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Differential blood pressure effects of oral glucose and intravenous L-arginine in healthy lean normotensive and obese hypertensive subjects

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We investigated the role of insulin and glucose in the pathophysiology of hypertension associated with obesity. The comparative effects of an oral glucose load and of an L-arginine infusion on plasma glucose, plasma insulin and blood pressures (BP) were assessed in lean normotensive and in obese hypertensive males. Oral glucose (75 g in 1–2 min) induced a small but significant lowering of BP in lean normotensives, but failed to modify BP in obese hypertensives. L-arginine infusion (30 min, 500 mg/kg total dose) reduced BP; significantly greater reductions in sytolic and diastolic BP were observed in obese hypertensives than in the control group. Both oral glucose and L-arginine induced greater increases in plasma insulin in obese hypertensives than in lean normotensives. Endothelial dysfunction which accompanies the insulin resistant state of obesity, glucose intolerance and hypertension, may account for the different BP effects induced by glucose and L-arginine in obese hypertensives and lean normotensives.
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Introduction

The role of insulin in the genesis of hypertension has been extensively reviewed.[1–7] In healthy subjects, insulin induces vasorelaxation and increases tissue blood flow;[8,9] these effects are diminished or lost in the subjects with endothelial dysfunction and/or insulin resistance.[10–13] Insulin resistance with compensatory hyperinsulinaemia has been observed in lean hypertensives, obese normotensives and hypertensives and in patients with type 2 diabetes mellitus.[2,14–18] Infusions of insulin have been shown to increase blood pressure (BP) in rats.[19,20] In addition to insulin, glucose *per se* may play a role in hypertension.[21–23] Infusion of glucose in rats, alone or combined with insulin, increases BP.[23] The BP effect of glucose is markedly accentuated in animals treated with an inhibitor of the nitric oxide (NO) synthesis.[23] These observations have lead to the proposal that elevated insulin and glucose levels may induce hypertension, particularly in the presence of endothelial dysfunction.

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In the present study we compared the effects of glucose and insulin on BP in obese hypertensives and lean normotensive subjects. Obese hypertensive subjects were employed as a model of endothelial dysfunction and hyperinsulinaemia (insulin resistance). The oral glucose load was employed to increase both blood glucose and insulin levels. An infusion of L-arginine was used to increase blood insulin with minimal changes in blood glucose. In addition, L-arginine has been shown to restore altered vascular responses to insulin in those conditions possibly due to increase production of NO.[24]

Methods

Subjects attending our Center for the Detection and Treatment of Silent Cardiovascular Risk Factors participated in the study. Only male subjects were included. The control group consisted of healthy, lean normotensive, glucose tolerant individuals, without immediate family history (first-degree relatives) of hypertension, obesity or type 2 diabetes mellitus. The obese hypertensive group consisted of otherwise healthy subjects with body mass index (BMI) $>28\ kg/m^2$, systolic BP (SBP) >140 mm Hg and diastolic BP (DBP) >90 mm Hg. All subjects were untreated and had serum creatinine levels <1.5 mg/dl. All subjects gave their consent approval.

BPs and pulse rates were taken in a supine position after a 15-min rest. The average of three consecutive readings was employed for the calculations. In future visits, BPs were taken in the same arm employing the same cuff.

After a 12-h period of fasting, patients were admitted (8–9 am) to the centre for an oral glucose tolerance test and to determine the effects of oral glucose on BP. A heparin lock was placed on one of the arm veins for repeated blood drawing. BPs and pulse rate measurements and blood samples for glucose and insulin levels were obtained before (baseline) and after the ingestion of glucose (75 g in 1–2 min).

After a 12-h period of fasting, patients were admitted (8–9 am) to the centre for an L-arginine test. A heparin lock was placed on one of the arm veins for repeated blood drawing, and an additional intravenous line was used for the L-arginine infusion (30 min intravenous infusion, 500 mg/kg total dose). BPs and pulse rate measurements and blood samples for glucose and insulin levels were obtained before (baseline), during and after the infusion of L-arginine.

Results are shown as mean values ± s.e.m. Significant differences between two groups were assessed by Student's *t*-test. Changes from baseline were assessed by analysis of covariance.

Results

The demographic and anthropometric characteristics of the study patients are shown in Table 1. In addition to higher body weight, BMI, waist to hip ratio (WHR) and BP, the obese hypertensives had higher fasting plasma insulin and glucose levels than lean normotensives.

The oral glucose load produced higher plasma glucose and plasma insulin levels in obese hypertensives than in lean normotensive control group. Glucose AUC averaged 45 ± 12 in lean normotensive and 135 ± 16 in obese hypertensives ($P < 0.01$). Plasma insulin AUC averaged 84 ± 16 in lean normotensives and 259 ± 39 in obese hypertensives ($P < 0.01$). Ingestion of glucose produced small, but significant reductions in SBP and DBP from baseline levels in lean normotensives; however, glucose failed to reduce BP in obese hypertensive individuals (Figure 1).

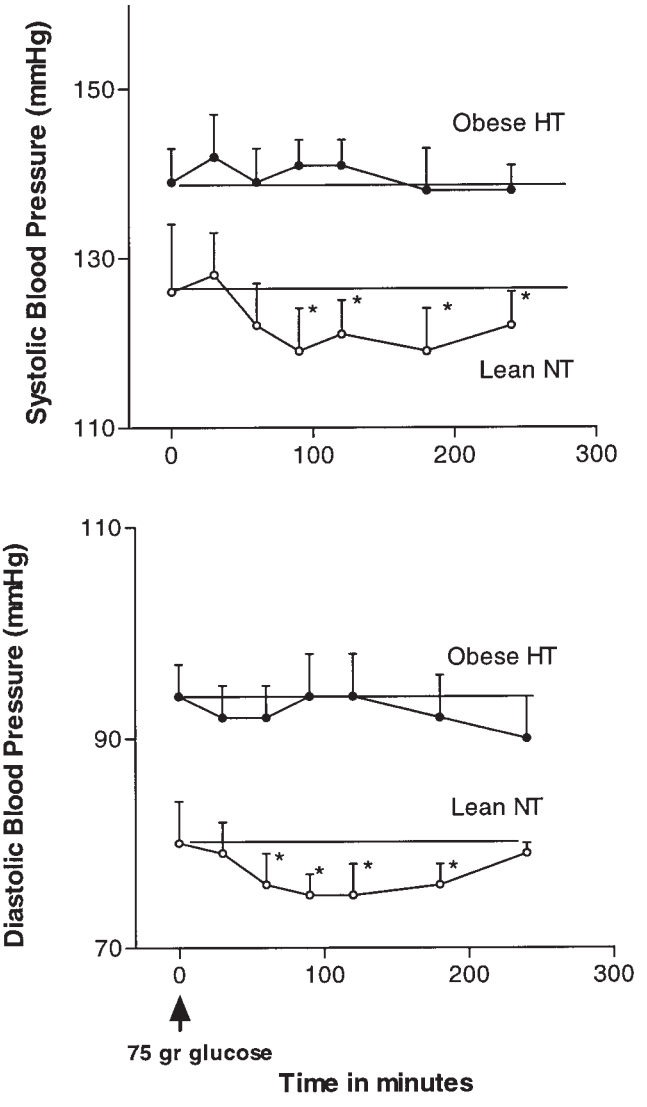

Figure 1 BP effects of oral glucose load in lean normotensives and obese hypertensives. An oral load of 75 g of glucose was administered. BP were measured before, during and after the ingestion of glucose. Shown are mean values ± s.e.m. for SBP and DBP. The solid line across the figures depicts the baseline BP levels.

Table 1 Subject characteristics

	Groups	
	Obese-HT	*Controls*
Weight	103 ± 4.2	68.7 ± 3.5**
Age	49.2 ± 2.8	40.0 ± 6.6
Body mass index	34.1 ± 2.3	23.8 ± 0.9**
Waist to hip ratio	1.01 ± 0.01	0.89 ± 0.02**
Systolic BP	142 ± 3.7	113.8 ± 5.2**
Diastolic BP	96.2 ± 3.2	76.8 ± 2.8**
Fasting glucose	104.6 ± 6.7	74.5 ± 2.4*
Fasting insulin	28.8 ± 6.4	14.5 ± 3.2*

Controls ($n = 5$); obese-hypertensives ($n = 10$). Shown are means ± s.e.m.
*$P < 0.01$, **$P < 0.001$ from the control group.

L-arginine infusion induced an increase in plasma insulin concentrations; associated with insignificant increases in plasma glucose. The L-arginine infusion produced significant greater reductions in SBP and DBP in obese hypertensives than in lean normotensives (Figure 2).

Discussion

In addition to insulin, glucose may be involved in the genesis of hypertension.[21–23] Interestingly, endo-

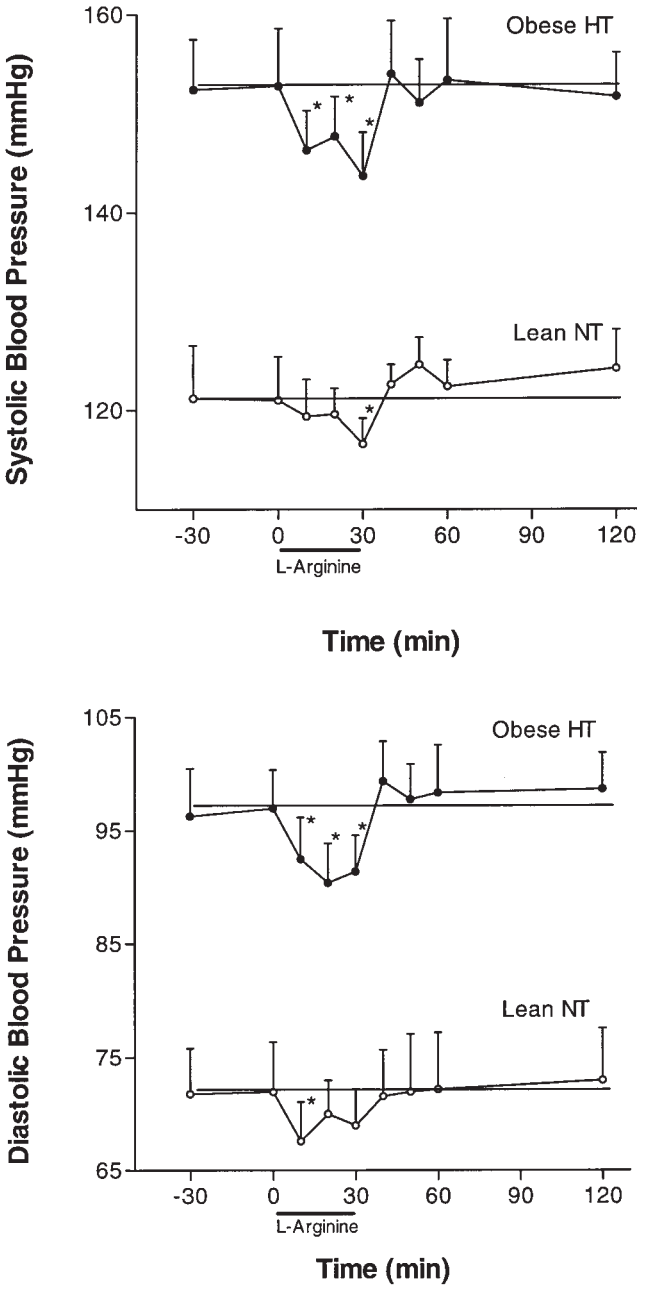

Figure 2 BP effects of an intravenous infusion of L-arginine in lean normotensives and obese hypertensives. A 30-min intravenous infusion of L-arginine was administered (500 mg/kg total dose) was given as a 30-min i.v. infusion. BP were measured before, during and after the ingestion of glucose. Shown are mean values ± s.e.m. for SBP and DBP. The solid line across the figures depicts the baseline BP levels.

thelial dysfunction favours vasoconstriction and BP elevations during glucose and insulin infusions.[10–14,23] Endothelial dysfunction has been observed in hypertensives, obese and type-2 diabetics; conditions characterised by the presence of insulin resistance, compensatory hyperinsulinaemia and glucose intolerance.[12–14] Consequently, both hyperinsulinaemia and hyperglycaemia may play a role in the hypertension of obesity.

The present study was undertaken to provide further understanding of the BP effects of glucose and insulin in humans. Although, chronic glucose and L-arginine infusions would have been preferable; however, due to ethical reasons, only acute changes in insulin and glucose were performed. Oral glucose was given to achieve increases in plasma glucose, associated with increases in plasma insulin due to endogenous secretion. L-arginine infusion was employed to induce increases in plasma insulin not associated with significant increases in plasma glucose. These procedures were applied in healthy, lean normotensives and in obese hypertensives. It was observed that the oral glucose load, produce only modest changes in BP. Lean normotensives showed a small, but significant reduction in BP; whereas, no significant change in BP was observed in the obese hypertensive group. Compared with the control group, the obese hypertensive individuals were in addition hyperinsulinaemic and glucose intolerant. It is known that endothelial dysfunction also accompanies obesity, hypertension, hyperinsulinaemia and glucose intolerance.[10–14] It is thus possible, that the small increase in glucose and insulin induced by oral glucose in lean normotensives produced a small, but significant BP reduction. In fact, insulin-induces vasodilation in normal subjects[8–14] and glucose induces minimal BP changes in healthy animals'.[23] The failure to observe BP lowering in obese hypertensives is most likely due to hyperglycaemia and hyperinsulinaemia in the presence of insulin resistance and to possible endothelial dysfunction. It is known that endothelial dysfunction potentiates the hypertensive responses to insulin and glucose.[10–14,23]

L-arginine, elevated plasma insulin, without significant increases in plasma glucose levels. Infusion of L-arginine was associated with BP lowering. The decrease in BP induced by L-arginine was significantly greater in obese hypertensives than in lean normotensives (present study). This effect could be due to the higher plasma insulin levels reached after L-arginine in obese hypertensives than in controls and to the fact that the hyperinsulinaemia was not associated with hyperglycaemia. The increases in plasma glucose might have antagonised the BP lowering action of insulin in the oral glucose test. Because endothelial dysfunction with poor NO-mediated vasodilation is present in obesity and hypertension, L-arginine through increases in NO formation, might have improved endothelial dysfunction in obese hypertensives. In fact, infusion of L-arginine has been shown to improve defective insulin-mediated vasodilation in subjects with endothelial dysfunction.[24]

In conclusion, when compared with lean normotensives, obese hypertensives present with fasting hyperinsulinaemia and elevated fasting plasma glucose levels, excessive hypersecretion of insulin to an oral glucose load and to an L-arginine challenge, impaired vasodilatory effect of an oral glucose load,

and enhanced BP lowering action of L-arginine. The presence of endothelial dysfunction-insulin resistance in obese hypertensives may account for these findings.

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References

1 Welborn TA *et al*. Serum insulin in essential hypertension and in peripheral vascular disease. *Lancet* 1966; **1**: 1336–1337.
2 Ferrannini E *et al*. Insulin resistance in essential hypertension. *N Engl J Med* 1987; **317**: 350–357.
3 Laakso M, Sarlund H, Mykkanen L. Essential hypertension and insulin resistance in non-insulin-dependent diabetes. *Eur J Clin Invest* 1989; **19**: 518–526.
4 Reaven GM. Relationships between insulin resistance and hypertension. *Diabetes Care* 1991; **14**: 33–38.
5 Denker PS, Pollock VE. Fasting insulin levels in essential hypertension: a meta-analysis. *Arch Int Med* 1992; **152**: 1649–1651.
6 Morris AD, Connell JMC. Insulin resistance and essential hypertension: mechanisms and clinical implications. *Am J Med Sci* 1994; **307** (Suppl 1): S47–S52.
7 Brands MW, Hall JE, Keen HL. Is insulin resistance linked to hypertension? *Clin Exp Pharmacol Physiol* 1998; **25**: 70–76.
8 Scherrer U, Randin D, Vollenweider L, Nicod P. Nitric oxide release accounts for insulin's vascular effects in humans. *J Clin Invest* 1994; **94**: 2511–2515.
9 Baron AD *et al*. Insulin-mediated skeletal muscle vasodilation contributes to both insulin sensitivity and responsiveness in lean humans. *J Clin Invest* 1995; **96**: 786–792.
10 Vollenweider P *et al*. Impaired insulin-induced sympathetic neural activation and vasodilation in skeletal muscle of obese humans. *J Clin Invest* 1994; **93**: 2365–2371.
11 Gudbjornsdottir S, Elam M, Sellgren J, Anderson EA. Insulin increases forearm vacular resistance in obese, insulin-resistant hypertensives. *J Hypertens* 1996; **14**: 91–97.
12 Steinberg HO *et al*. Obesity/insulin resistance is associated with endothelial dysfunction. *J Clin Invest* 1996; **97**: 2601–2610.
13 Higashi Y *et al*. Relationship between insulin resistance and endothelium-dependent vascular relaxation in patients with essential hypertension. *Hypertension* 1997; **29**: 280–285.
14 Pinkney JH, CDA Stehouwer, SW Coppack, JS Yudkin. Endothelial dysfunction: cause of the insulin resistance syndrome. *Diabetes* 1997; **46**: S9–S13.
15 Modan M *et al*. Hyperinsulinaemia: a link between hypertension, obesity and glucose intolerance. *J Clin Invest* 1985; **75**: 809–817.
16 DeFronzo RA. Insulin resistance, hyperinsulinemia, and coronary artery disease: a complex metabolic web. *J Cardiovasc Pharmacol* 1992; **20** (Suppl 11): S1–S16.
17 Maheux P *et al*. Additive effects of obesity, hypertension and type-2 diabetes on insulin resistance. *Hypertension* 1994; **24**: 695–698.
18 Yki-Jarvinen H. Role of insulin resistance in the pathogenesis of NIDDM. *Diabetologia* 1995; **38**: 1378–1388.
19 Brands MW, Hildebrandt DA, Miizelle HL, Hall JE. Sustained hyperinsulinemia increases arterial pressure in conscious rats. *Am J Physiol* 1991; **260**: R764–768.
20 Hall JE, Coleman TG, Mizelle HL, Smith MJ. Chronic hyperinsulinemia and blood pressure regulation. *Am J Physiol* 1990; **258**: F722–731.
21 Singer P *et al*. Postprandial hyperglycemia in patients with mild essential hypertension. *Hypertension* 1985; **7**: 182–186.
22 Reaven GM, Ho H. Sugar-induced hypertension in Sprague-Dawley rats. *Am J Hypertens* 1991; **4**: 610–614.
23 Brands MW, Fitzgerald SM. Chronic glucose infusion causes moderate hypertension in rats. *Am J Hypertens* 2000; **13**: 99–102.
24 Higashi Y *et al*. Renal response to L-arginine in salt sensitive patients with essential hypertension. *Hypertension* 1996; **27**: 643–648.