Improvement of Insulin Sensitivity for Glucose Metabolism With the Long-Acting Ca-Channel Blocker Amlodipine in Essential Hypertensive Subjects

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To clarify whether the long-acting calcium-channel blocker amlodipine restores insulin insensitivity in essential hypertension, insulin sensitivity tests were performed at the physiological steady-state insulin level (45 to 55 μU/mL) before and after amlodipine (2.5 to 7.5 mg/d) administration for 2 to 4 months in borderline and mild essential hypertensive subjects. Instead of somatostatin, Sandostatin (Sandoz, Basel, Switzerland) was used for the determination of steady-state plasma glucose (SSPG) in the same way as previously described. SSPG, which was initially high (212.9 ± 18.0 mg/dL, mean ± SE), was significantly reduced to 169.8 ± 14.7 after amlodipine treatment. Responses of ketone bodies during the test at 30 minutes, which reflect the insulin effect on lipolysis in adipose tissue and hepatic fatty acid oxidation, also improved after amlodipine treatment. Norepinephrine, noted to be mildly elevated after amlodipine treatment, decreased during the sensitivity test at 2 hours probably due to the sedative effect, without any change in the fractional extraction of Na. This indicates that the physiological level of insulin does not activate sympathetic nerve activity or stimulate Na reabsorption. The long-acting calcium-channel blocker amlodipine has significantly improved the initially decreased insulin sensitivity for glucose metabolism at least partially in borderline or mild essential hypertension.

IN ESSENTIAL HYPERTENSION, insulin resistance for glucose metabolism independent of diabetes and obesity has been reported by several investigators, including ourselves.[1-3] A significant correlation between insulin resistance and systolic or diastolic blood pressure (BP) was noted.[2,3] Whether this resistance is dependent on BP and is correctable with antihypertensive drugs remains to be determined.[4,5] It is possible that these abnormalities would be normalized on proper treatment of hypertension. We have recently reported an improvement of insulin sensitivity by the α_1-blocker bunazosin[3] in non-obese essential hypertension, confirming the previous report in obese hypertensive subjects.[6] Captopril was reported to improve insulin sensitivity.[7] Regarding the calcium-channel blockers, conflicting results were reported. Whereas nifedipine causes a deterioration, diltiazem or verapamil have no significant effect on insulin sensitivity.[8] Other investigators reported a slight improvement of insulin sensitivity (7% to 12%) following nifedipine treatment in hypertensive subjects.[9] We have therefore undertaken this study to investigate the effect of the long-acting Ca-channel blocker amlodipine on the insulin sensitivity for glucose and lipid metabolism. Sowers attributes the insulin resistance to the elevated intracellular calcium level in essential hypertension.[10] He also predicts that inadequate insulin action may lead to hypertension through decreased extrusion of cellular Ca^{2+} by Ca adenosine triphosphates,[11] the activity of which is maintained by insulin.[11] Calcium-channel blocker is postulated to correct the derangement of the intracellular cation, thus contributing to reverse the insulin insensitivity in essential hypertension.

SUBJECTS AND METHODS

Subjects

Thirteen non-obese hypertensive subjects with a mean age of 56 ± 4 years (mean ± SE) were recruited for the study. Hypertension was defined if either or both systolic or diastolic BP measured in the sitting position exceeded 140 and 90 mm Hg, respectively. On the oral glucose tolerance test (OGTT), six were normal, four had impaired glucose tolerance, and three were mildly diabetic. They had not been treated for hypertension, had no other endocrine, metabolic, hepatic, and renal dysfunctions, and were outpatients with daily regular activity. Two subjects whose BP did not decrease more than 5 mm Hg for either systolic or diastolic BP on amlodipine (Norvasc; Pfizer, New York, NY) treatment were excluded because of the possibility of the drugs not being taken regularly. Fourteen (seven each men and women) control subjects were non-obese, nondiabetic, and normotensive.

Insulin Sensitivity Test

The same method previously reported was used,[12,13] except that somatostatin was replaced by long-acting Sandostatin (octreotide acetate; Sandoz, Basel, Switzerland),[14] which was commercially available and subcutaneously injected (100 μg) 10 minutes before the test. After the completion of this study, intravenous infusion of Sandostatin (150 μg/2 h) has been used with the similar suppression of C-peptide reactivity (CPR), immunoreactive glucagon (IRG), and growth hormone (GH). Novolin R 40 insulin (Novo, Copenhagen, Denmark) was infused using an insulin infusion pump (Nipro SP-3HQ, Osaka, Japan) at a rate of 0.77 mU/min/kg body weight with an initial bolus injection (7.5 mU/kg). Glucose (6 mg/min/kg body weight) was infused through an antecubital vein in a 12% solution containing 5 mEq KCL. Blood samples were obtained basically every 30 minutes for 2 hours for the determination of glucose, free fatty acids (FFA), ketone bodies, triglyceride (TG), insulin, CPR, GH, and IRG.[15] Ketone bodies,[16] FFA, and TG were determined by an enzymatic method, and the other hormones by radioimmunoassay as described before.[3]

The study was approved by the hospital ethics committee, and informed consent was obtained from each subject.

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Statistical Analyses

Values are presented as the mean ± SEM. The significance of differences between control and hypertensive subjects was determined by ANOVA. The differences before and after amlodipine therapy and the hormonal and substrate responses during the insulin sensitivity test were studied using ANOVA and a paired *t* test.

RESULTS

Patient Profiles and OGTT Results Before and After Amlodipine Treatment

Compared with controls, systolic and diastolic BP, blood glucose, and immunoreactive insulin (IRI) in hypertensive subjects were significantly elevated before amlodipine treatment (Table 1). After amlodipine treatment (2.5 to 7.5 mg/d, 5.0 ± 0.6 mg/d) for 2 to 4 months (12.4 ± 1.3 wk), BP decreased from 153/90 to 140/84. Body mass index, fasting blood glucose, IRG, blood glucose, and IRI were not significantly different.

Steady-State Plasma Glucose and Insulin Before and After Amlodipine Treatment

The steady-state plasma insulin level was obtained between 90 and 120 minutes, and CPR, GH, and glucagon were suppressed below the basal level after 15 minutes throughout 2 hours as shown in altogether 26 insulin sensitivity tests in 13 subjects before and after amlodipine treatment (Fig 1). Steady-state plasma insulin levels, measured using human insulin as standard, and glucose in normal subjects were statistically the same as with the previous somatostatin method.

Steady-state plasma glucose (SSPG), which was initially elevated (212.9 ± 18.0 mg/dL) as compared with control values (104 ± 7, n = 14, $P < .01$ by ANOVA), was reduced significantly (to 169.8 ± 14.7) by 20% after amlodipine treatment (Fig 2). Of 13 hypertensive subjects, 11 exhibited a reduction of SSPG, indicating an improvement of the insulin effectiveness for glucose utilization at the steady-state insulin level. Steady-state plasma insulin levels before and after amlodipine treatment were 55.9 ± 11.3 and 49.5 ± 10.2 μU/mL, respectively, which were not statistically different.

Responses of Serum Lipids and Ketone Bodies During Insulin Sensitivity Test

Serum FFA levels were significantly reduced at 30 minutes during the insulin sensitivity test both before and after drug treatment (Fig 3). Although the reduction of FFA at 30 minutes seemed greater after amlodipine treatment, no statistical difference was noted. Serum levels of ketone bodies (3-hydroxybutyrate and acetoacetate) were reduced at 30 minutes after but not before amlodipine treatment (Fig 4). The similar significant reduction of serum TG was noted at 2 hours after amlodipine treatment (not shown). The difference of the above responses as compared with basal was also significant by ANOVA. The results indicate that insulin's effectiveness for lipid metabolism also seems to be improved after amlodipine treatment.

Serum Catecholamine Levels and Fractional Excretion of Na During Insulin Sensitivity Test

Serum epinephrine and norepinephrine levels were mildly decreased during the insulin sensitivity test, probably due to a sedative effect (Table 2). With amlodipine treatment for 2 to 4 months, norepinephrine increased in serum by 40% to 50% (Table 2).

The fractional excretion of Na was not affected with insulin infusion both before and after drug therapy.

DISCUSSION

Amlodipine therapy for 2 to 4 months in borderline or essential hypertensive subjects reduced SSPG by 20% with statistical significance. SSPG is roughly inversely correlated with the rate of glucose utilization in muscle and somewhat in liver.[17] This result indicates that insulin-mediated glucose utilization mainly in muscle improved after amlodipine treatment for 2 to 4 months. The steady-state insulin level at 2 hours in this study is 45 to 55 μU/mL, which is not different before and after amlodipine treatment and is about the same as the physiological meal-stimulated level in hyperinsulinemia often observed in hypertensive or obese subjects in our country.

Responses of FFA at 30 minutes during the insulin sensitivity test were not statistically different after amlodipine treatment as compared with before, but those of ketone bodies significantly improved. A similarly improved response was noted for the reduction of TG at 2 hours after

Table 1. Clinical Profiles of Hypertensive Subjects Before and After Amlodipine Therapy (mean ± SE)

									75-g OGTT	
Subject	n	Sex (M/F)	Age (yr)	BMI (kg/m²)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	FBS (mg/dL)	IRI (μU/mL)	ΣBS (mg·h/dL)	ΣIRI (μU·h/mL)
Control	14	7/7	58 ± 2.3	22.6 ± 0.6	128 ± 4	75 ± 3	96 ± 3	5.1 ± 0.7	245 ± 9	59 ± 7
Hypertensive										
Before amlodipine	13	9/4	56 ± 4	23.3 ± 0.5	153 ± 3†	90 ± 2†	102 ± 5	5.1 ± 0.8	353 ± 18†	87.6 ± 11.1*
After amlodipine	13	9/4	56 ± 4	23.0 ± 0.4	140 ± 3*‡	84 ± 2*‡	103 ± 4	4.8 ± 0.8	335 ± 12†§	79.4 ± 11.3*§

Abbreviations: BMI, body mass index; FBS, fasting blood glucose; BS, blood glucose.

*$P < .05$, †$P < .01$: by ANOVA *v* control.

*‡$P < .01$ by ANOVA and paired *t* test *v* before.

§OGTT was performed after the amlodipine treatment in seven subjects.

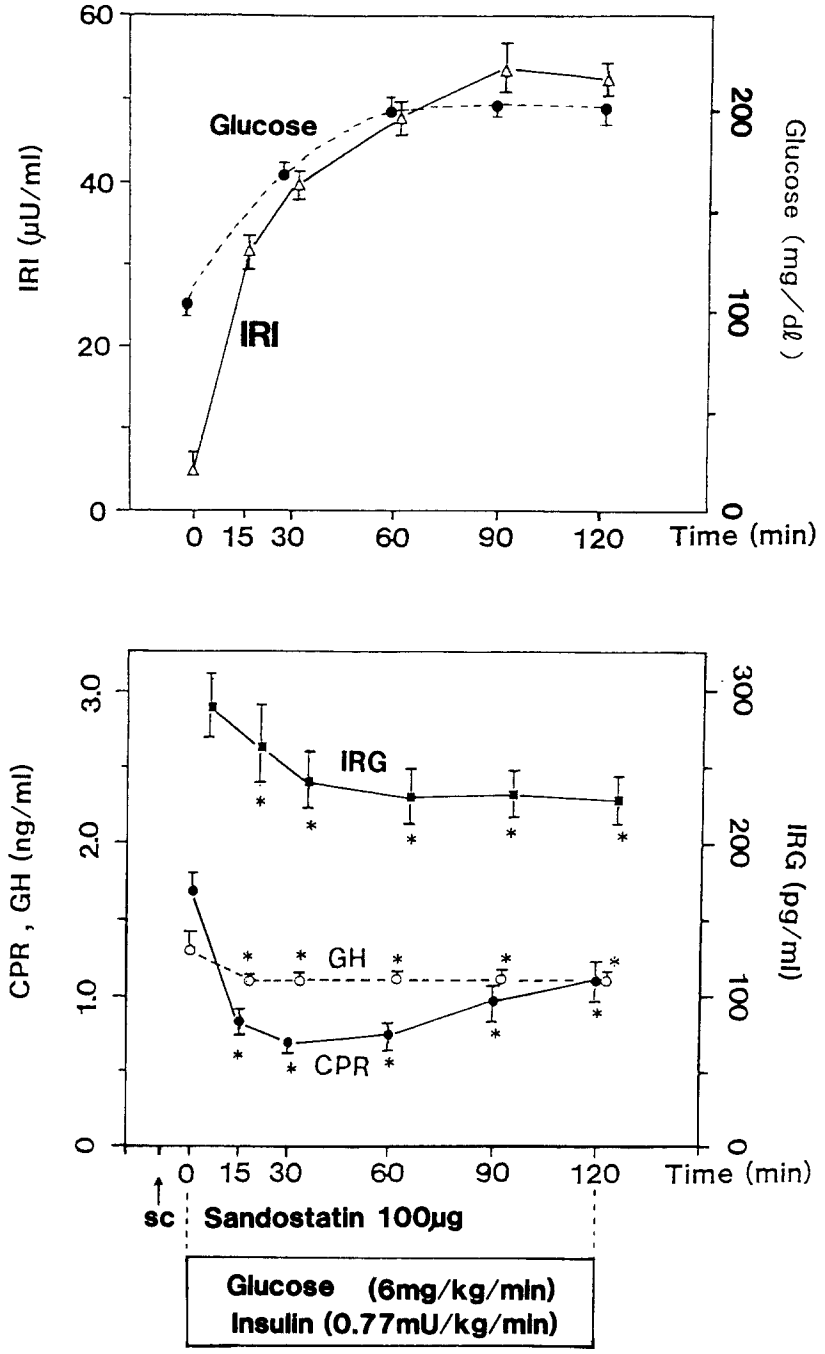

Fig 1. Plasma levels of glucose, IRI, CPR, IRG, and GH during the insulin sensitivity test using Sandostatin in a total of 26 insulin sensitivity tests in 13 subjects before and after amlodipine treatment (mean ± SE). *$P < .01$ *v* 0 minutes by paired *t* test. (●—●) glucose; (△—△) IRI; (■—■-) IRG; (○- -○) GH; (●—●-) CPR.

amlodipine treatment. A reduction of ketone bodies (3-hydroxybutyrate plus acetoacetate) during insulin infusion reflects insulin action in adipose tissue and liver, suggesting an improvement of insulin's effectiveness in these organs after amlodipine treatment.

Plasma epinephrine, which remained at the same level after amlodipine treatment, decreased during the infusion test, probably due to a sedative effect. Norepinephrine was mildly elevated after amlodipine treatment for 2 to 4 months and was similarly decreased during the test at 2 hours. At the present dose of physiological insulin, no elevations of catecholamine levels were observed, in contrast to the theory that insulin may stimulate adrenergic drive.[18] In non-obese subjects, a dose-dependent increase of plasma norepinephrine was reported in a euglycemic-hyperinsulinemic clamp study at a supraphysiological insulin dose (150 to 400 μU/mL). A subtle change of blood glucose at euglycemia may also stimulate norepinephrine secretion. In our study at the physiological level of insulin without a turbulance of the blood glucose level, norepinephrine and epinephrine are not stimulated.

The fractional excretion of Na before and after the insulin infusion was not significantly changed, indicating no effect of the present dose of insulin on Na absorption. In

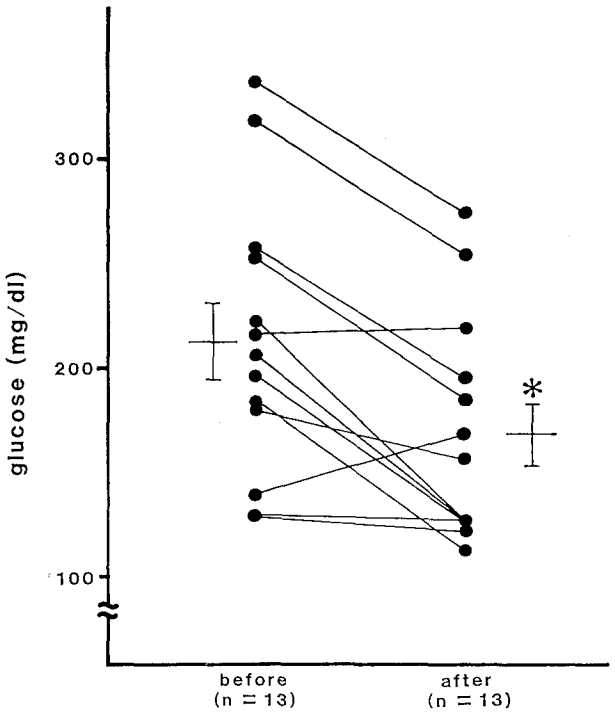

Fig 2. SSPG before and after amlodipine administration (mean ± SE). *P < .01 by ANOVA and paired *t* test.

the present study, KCL (5 mEq) was infused over 2 hours to compensate for the hypokalemic effect of insulin. At the higher level of insulin (149 ± 15 μU/mL), insulin was reported to stimulate Na reabsorption.[19] Friedberg et al[20] reported that hyperinsulinemia might potentiate the renal Na-retaining effect under hypokalemia. The results do not support the hypothesis, at least under a mild elevation of insulin, that hyperinsulinemia may elevate BP through a Na-retentive effect.

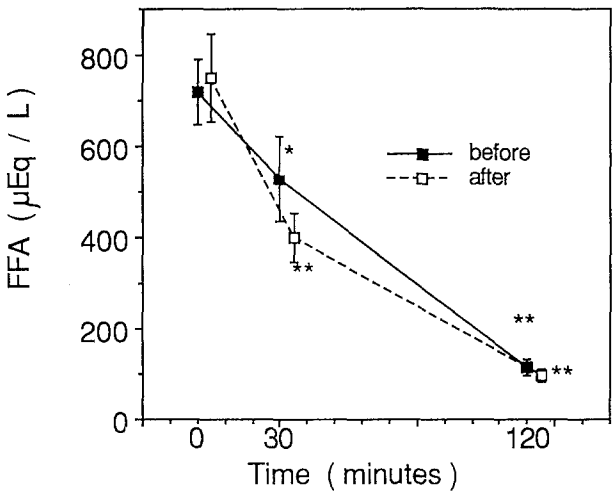

Fig 3. Changes in serum FFA levels during insulin sensitivity test before and after amlodipine administration (mean ± SE, n = 13). *P < .05, **P < .01: by paired *t* test *v* 0 minutes.

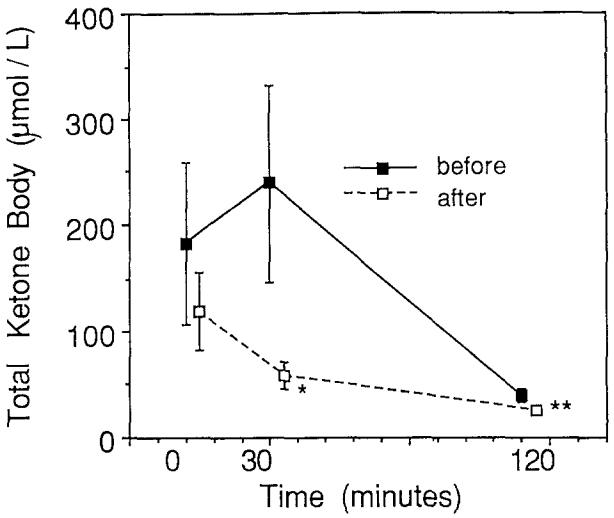

Fig 4. Changes in serum levels of total ketone bodies during insulin sensitivity test before and after amlodipine administration (mean ± SE). *P < .05, **P < .01: by paired *t* test *v* 0 minutes.

We have previously reported that insulin resistance observed in lean nondiabetic hypertensive subjects is correlated with BP and partially reversible after treatment with the α_1-blocker bunazosin.[3] A similar partial reversibility was noted with amlodipine treatment in the present study. Amlodipine belongs to the same dihydropyridine derivatives as nifedipine, but is more long-acting and displays very slow association and dissociation with the calcium channel.[21] Ferrari et al[22] have reported unaltered insulin sensitivity in normal young men with amlodipine treatment (5 mg/d) for 3 weeks. Amlodipine may not further enhance insulin sensitivity beyond normal, but has been shown to be effective in the partial reversal of insulin insensitivity in essential hypertension.

Captopril has been reported to improve insulin sensitivity in essential hypertension and also in hypertensive non–

Table 2. Serum Catecholamine Levels and Fractional Excretion of Na During Insulin Sensitivity Test Before and After Amlodipine Therapy (mean ± SE)

	0 min	120 min
Epinephrine (pg/mL)		
Before (n = 13)	60.7 ± 11.8	44.6 ± 9.1
After (n = 13)	59.9 ± 10.0	38.4 ± 7.6
Norepinephrine (pg/mL)		
Before	522 ± 47	419 ± 39
After	733 ± 46	601 ± 55
Fractional excretion of Na (%)		
Before	0.65 ± 0.12	0.90 ± 0.09
After	1.11 ± 0.20	1.17 ± 0.22

*P < .01 by paired *t* test.

insulin-dependent diabetes mellitus.[23] Whether complete normalization of BP around the clock with one drug or the combined use of these effective antihypertensive drugs may normalize insulin insensitivity remains to be determined.

As for the mechanism underlying the positive effect of amlodipine, amelioration of deranged cation metabolism such as elevated intracellular Ca^{2+} and/or decreased Mg^{2+} ions in essential hypertension may be postulated in addition to the hemodynamic factors (vasodilation). Sowers relates the attenuated insulin action to the above-mentioned cation derangement,[10] and in addition, insufficient insulin action further enhances intracellular Ca^{2+} due to the decreased Ca adenosine triphosphatase and/or Na-K adenosine triphosphatase,[24] which are insulin-sensitive.

Recently it has been reported that high levels of cytosolic calcium lead to inhibition of phosphoserine phosphatase in insulin target cells, and this effect may be mediated by phosphorylation and activation of inhibitor-1.[25] Decreased phosphoserine phosphatase may result in inappropriate dephosphorylation of glycogen synthase, GLUT-4, and other insulin-sensitive enzymatic steps, thus contributing to the insulin resistance. The long-acting calcium-channel blocker amlodipine improved the insulin sensitivity, possibly through correction of these derangements.

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