Insulin sensitivity is preserved despite disrupted endothelial function

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Shankar, Sudha S., Robert V. Considine, J. Christopher Gorski, and Helmut O. Steinberg. Insulin sensitivity is preserved despite disrupted endothelial function. Am J Physiol Endocrinol Metab 291: E691–E696, 2006. First published May 16, 2006; doi:10.1152/ajpendo.00006.2006.—It is well established that endothelial dysfunction and insulin resistance go hand in hand. However, it is unclear whether endothelial dysfunction per se is sufficient to impair insulin-mediated glucose uptake. We have previously reported that 4 wk of administration of the human immunodeficiency virus (HIV)-1 protease inhibitor indinavir to HIV-negative subjects induces endothelial dysfunction. Hence, we hypothesized that indinavir-induced endothelial dysfunction was associated with impaired insulin-mediated glucose disposal. We measured insulin-mediated glucose disposal at the level of the whole body, skeletal muscle, and vasculature by performing hyperinsulinemic euglycemic clamp, and vascular function studies, in a separate group of HIV-negative healthy nonobese subjects (n = 13) before and after 4 wk of daily oral indinavir. Four weeks of indinavir resulted in a 113% increase in 2-deoxyglucose uptake in adipose tissue. Thus our findings indicate that 1) endothelial dysfunction alone is insufficient to impair insulin-mediated glucose disposal, and 2) indinavir-induced endothelial dysfunction is likely due to a direct effect of the drug on the endothelium and is not coupled to the induction of insulin resistance.

It is widely accepted that endothelial dysfunction almost always occurs in the background of concomitant insulin resistance, and this is largely due to impairment of nitric oxide (NO)-dependent tone (24). Furthermore, Clerk et al. (3), Hogikyan et al. (8), Vincent et al. (26), and Youd et al. (27) have shown that impairment in endothelial function is likely to contribute, at least in part, to decreased rates of insulin-mediated glucose uptake in skeletal muscle by restraining the supply of substrate. However, it is unclear whether, in humans, endothelial dysfunction per se is sufficient to impair insulin-mediated glucose uptake.

We have recently reported that 4 wk of the human immunodeficiency virus (HIV)-1 protease inhibitor indinavir causes profound endothelial dysfunction in healthy, lean, HIV-negative subjects, attributable in large part, to a decrease in NO production/release (19). This impairment in endothelial function occurred in the absence of any changes in body weight, blood pressure, lipids, smoking habits, or other factors known to modulate endothelial function.

We hypothesized that severe endothelial dysfunction, as observed with indinavir, is accompanied by concomitant insulin resistance. We tested our hypothesis by studying the effect of indinavir, administered for 4 wk, on insulin sensitivity at the level of the whole body, skeletal muscle, adipose tissue, as well as vasculature in a group of HIV-negative healthy nonobese subjects.

METHODS

Subjects

The studies described were conducted at the Indiana University Medical Center between January 2005 and March 2006. All subjects were HIV negative healthy, nonobese (body mass index <30 kg/m²), normotensive by cuff measurements per Joint National Committee VI criteria (10), had normal 75-g oral glucose tolerance tests per American Diabetes Association criteria (1), had normal cholesterol levels per National Cholesterol Education Program III criteria (6), and were not taking any medications other than the study drug. Studies were approved by the Indiana University Human Subjects Institutional Review Board. All volunteers gave written informed consent. Subjects were instructed to maintain their usual dietary and physical activity habits during the study.

Study Drugs

All vascular drugs were diluted in normal saline, achieving concentrations of 25 μg/ml of methacholine chloride (MCH; Clinalfa, Laufelfingen, Switzerland) and 8 mg/ml of N5-monomethyl-L-arginine (L-NMMA; Calbiochem, San Diego, CA). Indinavir (Merck, West Point, NJ) was administered as two 400-mg capsules orally three times daily (every 8 h) on an empty stomach. Subject compliance was assessed by self-reporting, manual pill count, and measurement of plasma indinavir levels.

Protocol

All subjects were admitted to the Indiana University General Clinical Research Center 2 days before the study and were fed a weight-maintaining diet. All vascular and metabolic studies were performed after an overnight fast and abstinence from smoking. All the metabolic and vascular function measurements were done before and after 4 wk of daily oral indinavir at a dose of 800 mg three times a day. There was no change in the smoking status or physical activity patterns during the 4 wk of indinavir administration. The last dose of indinavir was administered at ~7 AM on the last day of the study before the assessment of vascular and metabolic function.

Study 1 (Fig. 1): whole body glucose disposal, insulin-mediated vasodilation, and skeletal muscle glucose uptake. Thirteen healthy subjects (12 men and 1 woman, mean age 40 ± 2 yr) were studied before and after 4 wk of daily oral indinavir.

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VASCULAR FUNCTION MEASUREMENTS. Hemodynamic measurements were obtained with the subjects in the supine position as previously described (2). Mean arterial pressure (MAP) is expressed in millimeters of mercury, and leg blood flow (LBF) is expressed in liters per minute. Changes in LBF are expressed as absolute (Δ) and percent change (%Δ) to adjust for differences at baseline. Vascular function was studied at baseline using a modified thermodilution technique, and then dose-response curves were constructed for LBF in response to graded intrafemoral artery infusions of 5, 10, and 15 μg/min of the endothelium-dependent vasodilator MCh. After the initial vascular function assessments, subjects underwent a 240-min euglycemic hyperinsulinemic clamp study at a dose of 120 mU·m⁻²·min⁻¹ of insulin (Humulin Insulin, Eli Lilly, Indianapolis, IN). During steady state of the clamp study, we measured skeletal muscle glucose uptake as well as insulin-mediated vasodilation. After completion of the measurement of insulin-mediated glucose uptake and insulin-mediated vasodilation during steady state of the clamp, we assessed the impact of a reduction in blood flow on skeletal muscle glucose uptake, using an intrafemoral artery infusion of the NO synthase inhibitor L-NMMA at a dose of 16 mg/min under steady-state conditions. All of the above measurements were repeated in the same sequence after 4 wk of daily oral indinavir at a dose of 800 mg three times a day.

METABOLIC STUDIES. After assessment of endothelial function, a 240-min hyperinsulinemic euglycemic clamp at a dose of 120 mU·m⁻²·min⁻¹ of insulin was initiated. The clamp technique was a modification of the Andres method (5). Subjects were studied in the supine position with a catheter inserted in an antecubital vein for infusion of insulin, glucose, and potassium. Arterial plasma glucose values were determined at 5-min intervals using a bedside glucose analyzer, and the glucose infusion rate was adjusted to maintain the target level of glycemia. Venous plasma glucose samples were determined at 20-min intervals for the first 3 h of the clamp study, and at 5-min intervals for the last hour of the clamp study. At steady state of the clamp study, blood glucose levels varied by <5%, and glucose infusion rates varied by <10%. Rate of whole body glucose uptake (M) was calculated as the mean glucose infusion rate at steady state normalized for body weight. Insulin sensitivity index was calculated as the ratio (M/I) of M to prevailing plasma insulin levels (I) at steady-state.

Arteriovenous glucose differences (a-vΔ), a measure of skeletal muscle glucose uptake, were calculated [(arterial glucose - venous glucose)] every 5 min during steady state of the clamp study. a-vΔ were also calculated during the infusion of L-NMMA. Leg glucose uptake (LGU) was calculated as the product of LBF times a-vΔ (LGU = LBF·a-vΔ).

Study 2: in vivo adipose tissue glucose uptake. We studied a separate group of four (2 men and 2 women, mean age 47 ± 3 yr) healthy HIV-negative nonobese subjects before and after 4 wk of daily oral indinavir at a dose of 800 mg three times daily. We obtained abdominal subcutaneous adipose tissue biopsy samples in our subjects before and after indinavir treatment using needle liposuction (4, 12). Immediately after harvest, the adipocytes were isolated by collagenase digestion (4). Basal and insulin-stimulated glucose uptake were measured using d-[U-14C]glucose as previously described (12); this method has been extensively validated by Kashiwagi et al. (11) as well as Sinha et al. (20–22). In brief, triplicates of adipocyte suspensions (6% fractional volume) were preincubated for 30 min with and without insulin (10⁻⁷ M) in 5% bovine serum albumin, and 10 mM HEPES-phosphate buffer, pH 7.40. Thereafter, d-[U-14C]glucose (0.25 μCi, ~0.85 μM) was added to each tube, and the incubation was continued for 60 min and then terminated by centrifugation through dinonylphthalate oil (ICN Biochemicals, Piscataway, NJ). Insulin-stimulated glucose uptake was expressed as a percent change above uptake in the absence of insulin for each individual.

Measurements

Subjects had body weight, height, basal heart rates, systolic and diastolic blood pressure, and fasting lipid measurements done before and 4 wk after indinavir therapy.

Analytic Methods

Total cholesterol and triglyceride levels were measured on a Kodak Ektachem 702 Analyzer with an enzymatic method (Eastman Kodak, Rochester, NY). High-density lipoprotein cholesterol was measured with the Magnetic HDL kit (Reference Diagnostics, Arlington, MA) and low-density lipoprotein cholesterol was calculated according to the Friedewald formula (7). Insulin was assayed by the Human Insulin RIA kit (Linco Research, St. Louis, MO). Glucose levels were assayed using YSI (Yellow Spring Instruments, Yellow Springs, OH) apparatus by the glucose oxidase method. Plasma indinavir levels were measured by high-performance liquid chromatography, with ultraviolet detection as previously described with slight modification (25). The coefficient of variation of quality control samples was <10%.

Statistical Analysis

Results are shown as means ± SE. Repeated-measures ANOVA was used to compare J) the endothelial response with graded doses of the endothelium-dependent vasodilator MCh and 2) glucose disposal rates over the duration of the clamp before and after 4 wk of indinavir administration. Paired t-test was used to compare differences in anthropomorphic, metabolic (lipid, glucose, and insulin levels), and vascular variables (resting LBF, insulin-mediated vasodilation, and response to L-NMMA) before and after indinavir. Statistical significance was accepted at a level of P < 0.05. Statistics were performed with the computer program Stat View IV (Abacus Concepts, Berkeley, CA).

RESULTS

Study 1: Whole Body Glucose Disposal, Insulin-Mediated Vasodilation, and Skeletal Muscle Glucose Uptake

Demographic, basal hemodynamic, and basal metabolic data of the study subjects before and after 4 wk of indinavir are shown in Table 1. Subjects had mean peak plasma indinavir...
levels of 13.65 ± 2.47 µM and mean trough levels of 1.02 ± 0.21 µM.

**Hemodynamic effects of indinavir.** Resting heart rate, systolic blood pressure, diastolic blood pressure, and MAP did not change in response to indinavir treatment.

Resting LBF did not change after indinavir (0.19 ± 0.01 vs. 0.21 ± 0.01 l/min; P = 0.09). Before indinavir, LBF increased in a dose-dependent and robust fashion in response to the endothelium-dependent vasodilator MCh with a maximum increment in LBF (%ΔLBF) in response to MCh of 228 ± 35% (P < 0.01 vs. baseline). After indinavir, LBF increased in a dose-dependent fashion. However, indinavir caused a significant blunting of the LBF response to MCh (Fig. 2) with a maximum %ΔLBF of 114 ± 28% (P < 0.01 vs. baseline; P < 0.01 vs. before indinavir). Thus in a distinctly separate subject group, we were able to reproduce our previous findings that 4 wk of indinavir significantly impair endothelium-dependent vasodilation (19).

Before indinavir, LBF increased in a robust fashion in response to the euglycemic hyperinsulinemic clamp. In response to insulin, LBF increased from 0.19 ± 0.01 l/min to 0.41 ± 0.04 l/min (P < 0.05), representing a 101 ± 14% increase in LBF. After indinavir, LBF increased from 0.21 ± 0.01 to 0.29 ± 0.03 l/min (P < 0.05) in response to insulin, representing a 35 ± 15% increase in LBF. Thus there was significant (P < 0.05) blunting of insulin-mediated vasodilation after indinavir (Fig. 3).

At baseline, administration of L-NMMA, an inhibitor of NO synthase, decreased steady-state LBF by 41 ± 6% (P < 0.01 vs. steady state). After indinavir, there was a significant blunting of the effect of L-NMMA to lower steady-state LBF (20 ± 6%; P < 0.01 vs. steady state; P < 0.05 vs. before indinavir).

**Metabolic effects of indinavir.** Fasting lipids and insulin levels as well as homeostasis model assessment of insulin resistance were unchanged after indinavir, compared with baseline (Table 1). Steady-state glucose concentrations were similar before and after indinavir (94.0 ± 1.2 vs. 91.8 ± 1.0 mg/dl; P = 0.2). Steady-state insulin concentrations were comparable before and after indinavir (313 ± 14 and 308 ± 13 µU/l, respectively; P = 0.8). Values for M during steady state were 8.9 ± 0.5 mg·kg⁻¹·min⁻¹ before indinavir, and they remained unchanged at 8.5 ± 0.5 mg·kg⁻¹·min⁻¹ after indinavir (P = 0.4). Rates of whole body glucose disposal remained comparable throughout the duration of the clamp study, before and after indinavir (Fig. 4). M/I was unchanged before and after indinavir (0.030 ± 0.003 vs. 0.029 ± 0.003; P = 0.7; Fig. 5). Plasma insulin levels at steady state of the clamp study were 5.17 ± 0.7; Fig. 5). Plasma indinavir levels at steady state of the clamp were 27.5 ± 2.3 and 29.3 ± 2.9 mg/dl (P = 0.7) before and after indinavir, respectively. In response to a decrease in LBF induced by L-NMMA, a-νΔ increased from 27.0 ± 2.1 to 37.7 ± 2.7 mg/dl.
(P < 0.01) before indinavir, and from 29.4 ± 2.7 to 39.6 ± 4.7 mg/dl (P < 0.01) after indinavir. The values for a-\(\Delta\) in response to L-NMMA were comparable before and after indinavir (P = 0.8).

**Skeletal muscle insulin sensitivity.** At steady-state hyperinsulinemia, LGU did not differ before and after indinavir (106.6 ± 10.6 mg/min before vs. 84.1 ± 11.8 mg/min after indinavir; P = 0.1). Rates of LGU decreased significantly in response to the administration of L-NMMA before indinavir (85.9 ± 9.2 mg/min; P < 0.05). In contrast, rates of LGU did not change in response to L-NMMA after indinavir (92.1 ± 12.2 mg/min; P = 0.6). Nevertheless, rates of LGU after administration of L-NMMA were comparable before and after indinavir (85.9 ± 9.2 mg/min before indinavir vs. 92.1 ± 12.2 mg/min after indinavir; P = 0.7). These results show that glucose uptake at the level of skeletal muscle is not affected by 4 wk of indinavir.

**Study 2: Ex Vivo Adipose Tissue Glucose Uptake**

Effect of indinavir on adipose tissue insulin-stimulated glucose uptake. Demographic, hemodynamic, and metabolic data of the study subjects before and after 4 wk of indinavir are shown in Table 2. Four weeks of indinavir administration did not result in any change of these study variables. Subjects had mean peak plasma indinavir levels of 13.62 ± 3.02 \(\mu\)M and mean trough levels of 0.23 ± 0.11 \(\mu\)M.

Maximal insulin-stimulated glucose uptake was not different after 4 wk of indinavir, compared with baseline (52.2 ± 18.8% before indinavir vs. 71.5 ± 33.4% after indinavir; P = 0.7).

**DISCUSSION**

In the present study, we tested the hypothesis that profound endothelial dysfunction is associated with concomitant insulin resistance.

The results of our studies show that 4 wk of indinavir in healthy subjects results in the following sustained effects: 1) significant endothelial dysfunction, thus confirming our earlier observations (19); 2) significant impairment of insulin-mediated vasodilation; 3) no impairment of whole body glucose uptake; 4) no change in a-\(\Delta\) or LGU during steady-state euglycemic hyperinsulinemia, as well as in response to the reduction of leg blood flow induced by L-NMMA, indicating that glucose extraction at the level of the skeletal muscle is not impaired by indinavir; and finally, 5) no impairment of insulin-stimulated glucose uptake at the level of adipose tissue.

Thus our findings from this study show for the first time that profound impairment in endothelium-dependent vasodilation after 4 wk of indinavir is not associated with a concomitant impairment of insulin sensitivity at the level of the whole body, skeletal muscle (leg), or adipose tissue. These findings indicate that indinavir has effects on the endothelium, independent of insulin sensitivity, revealing a scenario where there is uncoupling of endothelial function from insulin sensitivity. Furthermore, it is unlikely that insulin resistance is the pathophysiological basis for the endothelial dysfunction seen with indinavir.

There is considerable controversy as to whether primary impairment of endothelium-dependent vasodilation can lead to impaired insulin-mediated glucose uptake. Insulin-mediated glucose uptake depends on 1) the rate of blood flow for substrate delivery, 2) the rate of extraction of glucose by the skeletal muscle cells (a reflection of GLUT4 activity), and 3) the rate of substrate delivery.

**Table 2. Demographic characteristics of the adipose tissue glucose transport study subjects before and after 4 wk of daily oral indinavir**

<table>
<thead>
<tr>
<th></th>
<th>Before Indinavir</th>
<th>After Indinavir</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>24.4±1.5</td>
<td>24.1±1.6</td>
<td>0.4</td>
</tr>
<tr>
<td>WHR</td>
<td>0.89±0.04</td>
<td>0.88±0.01</td>
<td>0.7</td>
</tr>
<tr>
<td>Fasting plasma insulin</td>
<td>7.7±0.9</td>
<td>9.9±1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.8±0.2</td>
<td>2.3±0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>89±6</td>
<td>89±4</td>
<td>0.9</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>168±12</td>
<td>176±8</td>
<td>0.5</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>103±5</td>
<td>117±11</td>
<td>0.2</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>47±8</td>
<td>45±7</td>
<td>0.2</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>92±20</td>
<td>73±16</td>
<td>0.4</td>
</tr>
</tbody>
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Values are means ± SE for 4 subjects.

Fig. 5. Time course of glucose disposal rates throughout the hyperinsulinemic euglycemic clamp study before (pre-IDV) and after (post-IDV) 4 wk of indinavir (800 mg po 3 times daily). Values are means ± SE; n, no. of subjects.
the available capillary surface area for glucose uptake. Steady-state LBF increments in response to euglycemic hyperinsulinemia were significantly lower after 4 wk of indinavir compared with before indinavir conditions. This decrease in LBF could theoretically result in decreased glucose uptake.

\( a\cdot\Delta \) at steady-state hyperinsulinemia provides a good estimate of skeletal muscle glucose extraction in in vivo models such as ours. In our study, \( a\cdot\Delta \) did not decrease after 4 wk of indinavir. Furthermore, after an induction of decrease in LBF using L-NMMA, there was an appropriate compensatory increase in \( a\cdot\Delta \), both before and after indinavir. Together, these findings exclude a direct sustained effect of chronic indinavir on skeletal muscle glucose uptake/transport. Furthermore, these \( a\cdot\Delta \) responses also indicate that there is no significant capillary derecruitment after 4 wk of indinavir.

LGU at steady-state hyperinsulinemia, with and without superimposed L-NMMA infusion, is the product of LBF and \( a\cdot\Delta \) (LGU = LBF × \( a\cdot\Delta \)), and it is another index of skeletal muscle glucose uptake. Because insulin-stimulated LBF was decreased after 4 wk of indinavir, one might expect that LGU decreased commensurately. However, the \( a\cdot\Delta \) after indinavir was appropriately compensatory to prevent a reduction in LGU. Furthermore, LGU was maintained both before and after indinavir, in the face of an acute reduction in LBF induced by L-NMMA. Thus our findings with LGU further support our observation that indinavir does not have a sustained effect on skeletal muscle glucose uptake.

Thus, in this instance, despite significant impairment in endothelium-dependent vasodilation, there is no concomitant impairment in insulin sensitivity. The possible explanations for this finding include that 1) there needs to be an even greater impairment in endothelial function/flow for there to be an effect on insulin-mediated glucose uptake; or 2) that there is an increase in capillary recruitment compensatory to the impairment in endothelial function, which then maintains intact substrate delivery, and thus glucose uptake; or 3) that there is an upregulation of GLUT4 activity or number, compensatory to the fall in leg blood flow, that is sufficient to maintain intact insulin-mediated glucose uptake. Finally, on a speculative note, an increase in adiponectin in response to indinavir, as reported by Lee et al. (13), could theoretically exert a protective effect against the development of insulin resistance.

It is interesting to note that while we found no impairment in insulin sensitivity at the level of the whole body or skeletal muscle, we observed an impairment in insulin-mediated vasodilation. Steinberg et al. (23) and others (18, 28) have shown that insulin-mediated vasodilation is largely NO mediated. Given that indinavir significantly impairs NO-dependent tone, the impairment in insulin-mediated vasodilation seen with indinavir is more likely a result of the effect of indinavir on NO release from the vasculature than a sign of insulin resistance at the level of the vasculature.

The clamp studies outlined in this manuscript were performed at a dose of 120 mU·m^{-2}·min^{-1} of insulin. We chose this dose of insulin to completely suppress the effect of hepatic glucose output in our studies. Hence, it is possible that we could have missed a small change in insulin sensitivity at the level of the liver. However, given that the body mass index of some of our subjects were in the overweight category, and because there was no change in fasting glucose or insulin levels after indinavir, this is extremely unlikely. Finally, it is possible that we missed a small decrease in whole body glucose uptake of \(-5\%\) due to the relatively small number of subjects studied. However, the biological importance of such a small impairment in insulin sensitivity, if it exists, remains to be established.

Our findings regarding indinavir and insulin sensitivity are somewhat at variance with that reported by Noor et al. (16). However, in that study, the hyperinsulinemic euglycemic clamp was performed somewhat differently than ours; the dose of insulin used was 40 mU·m^{-2}·min^{-1}, as opposed to the 120 mU·m^{-2}·min^{-1} dose used in our studies, and steady-state was defined as the point at which plasma glucose was stable (60–180 min), rather than glucose infusion rate (at \(-240\) min) being stable, as was done in our study. Given the different study designs, it is clear that it is difficult to compare the findings from their study with ours. It is unlikely that our observations were due to poor subject compliance, because all our subjects had therapeutic levels of indinavir, and demonstrated other effects due to indinavir. Furthermore, at steady state of the clamp study, our subjects had plasma levels of indinavir that were within the therapeutically relevant range. Again, this suggests that even with adequate plasma indinavir levels, there is no sustained effect of indinavir on insulin sensitivity.

There have also been reports of acute, reversible insulin resistance induced by indinavir in a rodent (9) as well as human model (17). However, these effects have been short lived, dependent on ambient plasma indinavir levels, and ill sustained. Thus, although it appears that there may be an acute reversible effect of indinavir on glucose disposal, this phenomenon appears to be transient, with no significant sustained long-term effect.

Indinavir has been reported to acutely impair glucose transport in 3T3-L1 cells (14, 15), and thereby potentially contribute to indinavir-induced insulin resistance. Hence, we explored the possibility of adipose tissue as a potential site of sustained impaired glucose uptake secondary to longer period of use of indinavir. The results of our studies show that 4 wk of indinavir does not affect insulin-stimulated glucose uptake at the level of the adipocyte. This is in accordance with our findings at the level of the whole body, as well as skeletal muscle. We are the first to study and report the long-term effect of indinavir on insulin-stimulated glucose uptake in the adipocyte in the human in vivo model. Our findings differ from those of Murata et al. (14, 15); however, their study was done in 3T3-L1 cells, which differ from human adipocytes in several respects; furthermore, Murata et al. (14) reported an acute reversible effect, whereas our observations relate to a more chronic sustained effect. Thus it is possible that although acutely indinavir may have an effect on in vitro adipocyte glucose transport, there appears to be no sustained effect on insulin-stimulated glucose uptake at 4 wk in the intact human.

In summary, our study shows that the impairment in endothelium-dependent vasodilation seen after 4 wk of indinavir in healthy HIV-negative nonobese subjects occurs in the absence of impairment of insulin sensitivity, as measured by insulin-mediated glucose uptake at the level of the whole body, skeletal muscle, as well as adipose tissue. This indicates that indinavir appears to have direct effects on the endothelium, which are not coupled to insulin sensitivity. Further studies...
need to be done to better understand the mechanisms underlying these phenomena.

GRANTS

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