Original Article

Effect of Cilnidipine on Insulin Sensitivity in Patients with Essential Hypertension

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To clarify the effect of cilnidipine, a long-acting dihydropyridine Ca-antagonist that blocks both L- and N-type Ca\(^{2+}\)-channels, on insulin sensitivity, cilnidipine at 5 to 10 mg/day was administered to ten patients with essential hypertension for 12 weeks. Mean age and body mass index (BMI) were 57.7 ± 5.0 (SEM) years old and 27.1 ± 1.5, respectively. Blood pressure, serum levels of catecholamines, glucose and lipid were determined before and after the treatment. Insulin sensitivity was also measured by a euglycemic hyperinsulinemic clamp method using an artificial pancreas (STG-22; Nikiso, Tokyo, Japan) before and after the treatment. Cilnidipine administration significantly lowered blood pressure from 154/96 to 137/84 mmHg (p < 0.05). The glucose infusion rate was significantly increased by 20.8%, from 3.27 ± 0.36 to 3.95 ± 0.55 mg/kg/min (p < 0.05). HbA1C and serum lipid levels such as total cholesterol and triglyceride were not altered. In addition, cilnidipine treatment did not significantly increase serum norepinephrine levels (278 ± 25.2 vs. 332 ± 33.6 pg/ml). Our results suggest that cilnidipine improves insulin sensitivity, possibly due to its exerting a vasodilatory action without stimulating sympathetic nervous activity. (Hypertens Res 2003; 26: 383–387)

Key Words: insulin resistance, insulin sensitivity, long-acting calcium channel blocker, cilnidipine

Introduction

Insulin resistance is one of the major metabolic abnormalities causing hyperglycemia in patients with type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus: NIDDM) and/or obesity (1, 2). Recently, it has been reported that glucose intolerance and/or hyperinsulinemia are commonly observed in patients with essential hypertension (3, 4). In addition, it has been demonstrated using a euglycemic hyperinsulinemic clamp technique that resistance to insulin-stimulated glucose uptake exists in patients with essential hypertension (5, 6). Previous studies have revealed an increased prevalence of type 2 diabetes mellitus in hypertensive patients treated with diuretics and β-adrenoceptor blockers (7, 8). Some of the widely used antihypertensive agents have been demonstrated to modify insulin sensitivity and also alter the atherogenic risk profiles. β-Adrenoceptor blockers and thiazides decrease insulin sensitivity and worsen dyslipidemia (9–12), and angiotensin-converting enzyme (ACE) inhibitors and α1-blockers increase insulin resistance and are neutral or improve serum lipid profiles (9, 13–19). We previously demonstrated that captopril may decrease postprandial plasma glucose levels through augmenting a diminished postprandial forearm blood flow (14), indicating that vasodilatory hypotensive agents may increase skeletal muscle blood flow and hence improve insulin sensitivity. Baron et al. demonstrated that skeletal muscle blood flow has a profound effect on insulin sensitivity (20). In fact, recent studies using vasodilatory β-blockers with β2-agonism or α1-blockade have demonstrated that such drugs may improve insulin resistance (21–24).

On the other hand, a short-acting dihydropyridine Ca-channel antagonist, nifedipine, has been reported to worsen insulin sensitivity (25). However, long-acting Ca-channel antagonists such as amlodipine or barnidipine, which may not induce a greater activation of the sympathetic nervous system than that achieved by nifedipine, have been reported to improve insulin sensitivity, possibly through their gradual vasodilatory action (24, 26).
Recently, cilnidipine, a long acting Ca-channel antagonist that blocks both L- and N-type Ca\(^{2+}\)-channels, has become available in Japan. The N-type Ca\(^{2+}\)-channel exists specifically in neural cells. Thus, Ca-channel antagonist that blocks both L- and N-type Ca\(^{2+}\)-channels may suppress reflex increase in sympathetic nervous activity and may not activate the sympathetic nervous system in comparison with other L-type Ca-channel blockers. In the present study, we therefore studied the effects of cilnidipine on insulin sensitivity in patients with essential hypertension.

**Methods**

Ten hypertensive subjects (7 males and 3 females) were recruited for the study. The mean age was 57.7 ± 5.0 (SEM) years old and the mean body mass index was 27.1 ± 1.5. Each subject had been informed about the purpose and the risks of the study and had provided written consent to participate. The protocol was in accordance with the Declaration of Helsinki and was approved by the hospital ethics committee. During the run-in phase (4 to 6 weeks), all existing antihypertensive medications were discontinued. Patients were considered hypertensive if their systolic and/or diastolic blood pressure measured in the sitting position on the last two visits of the run-in period exceeded 140 and/or 90 mmHg. None of the patients had any other endocrine, metabolic, hepatic, or renal dysfunction. Patients were administered cilnidipine at 5 mg once a day. During the active treatment period, the dose of cilnidipine required to achieve blood pressure control of less than 140/90 mmHg was established within the first 4 weeks. The duration of the active treatment period was 12 weeks.

**Blood Pressure Measurements**

At each visit, systolic and diastolic blood pressure (Korotkoff phase V) and heart rate were recorded with a sphygmomanometer, and the mean of three blood pressure measurements at 1-min intervals was recorded.

**Measurement of Insulin Sensitivity**

Insulin sensitivity was evaluated using the euglycemic hyperinsulminemic clamp technique with an artificial pancreas (Model STG-22; Nikiso Co. Ltd., Tokyo, Japan) as described previously (27, 28). It was performed at the end both of the run-in period and of the active treatment period. The patients fasted overnight and ingested only their study drug on the morning of the clamp procedure at the end of the active treatment period. Three cannulae were positioned intravenously, one in an antecubital vein for glucose, another inserted in an antecubital vein in the contralateral arm for insulin infusion, and the third inserted distally in the contralateral arm for extraction of venous blood samples for plasma glucose determination every 3 min. Human regular insulin (Novolin R, Novo Nordisk, Malmo, Sweden) was infused as a priming dose for the first 10 min and then as a continuous infusion at 56 mU/m² body surface per min. When the plasma glucose had stabilized at around 80 mg/dl, the insulin infusion was continued for a further 120 min to maintain a constant, steady state hyperinsulinemia. In parallel, a glucose infusion (200 mg/ml) was started and the infusion rate was adjusted to maintain a steady state plasma glucose (SSPG) level at 80 mg/dl. The amount of glucose needed to maintain euglycemia, the glucose infusion rate (GIR, mg/kg/min), was calculated as the mean of all values obtained for the final 30 min. To correct for differences in the insulin levels achieved during the clamp, GIR was divided by the steady-state plasma insulin concentration to obtain the insulin sensitivity index (mg/kg/min/µU/ml).

**Laboratory Analysis**

At the end of the run-in period and the active treatment period, levels of glucose and insulin were determined before and after the clamp with a glucose oxidase method and a specific enzyme immunoassay (Boehringer, Manheim, Germany), respectively. Concentrations of total cholesterol, triglycerides, and other routine laboratory parameters were determined before each glucose clamp using an automated chemical analyzer. The high-density lipoprotein (HDL)-cholesterol level was measured by the precipitation method. Plasma norepinephrine, epinephrine, and dopamine levels were also determined before each clamp using the chemiluminescence method after separation by high performance liquid chromatography (HPLC).

**Statistics**

All data were expressed as the mean ± SEM. Statistical differences were analyzed by paired Student’s t-test, and considered to be significant when the p value was less than 0.05.

**Results**

Blood pressure was decreased from 154 ± 4.3/96 ± 3.9 to 137 ± 2.8/84 ± 3.0 mmHg (p < 0.05) after administration of cilnidipine (average final dose: 7.5 mg/day). The body weight and body mass indices were not changed. Cilnidipine did not affect any of the parameters in regard to glucose and lipid metabolisms (Table 1).

Figure 1 shows the GIR before and after treatment. Cilnidipine significantly augmented GIR from 3.27 ± 0.36 to 3.95 ± 0.55 mg/kg/min (p = 0.05). When the insulin sensitivity index was calculated, it was found to be increased from 0.481 ± 0.127 to 0.576 ± 0.292 mg/kg/min/µU/ml, although the statistical significance was marginal. However, plasma concentrations of norepinephrine, epinephrine, and dopa-
Table 1. Fasting Levels of Plasma Glucose and Insulin, Serum Lipids, and Catecholamines before and 12 Weeks after Cilnidipine Treatment

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>112 ± 7.9</td>
<td>116 ± 6.8</td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>9.2 ± 1.1</td>
<td>14.9 ± 5.5</td>
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<tr>
<td>HbA1c (%)</td>
<td>6.0 ± 0.3</td>
<td>6.0 ± 0.3</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>190 ± 11.7</td>
<td>200 ± 6.2</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>143 ± 15.6</td>
<td>178 ± 30.0</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>48.8 ± 2.1</td>
<td>47.7 ± 1.8</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>278 ± 15.2</td>
<td>332 ± 33.6</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>45.7 ± 8.5</td>
<td>34.4 ± 4.2</td>
</tr>
<tr>
<td>Dopamine (pg/ml)</td>
<td>11.2 ± 0.83</td>
<td>13.1 ± 1.82</td>
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Each value indicates the mean ± SEM. HDL, high density lipoprotein.

![Fig. 1. Changes in glucose infusion rate before and 12 weeks after the treatment with cilnidipine. Values are expressed as mean ± SEM. * p < 0.05 vs. before the treatment.](image)

Discussion

We have demonstrated that cilnidipine improves insulin sensitivity by 21% in patients with essential hypertension. However, the effects of Ca-antagonists on insulin sensitivity are still controversial. Short-acting nifedipine administered two times daily has been reported to worsen insulin sensitivity (25), while diltiazem has been reported not to affect insulin sensitivity as measured by the clamp technique (11). However, with respect to long-acting nifedipines, nifedipine GITS (150 mg/day) was demonstrated to improve insulin sensitivity slightly as measured by the SSPG method (28), and Procardia XL (30–60 mg/day) was shown not to change insulin sensitivity as measured by the clamp method (18). Very recently, amlodipine, which has the longest half-life (T½) of more than 37 h, was reported to increase insulin sensitivity by 20% using the SSPG method (26). We also previously reported that barnidipine, the T½ of which is 4.8 h after oral administration of 10 mg, improved insulin sensitivity by 41% (24). Thus, the previous studies using dihydropyridine Ca-antagonists are sometimes irreconcilable.

Based on the hemodynamics resulting from administration of dihydropyridines, these drugs might improve insulin sensitivity. However, the abrupt vasodilatation might activate the sympathetic nervous system, resulting in the release of catecholamine from the nerve endings, and thereby in attenuation of insulin release from the pancreatic β cells and blunting of the action of insulin in the peripheral tissues. In the present study, plasma norepinephrine levels were not significantly altered. This is consistent with the previous study demonstrating a decrease in urinary norepinephrine excretion after cilnidipine treatment in hypertensive diabetics (29). However, this is in marked contrast to our previous study in which barnidipine improved insulin sensitivity; in that study, even barnidipine with a rather longer plasma T½ resulted in a 1.66-fold increase in plasma norepinephrine. Because of its rather longer plasma T½, a gradual vasodilatation may overcome a slight increase in the sympathetic nervous system, resulting in an improvement of insulin sensitivity. The T½ of cilnidipine has been reported to be 2.1–2.5 h after oral administration of 5–20 mg (30). Although this T½ is shorter than that of amlodipine or barnidipine, cilnidipine did improve insulin sensitivity by 21%. Based on the absence of a change in plasma norepinephrine levels, it is likely that cilnidipine, which blocks both of the L- and N-type Ca²⁺-channels, does not stimulate the sympathetic nervous system. In fact, the increase in plasma norepinephrine levels after a cold pressor stress has been reported to be smaller during cilnidipine treatment than during amlodipine treatment (37). The improved insulin sensitivity achieved by cilnidipine administration in the present study might be at least partially attributable to the drug’s blocking of N-type Ca²⁺-channels as well as L-type Ca²⁺-channels.

Cilnidipine has been proven to improve insulin resistance in animal models of diabetes mellitus (Otsuka Long-Evans fatty rats) and insulin resistance and hypertension (fructose-fed rats) (32, 33). In the latter model, cilnidipine reduced an increase in type 2 fibers. Type 2 fibers of skeletal muscles are more insulin-resistant than type 1 fibers because of the difference in the densities of insulin receptors and glucose transporter 4 (GLUT4) contents (34). Such an effect of cilnidipine on muscle fiber composition may be another reason for the improved insulin sensitivity, although the exact mechanisms remain to be clarified.

The effects of hypotensive agents on insulin sensitivity have been variously investigated using a euglycemic hyperinsulinemic clamp, SSPG, or minimal model assessment method. However, several large-scale intervention trials,
such as the Captopril Prevention Project (CAPPP), the Heart Outcomes Prevention Evaluation Study (HOPE), the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT) and the Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE), have reported the long-term effects of hypotensive drugs on the incidence of newly developed diabetes mellitus in hypertensives (35–38). ACE inhibitors were reported to reduce the incidence of newly developed diabetes by 16% or 34% when compared to that with diuretics/β-blockers or placebo in CAPPP and HOPE, respectively. Nifedipine GITS, a Ca-antagonist, has also been shown to reduce the new onset of diabetes by 23% in comparison with the onset rate in diuretics. Very recently, the angiotensin-receptor blocker losartan was reported to lower the incidence of diabetes by 23% in comparison with the onset rate in diuretics. Very recently, the angiotensin-receptor blocker losartan was reported to lower the incidence of diabetes by 23% in comparison with the onset rate in diuretics. Very recently, the angiotensin-receptor blocker losartan was reported to lower the incidence of diabetes by 23% in comparison with the onset rate in diuretics. Very recently, the angiotensin-receptor blocker losartan was reported to lower the incidence of diabetes by 23% in comparison with the onset rate in diuretics. Very recently, the angiotensin-receptor blocker losartan was reported to lower the incidence of diabetes by 23% in comparison with the onset rate in diuretics. Very recently, the angiotensin-receptor blocker losartan was reported to lower the incidence of diabetes by 23% in comparison with the onset rate in diuretics. Very recently, the angiotensin-receptor blocker losartan was reported to lower the incidence of diabetes by 23% in comparison with the onset rate in diuretics. Very recently, the angiotensin-receptor blocker losartan was reported to lower the incidence of diabetes by 23% in comparison with the onset rate in diuretics.

In conclusion, a long-acting Ca-channel blocker, cilnidipine, improved insulin sensitivity without affecting plasma lipid profiles in the present study. The favorable effects of cilnidipine on glucose metabolism are of clinical importance for the treatment of hypertensive patients with insulin resistance and/or diabetes mellitus.

References
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