in fructose-fed rats (20). These studies suggest that hypertriglyceridemia may be causally involved in the development of hypertension in fructose-fed rats and human subjects. However, so far, there was no compelling evidence to compare the direct role of hypertriglyceridemia in regulation of BP under normal and insulin resistant conditions. Our observations provide evidence to demonstrate that the direct pressor effect induced by short-term hypertriglyceridemia was diminished in rats with fructose-induced insulin resistance.

Recent studies have suggested that hypertriglyceridemia can induce an endothelial dysfunction throughout the production of an oxidative stress (1, 2, 4) and enhance endothelin-1 release (17), which can eventually lead to increase in BP. On the other hand, elevated triglyceride levels have been documented to enhance  $\alpha$ -1 adrenergic receptor mediated pressor response in human subjects (10). Our previous study (14) and other report (19) have also shown that sympathectomy or ganglion blockade can significantly attenuate the elevated BP in fructose-induced hypertensive model and Prague hereditary hypertriglyceridemic rats with genetic hypertension, suggesting an inducing role of sympathetic neural mechanism in hypertriglyceridemia-associated hypertension. Furthermore, chronic hyperlipidemia could exacerbate the response to vascular injury that lead to intimal proliferation and connective tissue matrix accumulation in the disease artery in rabbits (7). Sustained hyperinsulinemia has been demonstrated to cause vascular medial hyperplasia, arterial stiffness and luminal narrowing, and hence lead to increase in the peripheral vascular resistance and BP (5, 7). Therefore, it is likely that structural alterations in the cardiovascular system under chronic hypertriglyceridemia and hyperinsulinemia/insulin resistance could be the dominant factors for the different pressor responses to lipofundin infusion between control and fructose-fed rats. However, the underlying mechanisms remain to be further elucidated.

On the other hand, insulin has been documented to stimulate the sympathetic nerve system (23) and also promote renal sodium retention (8), which can lead to an increase in BP. To avoid any potential effects of hyperinsulinemia-induced pressor responses

on data interpretation, we used somatostatin to inhibit endogenous insulin secretion and combined with low-dose insulin infusion and variable glucose infusion to keep insulin and glucose levels basal throughout the present experiment. Our data showed that acute increase in plasma triglyceride concentration can directly raise the BP level, independent of insulin-mediated pressor actions in control and fructose-fed rats.

In addition, our recent study (13) has shown that insulin-mediated pressor effect and nitric oxide release exhibited in control rats were also diminished in fructose-fed rats. Taken together with the present result, these observations suggest that hypertriglyceridemia and hyperinsulinemia associated with insulin resistance are the significant contributing factors in the development of fructose-induced hypertension. Furthermore, the attenuated acute hemodynamic responses induced by elevated plasma triglyceride and insulin levels implicate that sustained hypertriglyceridemia and hyperinsulinemia-induced chronic vascular structure changes instead may be vital in setting of BP in this hypertensive model.

Previous report suggests that the rodent model is suitable for generating clinical relevant data on the link between lipid metabolism and cardiovascular responses in which fatty acid oxidation and metabolism in rats and humans are similar (28). Consistently, the dyslipidemia associated with insulin resistance has been documented to contribute to elevated BP in both humans and rodent models (3, 21, 24). Therefore, the present result may be of clinical importance to delineate the potential role of hypertriglyceridemia in the regulation of BP under the state of insulin resistance in human subjects.

Previous investigations showed that a 20% triglyceride emulsion alone induced significant hypertriglyceridemia but only increased relatively small amount of NEFA in rats and humans (10, 28). Thus, the elevated plasma triglyceride levels seem to play a dominant role in the lipofundin-induced pressor response in the present study. However, the potential pressor effects to elevated NEFA (12) during acute lipofundin infusion may be small, but can not be completely ignored.

Collectively, our results demonstrate that hypertriglyceridemia-induced prolonged pressor responses was attenuated in rats with fructose-induced insulin resistance, suggesting that the other pressor mechanisms instead of the direct pressor effect of hypertriglyceridemia may be predominant in maintenance of elevated BP in fructose-fed rats.

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