Diminution of Hypertriglyceridemia-Induced Pressor Effect under Hyperinsulinemic Condition in Normal and Fructose-Induced Insulin Resistant Rats

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Abstract

This study aimed to evaluate the effect of hyperinsulinemia on hypertriglyceridemia-induced pressor response in normal and fructose-induced insulin resistant rats. The rats were divided into six groups of eight rats and were fed a fructose-enriched diet (F_{INS}, F_{INS+TG}) or a regular chow diet (C, C_{TG}, C_{INS}, C_{INS+TG}) for 8 wks. The acute experiment was conducted at the end of wk 8 and consisted of a 30-min basal period and followed by a 120-min test period. After the basal period, somatostatin (1.3 μg/kg/min) combined with regular insulin (0.6 or 4 mU/kg/min) and variable glucose infusion were given to clamp euglycemia and euinsulinemia in C and C_{TG} or euglycemia and hyperinsulinemia in C_{INS}, C_{INS+TG}, F_{INS} and F_{INS+TG}. During test period, lipofundin (a triglyceride emulsion) was infused into C_{TG}, C_{INS+TG}, F_{INS+TG} and saline instead was infused into C, C_{INS}, F_{INS}. Plasma insulin and triglyceride levels were significantly higher in fructose-fed rats than in normal rats. During the test period, the lipofundin infusion (1.2 ml/kg/hr) increased plasma triglyceride levels by 368 ± 39, 351 ± 71 and 489 ± 38 mg/dl compared with their baseline levels in lipid-infused groups. During the test period, low-dose insulin infusion kept plasma insulin at basal levels in C and C_{TG} and high-dose insulin infusion increased plasma insulin levels about 6 times the baseline insulin level in C. Glucose infusion rate (GIR) was significantly higher in rats with high insulin infusion than those with low insulin infusion. The increase in GIR was lower in fructose-fed groups than in control groups under similar hyperinsulinemia. Rats with or without lipofundin infusion did not alter GIR during the test period. The present results demonstrated that hypertriglyceridemia-induced pressor response was diminished under hyperinsulinemic condition in both normal and fructose-induced insulin resistant rats.

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

Introduction

Hypertriglyceridemia and hyperinsulinemia associated with insulin resistance have been postulated to contribute to elevated blood pressure in clinical and animal studies and they also are the main features of metabolic syndrome (7, 13, 18, 19, 27). Accordingly, high triglycerides and nonesterified fatty accids (NEFAs) have been documented to associate with activation of sympathetic nervous system (8, 10) and cause endothelial dysfunction through the production of an oxidative stress (1, 4) in studies of animals and human subjects. On the other hand, previous studies have shown that insulin can promote renal sodium retention (6), induce sympathetic neural activation (19) and nitric oxide (NO) release (9), leading to change in blood pressure. It is likely that hypertriglyceridemia and hyperinsulinemia-induced pressor effects might interact somehow to affect the regulation of blood pressure under the state of insulin resistance.

The possible interaction of pressor actions induced by hypertriglyceridemia and hyperinsulinemia under state of insulin resistance remains elusive. On the other hand, although the precise mechanism has not been clearly elucidated, it has been proposed that hypertension in fructose-fed rats is secondary to the development of hypertriglyceridemia (12, 15, 23) and insulin resistance /hyperinsulinemia (11, 14). Thus, the fructose-induced hypertensive rat is an appropriate animal model for evaluating the effect of hyperinsulinemia on hypertriglyceridemia-induced pressor response under state of insulin resistance.

The aim of this study was to use somatostatin and blood substrate clamp technique to quantify functionally the triglyceride-induced pressor action under normal and hyperinsulinemic conditions in normal and fructose-induced insulin resistant rats. The present study is important to help in understanding the role of hypertriglyceridemia and hyperinsulinemia in the pathogenesis of insulin-resistant associated hypertension.

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, ROC). The rats were housed in regular cages in an animal room with a constant temperature of $22 \pm 1°C$ 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 six groups of eight rats: rats in group C, C_{TG}, C_{INS} and C_{INS+TG} were fed a regular chow diet. Rats in group F_{INS} and F_{INS+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-polyurethane implantation tubing MPT40 (0.040 in. O.D. × 0.025 in. I.D.) in the left femoral artery for blood pressure (BP) measurement and blood sampling and MPT33 tubing (0.033 in. O.D. × 0.014 in. I.D.) in the right femoral vein for solution infusion. The proximal ends of the tubes were sealed off and placed in subcutaneous pockets under scapular area of rats. After recovering for 3-4 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 exterized 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

The clamp experiment contained a 30-min basal period followed by a 120-min test period. After the basal period, constant infusion of the following solutions was began and was continued throughout the experiment. Somatostatin (1.3 μg/kg/min, BACHEM, King of Prussia, PA, USA) was infused to suppress endogenous insulin and glucagon secretion. Low-dose insulin (0.6 mU/kg/min, Actrapid, Novo Nordisk A/S, Denmark) was replaced in groups C and C_{TG} to maintain an insulin level similar to basal. On the other hand, high-dose insulin infusion (4 mU/kg/min) was given in groups C_{INS}, C_{INS+TG}, F_{INS} and F_{INS+TG} to maintain a comparable high insulin level among groups. In addition, a primed, continuous peripheral infusion of 50% dextrose began at time 0 in order to quickly clamp blood glucose at 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 groups C_{TG}, C_{INS+TG} and F_{INS+TG} and F_{TG}, respectively during the test period to create a comparable and pathophysiologically high triglyceride level. Plasma triglyceride levels during the test period were increased by 368 ± 39, 351 ± 71 and 403 ± 62 mg/dl compared with their baseline values in groups C_{TG}, C_{INS+TG} and F_{INS+TG}, respectively. The same infusion rate of saline instead of lipofundin was given into the above pair-matched control groups C, C_{INS} and F_{INS}. Previous studies have shown that acute administration of a triglyceride emulsion alone without heparin could create a prominent hypertriglyceridemia but only increase relatively small amount of plasma NEFAs (7, 18). Blood samples of 0.05 ml were obtained from the femoral artery every 10-15 min for measuring 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 and 120 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 study in anesthetized rats (21).

BP Measurements

Direct BP 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 (Spectamed 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, Rochi 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).

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 ± SEM.

Results

Body Weight, Mean Arterial Blood Pressure (MAP), Heart Rate

Pre-experimental body weights were similar between control groups (469 ± 5, 471 ±5, 484 ±9, 488 ± 9 g in groups C, C_{TG}, C_{INS}, C_{INS+TG}) and were slightly higher in fructose-fed groups (518 ± 4 and 522 ± 8 g in groups F_{INS}, F_{INS+TG}). As shown in Figure 1, fructose-fed groups have higher MAP levels than those in control groups in the basal period. During the test period, lipofundin infusion significantly increased MAP in control rats with low-dose insulin infusion
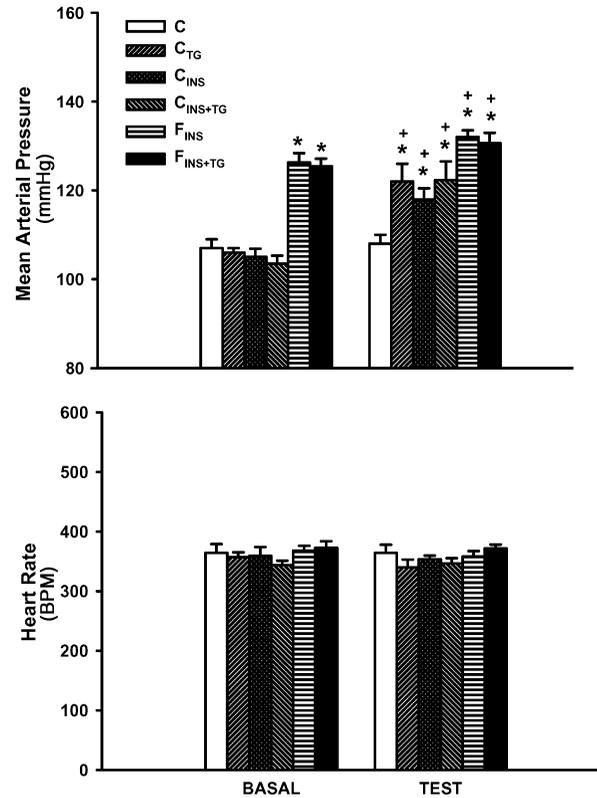

Fig. 1. Changes in the mean arterial pressure and heart rate. BASAL, basal period; TEST, test period; C, control rats with low-dose insulin infusion during the test period; C_{TG}, control rats with low-dose insulin and lipofundin infusion during the test period; C_{INS}, control rats with high-dose insulin infusion during the test period; C_{INS+TG}, control rats with high-dose insulin and lipofundin infusion during the test period; F_{INS}, fructose-fed rats with high-dose insulin infusion during the test period; F_{INS+TG}, fructose-fed rats with high-dose insulin and lipofundin infusion during the test period. N = 8/group. *, $P < 0.05$ *vs.* the value from the corresponding period of C; +, $P < 0.05$ *vs.* the baseline value of the same group.

but not in those with high-dose insulin infusion. Moreover, lipofundin administration failed to change MAP in fructose-fed rats with high insulin infusion. When compared with their baseline levels, high insulin infusion significantly increased MAP in control rats (C_{INS}, C_{INS+TG}), but this insulin-stimulated pressor effect was significantly attenuated in fructose-fed rats (F_{INS}, F_{INS+TG}). Heart rates did not significantly change between experimental groups in the same corresponding period throughout the whole experiment and between basal and test periods within the same group.

Plasma Insulin, Triglyceride, Glucose Concentrations, and Glucose Infusion Rate (GIR)

Figure 2 (upper panel) showed that plasma

glucose levels did not change between experimental groups throughout the experiment and between the basal and test periods within the same group. As shown in Figure 2 (middle and lower panels), plasma insulin and triglyceride levels were significantly increased in rats fed a fructose-enriched diet for 8 wks. During the test period, high-dose insulin infusion (4 mU/kg/min) significantly increased plasma insulin about 6 times the baseline value of group C. Lipofundin infusion significantly elevated plasma triglyceride levels in C_{TG}, C_{INS+TG}, F_{INS+TG} compared with their pair-matched control groups with saline infusion (368 ±39 $vs.$ 85 ±12, 425 ±75 $vs.$ 76 ±10, 819 ±88 $vs.$ 380 ±66 mg/dl in C_{TG} $vs.$ C, C_{INS+TG} $vs.$ C_{INS}, F_{INS+TG} $vs.$ F_{INS}, respectively).

During the test period, the GIR was significantly higher in rats with high insulin infusion than those with low insulin infusion. However, increase in GIR was significantly lower in fructose-fed groups than in control groups under similar hyperinsulinemia. Lipofundin infusion did not alter GIR in experimental rats.

Discussion

Hypertriglyceridemia has been documented to be causally involved in the development of hypertension in fructose-fed rats (23) and human subjects (12). However, so far, there was no compelling evidence to evaluate the interplay of hyperinsulinemia and hypertriglyceridemia in BP control under normal and insulin resistant conditions. In this study, we compared quantitatively the effect of hyperinsulinemia on hypertriglyceridemia-induced pressor responses in normal and fructose-induced insulin resistant rats. Our results demonstrate that in absence of hypoglycemia the hypertriglyceridemia-induced pressor effect seen under basal insulin condition was diminished under hyperinsulinemic condition in both normal and fructose-induced insulin resistant rats.

Our recent studies (9, 16) focused on the characteristic of individual pressor response induced by hyperglyceridemia or hyperinsulinemia in normal and fructose-induced insulin resistant rats, have demonstrated that under euglycemic condition both short-term infusion of a triglyceride emulsion and an insulin solution to mimic pathophysiological triglyceride and insulin levels could induce significant pressor responses respectively in normal rats. Both of these pressor responses were attenuated under the state of fructose-induced insulin resistance in rats. In the present study, we further showed that increase in plasma triglyceride concentrations did not display a synergistic effect on hyperinsulinemia-induced pressor response in fructose-fed and control rats, implicating that hypertriglyceridemia and hyperinsulinemia-
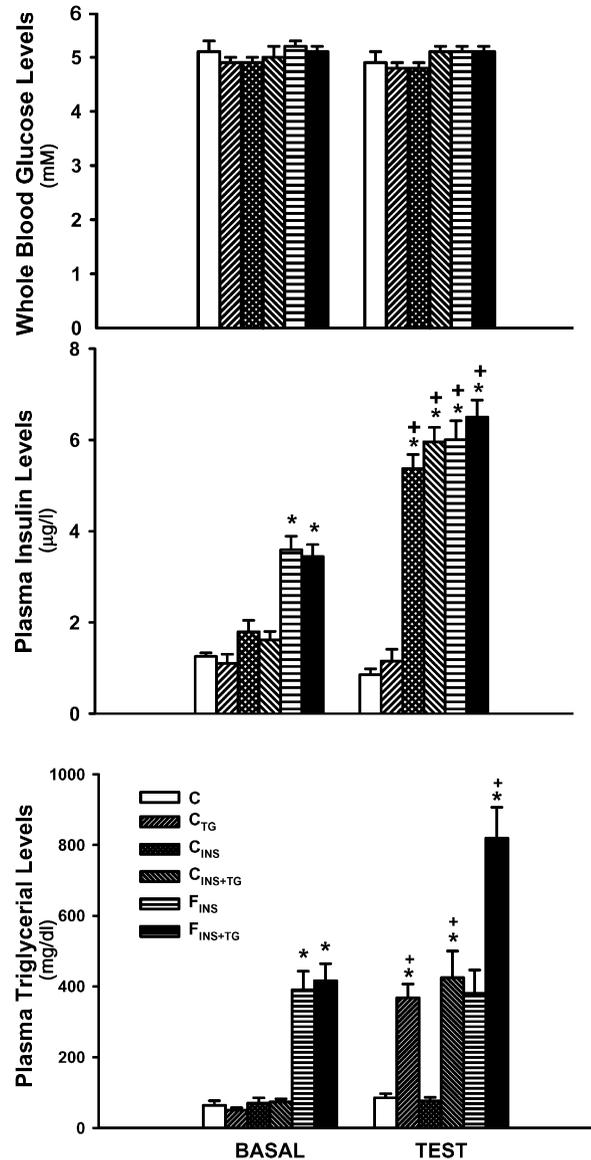

Fig. 2. Changes in whole blood glucose, plasma insulin and triglyceride concentrations. For abbreviations see Figure 1. N = 8/group. *, $P < 0.05$ $vs.$ the value from the corresponding period of C; +, $P < 0.05$ $vs.$ the baseline value of the same group.

mediated pressor effects may be mediated mainly by the same underlying mechanism in either normal or insulin resistant conditions.

Although the pathogenic mechanisms of acute hypertriglyceridemia and hyperinsulinemia-induced pressor actions were not further investigated in the present study, the previous reports have demonstrated that activation of sympathetic nervous system may play an inducing role in hypertriglyceridemia-induced pressor response in human (8) and animal studies (11, 14). On the other hand, insulin infusion in the absence of changes in blood glucose has been documented to
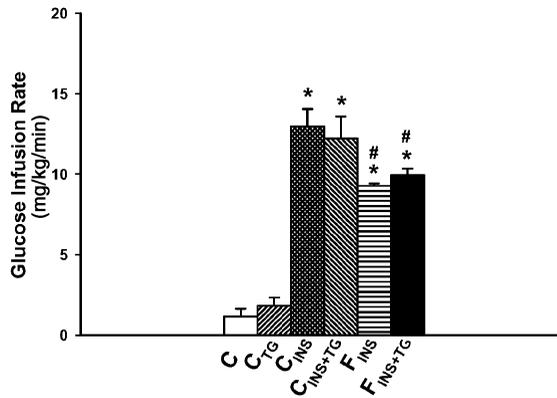
Fig. 3. Change in glucose infusion rate during test period. For abbreviations see Figure 1. N = 8/group. *, $P < 0.05$ *vs.* the value from the corresponding time point of C; #, $P < 0.05$ *vs.* the value from the corresponding period of C_{INS}.

induce sympathetic neural activation in normal man (22) and to enhance pressor responses to norepinephrine in rat mesenteric vasculature (25). Therefore, it is likely that sympathetic neural activation induced by the elevation of plasma triglyceride and insulin concentrations may be the common underlying mechanism of their pressor actions in normal and fructose-fed rats in the present study.

On the other hand, postprandial hypertriglyceridemia has been reported to enhance oxidative stress and decrease endothelial nitric oxide release, resulting in endothelial dysfunction and an increase in vascular tone along with blood pressure (1, 4). This triglyceride-mediated action could counteract peripheral vasodilatory effect of insulin (3) and further enhance insulin-stimulated pressor response *via* sympathetic neural activation. The present result implicates that the contribution of this enhancing action of hypertriglyceridemia on insulin-induced pressor response (3) is trivial in this hypertensive model. Our observations suggest that acute hypertriglyceridemia and hyperinsulinemia may induce blood pressure elevation *via* a common pathway, likely sympathetic neural activation but not direct vascular effect.

The present result demonstrates that insulin resistance is not a significant contributing factor to change the elevated BP induced by short-term increase in plasma triglyceride and insulin levels in fructose-fed rats. Hyperinsulinemia and insulin resistance are coexisted and both are considered to participate in development of hypertension in this fructose-induced and other insulin resistance-associated hypertensive models (7). Previous study has demonstrated that vascular insulin resistance in fructose-fed rats leads to blunt insulin's vasodilatory effects and may result in the increase in vascular tone and blood pressure (26). Taken together with the present result, our observation suggests that

this chronic vascular effect induced by insulin resistance seems to play an important role in setting of blood pressure but not in short-term hypertriglyceridemia and hyperinsulinemia-induced pressor responses in this fructose-induced hypertensive model.

Fatty acid oxidation and metabolism have been reported to be similar in rats and humans (24), so that the rodent model has been speculated to be suitable for generating clinical relevant data on the link between lipid metabolism and cardiovascular responses. Consistently, the dyslipidemia associated with insulin resistance has been documented to contribute to elevated BP in both humans and rodent models (2, 17, 20). Therefore, the present result may be of clinical importance to delineate the potential interplay of hypertriglyceridemia and hyperinsulinemia in regulation of BP under the state of insulin resistance in human subjects.

On the other hand, the sustained increase in plasma insulin level has been documented to have diverse arterial pressure responses in rats and in other species (*i.e.* human and dog) (6). The reason is not definitely known but may be due to species difference in the pressor and depressor actions of insulin. The present result indicates that the pressor actions of triglyceride and insulin (not including the depressor action of insulin) may be mediated by the same pathway such as stimulating sympathetic nervous activity. The differences of species in insulin-mediated hemodynamic actions do not seem to affect the data interpretation and significance of this paper.

Clerk *et al.* (5) has shown that infusion of triglycerides (10% intralipid, 20 µl/min) and heparin impairs insulin-mediated capillary recruitment and muscle glucose uptake under 2 h hyperinsulinemic euglycemic clamp study. They conclude that acute elevation of plasma NEFAs blocks these insulin-mediated hemodynamic and metabolic actions. However, lipofundin infusion alone without heparin leading to increase mainly plasma triglyceride levels (8, 24) did not change GIR under euglycemia and euinsulinemic or hyperinsulinemic conditions in normal and fructose-induced insulin resistant rats. These investigations suggest that the elevation of plasma NEFAs instead of triglycerides is critical to suppress insulin-mediated capillary recruitment and muscle glucose uptake. Further studies are needed to clarify this issue. In addition, the change in GIR was not associated with hypertriglyceridemia and hyperinsulinemia-induced pressor responses in the present study, indicating that it may not play a significant role in hypertriglyceridemia and hyperinsulinemia-induced pressor effects.

In conclusion, our results demonstrate that acute hypertriglyceridemia-induced pressor response per se was significantly attenuated under hyperinsulinemic condition and this diminution of triglyceride-mediated

pressor action was exhibited both in normal and fructose-induced insulin resistant rats, suggesting that the potential interplay between hypertriglyceridemia and hyperinsulinemia-induced hemodynamic responses might play an important role in development of insulin resistance-associated hypertension.

Acknowledgments

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