Intralipid Enhances α1-Adrenergic Receptor–Mediated Pressor Sensitivity

Adetola T. Haastrup, Konrad T. Stepniakowski, Theodore L. Goodfriend, Brent M. Egan

Abstract—The dyslipidemia in obese hypertensive persons may contribute to their increased vascular α-adrenergic receptor reactivity and tone. To further examine this notion, we conducted 2 studies of pressor sensitivity to phenylephrine, an α1-adrenergic receptor agonist, in lean normotensive subjects. In the first study (n=6), pressor responses to phenylephrine were obtained before and during a saline and heparin infusion. On another day, pressor reactivity to phenylephrine was measured before and during infusion of 20% Intralipid at 0.5 mL · m⁻² · min⁻¹ with heparin at 1000 U/h to increase lipoprotein lipase activity and raise nonesterified fatty acids (NEFAs). In the second study (n=8), baseline reactivity to phenylephrine was obtained on 2 separate days and repeated after raising NEFAs and triglycerides either with 0.8 mL · m⁻² · min⁻¹ of 20% Intralipid alone or together with heparin. The infusion of saline and heparin did not significantly change plasma NEFAs from baseline (516±90 versus 512±108 μmol/L, respectively; P=NS) or the dose of phenylephrine required to raise mean blood pressure by 20 mm Hg ([PD₂₀PE]; 1.00±0.14 versus 0.95±0.10 μg · kg⁻¹ · min⁻¹, respectively, P=NS). Intralipid at 0.5 mL · m⁻² · min⁻¹ with heparin raised plasma NEFAs to 793±30 μmol/L per liter (P<0.05 versus baseline) and reduced PD₂₀PE from 1.01±0.10 to 0.80±0.09 μg · kg⁻¹ · min⁻¹ (P<0.05). Compared with baseline, Intralipid alone increased plasma NEFAs to 946±80 μmol/L (P<0.05), and NEFAs increased further with the addition of heparin to 2990±254 μmol/L (P<0.01). Despite an apparently greater increase of plasma NEFAs with Intralipid and heparin, Intralipid alone and together with heparin similarly reduced PD₂₀PE. Across all study conditions, changes in levels of triglycerides and NEFAs correlated with changes in mean arterial pressure responses to phenylephrine, especially at the 0.4-μg · kg⁻¹ · min⁻¹ infusion rate of phenylephrine (r=0.64, P<0.01 and r=0.54, P<0.01, respectively). These data suggest that raising levels of plasma NEFAs and/or triglycerides enhances α1-adrenergic receptor–mediated pressor sensitivity. The findings suggest that lipid abnormalities in obese hypertensives, which include elevated NEFAs and triglycerides, contribute to greater vascular α1-adrenergic reactivity.

Key Words: fatty acids  phenylephrine  receptors, adrenergic  blood pressure

Insulin resistance is associated with a cluster of cardiovascular risk factors including hypertension, but the intermediary mechanisms linking metabolic and hemodynamic abnormalities are not well defined.1–7 Abdominally obese hypertensive persons have increased vascular α-adrenergic tone and reactivity,8 as well as increased plasma concentrations9 and turnover of nonesterified fatty acids (NEFAs) that are highly resistant to suppression by insulin.10 Evidence implicates abnormalities of NEFAs as one potential pathogenic link between abdominal obesity and hypertension.10,11–12 We observed a positive correlation between plasma fatty acids during euglycemic clamp and blood pressure (BP) in obese subjects that was independent of hyperinsulinemia and insulin-mediated glucose disposal.10 In minipigs, raising fatty acid levels increases systemic vascular resistance and BP.13 Our previous research has shown that raising fatty acids in the dorsal hand vein of normal volunteers to concentrations observed in obese hypertensives significantly increases vasoconstrictor responses to phenylephrine as well as a neurone- flex stimulus.11,14 These observations raise the possibility that the elevated NEFAs in obese hypertensives contribute to the heightened vascular α-adrenergic reactivity and tone in these subjects.

The dorsal hand veins are a readily accessible vascular bed in which large changes in fatty acids can be achieved without significant systemic effects. While this model is useful in assessment of the local actions of fatty acids on vascular reactivity, the more complex and integrated effects of fatty acids on systemic vascular pressor reactivity are probably of greater importance in BP regulation. Consequently, the primary purpose of this study was to extend our observations on the local effects of fatty acids on vascular α1-adrenergic receptor–mediated reactivity to the systemic circulation. A secondary objective was to examine the possible role of elevation of triglycerides in pressor reactivity, since these lipids are elevated in obese hypertensives and other groups with insulin resistance.15 Moreover, triglycerides have also been implicated in BP regulation and vascular reactivity.16,17

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Methods

Human Volunteers

Fourteen lean (body mass index [BMI] ≤ 25.4 kg/m²) normotensive subjects with BP consistently ≤ 140/90 mm Hg were recruited by advertisement and were paid. Subjects provided written informed consent approved by the Office of Research Integrity and Risk Protection. Volunteers underwent a medical history, physical examination, and laboratory evaluation to determine eligibility. Subjects avoided all medications for 2 weeks and caffeine-containing beverages the night before the study.

Physiological Measurements: Blood Pressure

BPs were determined by mercury sphygmomanometry. During the screening visit, BP was measured in triplicate after subjects rested for 5 minutes in the seated position. To qualify, all readings had to be ≤ 140/90 mm Hg. Mean BP (mm Hg) was calculated as diastolic BP plus (systolic BP – diastolic BP)/3.

Biochemical Measurement

Blood for NEFAs was obtained in prechilled Eppendorf tubes. In study 1, samples were collected in tubes containing EDTA and paraaxon (Sigma Chemical Co) to inhibit lipolysis in vitro. In study 2, samples were collected in tubes containing 80 μL of 0.2 mol/L EGTA to inhibit in vitro lipolysis.19 The plasma was stored at −70°C before analysis of total plasma NEFAs by the 63Ni method.20

Protocol

For both studies, each subject reported to the General Clinical Research Center clinical physiology laboratory at 8 AM after an overnight fast. Room temperature was maintained at 75°F. With the patient supine, intravenous catheters were placed in each antecubital vein. One catheter was used for blood sampling and the other for infusions. BP was measured every 5 minutes during the phenylephrine infusion when the interval was reduced to every 3.5 minutes.

Studies 1 and 2

After a 30-minute baseline period with BPs measured at 5-minute intervals, phenylephrine was infused sequentially at 0.2 for 10 minutes and then at 0.4, 0.8, 1.2, 1.6, 2.0, and 2.4 μg · kg⁻¹ · min⁻¹ for 7 minutes each. The phenylephrine infusion was terminated if BP increased by ≥ 50/30 mm Hg. BPs were measured at 5-minute intervals during a 30-minute recovery period.

Study 1

Thirty minutes after the first phenylephrine infusion, saline was infused at 0.5 mL · m⁻² · min⁻¹. Heparin was given as a 200-U bolus followed by a continuous infusion of 1000 U/h on the control day. On the experimental day, 20% Intralipid was infused at 0.5 mL · m⁻² · min⁻¹ together with heparin at the rate noted. The sequence of the 2 study days was randomized. During the infusion of saline or Intralipid and heparin, blood samples were obtained at 15, 30, 45, and 60 minutes for measurement of NEFAs. After 60 minutes of the saline or Intralipid and heparin infusion, the phenylephrine infusion was repeated.

Study 2

After a 30-minute recovery period following the first phenylephrine infusion, 20% Intralipid was infused at 0.8 mL · m⁻² · min⁻¹ on 2 separate days. On one day, Intralipid was infused alone. On the other day, Intralipid was combined with heparin as described above. The sequence of the 2 study days was randomized. During the infusion of Intralipid + heparin, blood samples were obtained at 30, 45, and 60 minutes for measurement of NEFAs. After 60 minutes of Intralipid + heparin, a second phenylephrine infusion was carried out while Intralipid + heparin was continued.

Data Analysis

Data are presented as mean ± 1 SEM. The dose-response curves to phenylephrine were analyzed with linear regression on Sigma Plot (Jandel Scientific Inc). The phenylephrine dose that increased mean BP by 20 mm Hg, ie, the PD20PE, for each curve was derived from this analysis. All other analyses were done with SPSS 6.0 (SPSS Inc). A comparison of the effects of saline and heparin, Intralipid alone, and Intralipid with heparin on the phenylephrine dose-systemic pressor response curve versus either the baseline dose-response curve or among the various treatment conditions was analyzed by 2-factor ANOVA. Changes in plasma NEFAs before and after the infusion of Intralipid + heparin were assessed using a 2-sided, Student’s paired t test. Pearson correlation coefficients were used to assess the relationship between changes in plasma NEFAs and triglycerides and changes in pressor reactivity to phenylephrine. Values of P ≤ 0.05 were considered significant.

Results

The characteristics of volunteers in study 1 and study 2 are shown in Table 1. The low mean values for BMI, BP, and triglycerides, as well as the normal HDL cholesterol values (study 2), suggest that this group of healthy volunteers had normal insulin sensitivity.

Phenylephrine Pressor Reactivity

The dose of phenylephrine required to raise mean BP by 20 mm Hg (PD20PE) served as the main index of pressor reactivity. PD20PE values under baseline conditions, ie, before the infusion of saline and heparin or Intralipid + heparin, ranged from 1.00 ± 0.14 to 1.07 ± 0.11 μg · kg⁻¹ · min⁻¹ in 2 different groups of healthy volunteers each studied on 2 separate days. Saline and heparin did not significantly alter the PD20PE from baseline values (1.00 ± 0.14 to 0.95 ± 0.10 μg · kg⁻¹ · min⁻¹, P = NS). In contrast, the infusion of Intralipid together with heparin in study 1 reduced the PD20PE from a baseline value of 1.01 ± 0.10 to 0.80 ± 0.10 μg · kg⁻¹ · min⁻¹, P < 0.05 (Figure 1). In study 2, the PD20PE declined from 1.07 ± 0.11 μg · kg⁻¹ · min⁻¹ at baseline to 0.76 ± 0.17 μg · kg⁻¹ · min⁻¹ with Intralipid plus heparin and from 1.03 ± 0.07 to 0.76 ± 0.11 μg · kg⁻¹ · min⁻¹ with Intralipid alone (Figure 1). The higher infusion rate of Intralipid (0.8 versus 0.5 mL · m⁻² · min⁻¹) with heparin showed a marginally significant tendency to greater enhancement of phenylephrine pressor reactivity (F = 3.7, P = 0.07). Addition of heparin to 0.8 mL · m⁻² · min⁻¹ Intralipid did not significantly reduce the PD20PE below that with Intralipid alone. None of the Intralipid infusions either with or without heparin altered baseline BP.

Table 1. Characteristics of Subjects in Study 1 and Study 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Age, y</td>
<td>29 ± 2</td>
<td>31 ± 1</td>
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<tr>
<td>BMI, kg/m²</td>
<td>22.6 ± 1.2</td>
<td>22.5 ± 0.8</td>
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<tr>
<td>Gender, F/M</td>
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<td>5/3</td>
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<tr>
<td>SBP, mm Hg</td>
<td>105 ± 3</td>
<td>107 ± 4</td>
</tr>
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<td>DBP, mm Hg</td>
<td>68 ± 2</td>
<td>68 ± 3</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>80 ± 2</td>
<td>81 ± 3</td>
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<tr>
<td>Triglycerides, mmol/L</td>
<td>1.11 ± 0.3</td>
<td>0.82 ± 0.1</td>
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<tr>
<td>LDL cholesterol, mmol/L</td>
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<td>2.72 ± 0.3</td>
</tr>
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</table>
The phenylephrine dose-pressor response curves were also analyzed to assess changes in \( \alpha_1 \)-adrenoceptor–mediated reactivity. This analysis was truncated at the 0.8-µg · kg\(^{-1} \) · min\(^{-1} \) phenylephrine infusion, since some subjects did not receive higher doses due to pressor responses that exceeded \( \geq 50/30 \) mm Hg. The 2-factor ANOVA performed on the dose-response curves indicated that the infusion of saline/heparin did not augment pressor responses to phenylephrine (Figure 2). Intralipid, either with or without heparin, enhanced pressor responses to phenylephrine. There were no significant differences in pressor reactivity to phenylephrine among the 3 infusions of Intralipid with and without heparin.

**Effects of Saline or Intralipid With Heparin on Plasma NEFAs and Triglycerides**

The differences in plasma NEFAs with each of the 4 different infusions are shown in Figure 3. The infusion of saline and heparin did not significantly increase plasma NEFAs above basal values except for a transient increase of \( \approx 50\% \) at the 120-minute point, which followed the last (highest) phenylephrine dose received by each subject (data not shown). NEFAs rapidly returned to previously measured values after the 120-minute point. In study 1, the infusion of 20% Intralipid at 0.5 mL · m\(^{-2} \) · min\(^{-1} \) with heparin significantly increased plasma NEFAs to \( \approx 60\% \) above control values at 1 hour, with concentrations remaining relatively constant for the duration of the infusion. In study 2, infusion of 20% Intralipid at 0.8 mL · m\(^{-2} \) · min\(^{-1} \) raised plasma NEFAs values \( \approx 1.5\)-fold compared with control within 1 hour, with levels remaining stable thereafter. The addition of heparin to Intralipid raised the measured level of plasma NEFAs to roughly 4-fold above basal values (Figure 3).

The changes in plasma triglycerides with the various infusions are also shown in Figure 3. In study 1, the NaCl/heparin infusion did not change triglycerides from basal levels (\( P = 0.70 \)), whereas the Intralipid/heparin infusion raised triglycerides (\( P < 0.000 \)). The infusion of Intralipid/heparin in study 2 induced an approximate 4-fold increase in triglycerides compared with a 2-fold increase by Intralipid/heparin infusion in study 1 (\( P = 0.04 \)). The effect of Intralipid alone on triglycerides (3.0 ± 0.4 mmol/L) was not different from that of Intralipid and heparin combined (3.5 ± 0.4 mmol/L, \( P = 0.09 \)) in study 2 but was significantly different from triglycerides during Intralipid/heparin in study 1 (\( P = 0.05 \)).

**Correlations Between Changes in NEFAs and Triglycerides and Changes in Pressor Responses to Phenylephrine**

Positive correlations were seen between both changes of NEFAs and triglycerides and changes in pressor reactivity at these doses (Table 2). Correlations were stronger with
changes of triglycerides than with NEFAs and changes of pressor responses. The strongest correlations between changes of lipids and pressor reactivity were observed at the 0.4-μg · kg⁻¹ · min⁻¹ phenylephrine infusion rate. At this dose, changes of NEFAs and triglycerides correlated strongly and positively with changes in mean arterial pressure ($r=0.54$, $P<0.01$ and $r=0.64$, $P<0.01$, respectively). Partial correlation analysis was carried out to examine the relationship between changes of lipids and pressor reactivity at the 0.4-μg · kg⁻¹ · min⁻¹ phenylephrine infusion rate. The relationship between triglycerides and pressor reactivity remained significant after controlling for NEFAs, while the relationship between NEFAs and pressor reactivity was not statistically significant after controlling for triglycerides. Both plasma triglycerides and NEFAs also demonstrated an inverse relationship with PD$_{25P}$. However, the relationship was significant with triglycerides ($r=-0.51$, $P<0.05$) and not with NEFAs ($r=-0.26$, $P>0.05$).

**Discussion**

The principal finding of this study is that raising NEFAs and/or triglycerides systemically with Intralipid increases pressor sensitivity to phenylephrine. The triglyceride concentrations achieved during the infusion of Intralipid either with or without heparin in normal volunteers are comparable to values measured in obese hypertensive patients. These patients also have elevated plasma NEFAs that are highly resistant to suppression with insulin. The plasma triglyceride and NEFA values attained during the Intralipid±heparin infusions in this study are also comparable to levels seen in patients with familial combined hyperlipidemia, a genetic disorder associated with hypertension. Collectively, these observations raise the possibility that the lipid abnormalities associated with insulin resistance, which include elevations of both fatty acids and triglycerides, contribute to the enhanced vascular α₁-adrenergic reactivity and tone in overweight subjects with elevated BPs.

The results of the present investigation extend our previous work. We demonstrated that raising fatty acids locally in dorsal hand veins of lean normotensives to levels seen in obese hypertensives significantly reduced the dose of phenylephrine that induced 50% of the maximum venoconstrictor response. Raising fatty acids locally also enhanced the reflex venoconstrictor response to thigh-cuff inflation in dorsal hand veins. The effects of raising NEFAs locally appeared relatively specific for the α₁-adrenergic receptor, since responses to angiotensin and clonidine were not significantly altered.

Before discussion of how NEFAs and/or triglycerides could affect α₁-adrenergic receptor activity, it may be appropriate to consider the possibility that Intralipid affects the vasculature independently of changes in NEFAs and triglycerides. This possibility appears remote, since dietary fat acutely impaired endothelium-dependent dilation in normal volunteers, which was consistent with the effects of Intralipid and heparin that suppressed endothelium-dependent dilation in healthy subjects. cis-Ulnsaturated fatty acids also suppressed nitric oxide synthase activity and endothelium-dependent dilation in vitro. Thus, dietary fat, Intralipid with heparin, and fatty acids all produced consonant effects on endothelial function.

Other studies indicate that raising lipids elicits hemodynamic effects. In rats, raising portal venous oleate increased BP to a greater extent than the systemic infusion of the same
amount of fatty acid. The pressor effect of the portal olate infusion was abolished by prazosin, an α₁-adrenergic receptor blocker, but not by losartan, an angiotensin type 1 receptor antagonist. In minipigs, raising fatty acids systemically with Intralipid and heparin increased systemic vascular resistance and arterial pressure. These findings suggest that abnormalities of NEFAs may contribute to increased vascular α-adrenergic reactivity and tone in obese hypertensives.

In this study, Intralipid, both with and without heparin, enhanced vascular reactivity to phenylephrine. Each of the infusions containing Intralipid significantly raised both triglycerides and fatty acids as previously reported. The control infusion of saline/heparin showed no significant effect on NEFAs, triglyceride levels, or the BP response to phenylephrine. This observation suggests that the enhanced pressor response to phenylephrine observed with Intralipid infusions arises from the acute increase of fatty acids and/or triglycerides. Heparin, which was added to activate lipoprotein lipase in vivo and enhance the hydrolysis of fatty acids from triglycerides, is not known to have pressor effects.

While heparin and saline did not affect pressor responses to phenylephrine, heparin complicates the quantification of plasma NEFAs by virtue of its capacity to induce a sustained activation of lipoprotein lipase in vitro. Despite efforts to rapidly separate and freeze plasma, measured plasma NEFAs may be artificially elevated 2- to 3-fold by failure to adequately restrain in vitro lipolysis that has been activated by heparin. A careful methodological study has shown that paraoxon inhibits lipoprotein lipase activity in vitro and prevents this artifact to raise measured NEFA values. For this reason, in study 1, blood samples for NEFAs were quickly placed into tubes containing paraoxon. On the basis of published reports in the literature, we anticipated a 2- to 3-fold elevation in plasma NEFAs with the combined infusion of 20% Intralipid at 0.5 mL · m⁻² · min⁻¹ with heparin. However, none of the previous studies inhibited lipoprotein lipase activity in vitro with paraoxon. The measured increase of plasma NEFAs of ~60% was far less than the expected increase of 200% or more. The effectiveness of paraoxon at inhibiting lipolysis in vitro may explain the difference between the relatively small increase of plasma NEFAs in study 1 compared with the predicted increase based on the published literature.

Concern about the cholinesterase inhibitory effects of paraoxon led to logistical problems in study 1. Therefore, we used another method for inhibiting lipoprotein lipase activity in vitro in study 2, viz., EGTA. Based on the published literature, we projected roughly a 4-fold elevation of plasma NEFAs in study 2 when Intralipid was infused at 0.8 mL · m⁻² · min⁻¹ with heparin. Unlike study 1, the predicted and measured increases of plasma NEFAs were in close agreement with those in study 2. Among the more likely explanations for the large difference in measured NEFA concentrations between the 2 studies, despite the comparatively modest difference in Intralipid infusion rates, is that in vitro lipolysis was more effectively inhibited in study 1 with paraoxon than with EGTA in study 2.

When data from study 1 and study 2 were combined, plasma triglycerides during the infusions of Intralipid±heparin showed a significant correlation with changes in mean arterial pressure in response to phenylephrine (Table 2) and with the PD₂₅₀, an index of vascular α₁-adrenergic receptor–mediated pressor sensitivity. This is consonant with the observation that BP correlated positively with hypertriglyceridemia in rats. Other studies observed that high triglycerides are associated with arterial contraction, increased vascular tone, endothelial dysfunction, and changes in membrane ion transport. A role for triglycerides in enhancing pressor reactivity is also supported by our observation that infusions of Intralipid alone and with heparin in study 2 had comparable effects on plasma triglycerides and PD₂₅₀ values despite significant differences in plasma NEFAs.

Analyses also showed a positive correlation between changes of NEFAs and mean arterial pressure responses to phenylephrine. Because plasma triglycerides and NEFAs both increased with the Intralipid±heparin infusions, the 2 lipids may interact to enhance vascular α₁-adrenoceptor reactivity. Based on our data and analysis, an argument can be made for a greater role for triglycerides than NEFAs in the enhanced pressor reactivity to phenylephrine. More specifically, the strongest correlation between changes of triglycerides and NEFAs and changes in pressor reactivity were seen at the 0.4-µg · kg⁻¹ · min⁻¹ phenylephrine infusion rate. In partial correlation analysis, the change of triglycerides correlated with the change of the mean arterial pressure response to phenylephrine after controlling for changes in NEFAs (partial r=0.378, P=0.05). In contrast, changes of NEFAs no longer correlated significantly with changes of mean arterial pressure after controlling for the change in triglycerides (partial r=0.16, P>0.05).

Attempting to determine whether triglycerides or NEFAs had the greater effect on pressor reactivity by partial correlation analysis is confounded by several variables. (1) First are the effects of in vitro lipolysis, which would create a disparity between actual and measured NEFA concentrations. (2) Individual NEFAs may have different effects on vascular reactivity; thus, correlations between changes of total NEFAs and pressor reactivity may underestimate the effect of changes in individual fatty acids. (3) The relationship between triglycerides and vascular reactivity may be mediated at least partially by hydrolysis of fatty acids from the glycerol backbone by lipoprotein lipase on the endothelium.

In summary, the major finding of this study is that acutely raising levels of fatty acids and triglycerides with Intralipid increased systemic pressor reactivity to phenylephrine, an α₁-adrenergic receptor agonist. The separate role of NEFAs and triglycerides in the enhanced pressor reactivity is not clarified by this investigation. Nevertheless, the findings raise the possibility that the dyslipidemia observed among insulin-resistant subjects, which includes elevations of NEFAs and triglycerides, contributes to elevated BP by enhancing vascular α₁-adrenergic receptor–mediated reactivity and tone.

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References


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