Troglitazone Antagonizes Metabolic Effects of Glucocorticoids in Humans

Effects on Glucose Tolerance, Insulin Sensitivity, Suppression of Free Fatty Acids, and Leptin

Steven M. Willi,1 Adele Kennedy,2 Penny Wallace,2 Elizabeth Ganaway,2 Nikki L. Rogers,2 and W. Timothy Garvey2

Glucocorticoids induce insulin resistance in humans, whereas thiazolidinediones enhance insulin sensitivity. Although the effects of glucocorticoids and thiazolidinediones have been assessed in isolation, interaction between these drugs, which both act as ligands for nuclear receptors, has been less well studied. Therefore, we examined the metabolic effects of dexamethasone and troglitazone, alone and in combination, for the first time in humans. A total of 10 healthy individuals with normal glucose tolerance (age 40 ± 11 years, BMI 31 ± 6.1 kg/m2) were sequentially studied at baseline, after 4 days of dexamethasone (4 mg/day), after 4–6 weeks on troglitazone alone (400 mg/day), and again after 4 days of dexamethasone added to troglitazone. Key metabolic variables included glucose tolerance assessed by blood glucose and insulin responses to an oral glucose tolerance test (OGTT), insulin sensitivity evaluated via hyperinsulinemic-euglycemic clamp, free fatty acids (FFAs) and FFA suppressibility by insulin during the clamp study, and fasting serum leptin. Dexamethasone drastically impaired glucose tolerance, with fasting and 2-h OGTT insulin values increasing by 2.3-fold (P < 0.001) and 4.4-fold (P < 0.001) over baseline values, respectively. The glucocorticoid also induced a profound state of insulin resistance, with a 34% reduction in maximal glucose disposal rates (GDRs; P < 0.001). Troglitazone alone increased GDRs by 20% over baseline (P = 0.007) and completely prevented the deleterious effects of dexamethasone on glucose tolerance and insulin sensitivity, as illustrated by a return of OGTT glucose and insulin values and maximal GDR to near-baseline levels. Insulin-mediated FFA suppressibility (FFA decline at 30 min during clamp/FFA at time 0) was also markedly reduced by dexamethasone (P = 0.002). Troglitazone had no effect per se, but it was able to normalize FFA suppressibility in subjects coadministered dexamethasone. Futhermore, the magnitudes of response of FFA suppressibility and GDR to dexamethasone were proportionate. The same was true for the reversal of dexamethasone-induced insulin resistance by troglitazone, but not in response to troglitazone alone. Leptin levels were increased 2.2-fold above baseline by dexamethasone. Again, troglitazone had no effect per se but blocked the dexamethasone-induced increase in leptin. Subjects experienced a 1.7-kg weight gain while taking troglitazone but no other untoward effects. We conclude that in healthy humans, thiazolidinediones antagonize the action of dexamethasone with respect to multiple metabolic effects. Specifically, troglitazone reverses both glucocorticoid-induced insulin resistance and impairment of glucose tolerance, prevents dexamethasone from impairing the antilipolytic action of insulin, and blocks the increase in leptin levels induced by dexamethasone. Even though changes in FFA suppressibility were correlated with dexamethasone-induced insulin resistance and its reversal by troglitazone, a cause-and-effect relationship cannot be established. However, the data suggest that glucocorticoids and thiazolidinediones exert fundamentally antagonistic effects on human metabolism in both adipose and muscle tissues. By preventing or reversing insulin resistance, troglitazone may prove to be a valuable therapeutic agent in the difficult clinical task of controlling diabetes in patients receiving glucocorticoids. Diabetes 51:2895–2902, 2002

Glucocorticoids induce insulin resistance in humans (1–4) and can cause or aggravate diabetes. Furthermore, in patients receiving adrenal-suppressive doses of glucocorticoids, diabetes is quite difficult to control and often requires very high doses of insulin. Mechanisms responsible for glucocorticoid-induced insulin resistance involve desensitization of the glucose transport system. Studies in animals (5–8) as well as humans (1–4,9) have shown that glucocorticoid excess results in decreased insulin-stimulated glucose uptake in muscle, and this occurs in the absence of any consistent effect on insulin receptor number or ligand affinity (5,10,11). Additional studies in rodent skeletal muscle indicate that glucocorticoid administration disrupts insulin-mediated recruitment of glucose transporters to the cell surface, without affecting expression of the insulin-responsive GLUT4 transporter isoform (12,13). In
cultured cells (14–16), dexamethasone treatment acutely impairs glucose transporter translocation in response to insulin and, with more chronic exposure, reduces basal glucose transport activity associated with decreased expression of GLUT1 transporters (17). In basal cells, the effects of glucocorticoids to block transporter translocation are associated with a redistribution of cell surface transporters into the cell interior (14–16). Thus, glucocorticoid-induced insulin resistance is caused by defects in the glucose transport system that block insulin’s ability to mobilize intracellular glucose transporters to the plasma membrane.

A new class of insulin-sensitizing medications, the thiazolidinediones, have been developed to treat diabetes (18). Troglitazone is the prototype member of this drug class to be used therapeutically, and it has been shown to enhance insulin sensitivity in humans (19–21). Thiazolidinediones increase insulin sensitivity by interacting with peroxisome proliferator–activated receptor-γ (PPAR-γ) located in the nucleus, which exerts profound metabolic influence through its ability to regulate gene transcription (22–24). PPAR-γ expression is highest in adipose tissue, where ligand activation is also critical for adipocyte differentiation (23–26). Perhaps as a consequence of drug action in adipocytes, troglitazone has been shown to lower circulating free fatty acid (FFA) levels (21). Because FFAs can induce muscle insulin resistance (27–29), investigators have speculated that the drug’s effect on muscle insulin sensitivity arises secondarily due to a primary action to suppress lipolysis in adipocytes. On the other hand, PPAR-γ mRNA is also clearly expressed in skeletal muscle (30–32). In fact, troglitazone directly alters gene expression in cultured human muscle cells (32) and enhances insulin sensitivity in vivo even in the absence of adipose tissue (33), suggesting the drug has direct effects on skeletal muscle glucose uptake.

It is clear, then, that glucocorticoids decrease and thiazolidinediones increase insulin sensitivity. Because both drugs alter gene expression by binding to specific nuclear receptors, we hypothesized that thiazolidinediones could antagonize the metabolic effects of glucocorticoids. Such an effect could be exploited clinically to treat diabetes in patients with endogenous or exogenous hypercortisolism. Although numerous studies have examined the independent effects of glucocorticoids or troglitazone on insulin-stimulated glucose uptake, the ability of thiazolidinediones to reverse glucocorticoid-induced insulin resistance has not been studied in humans. To explore this issue, we have studied the metabolic effects of glucocorticoids and troglitazone, alone and in combination, in healthy individuals. The key study variables were glucose tolerance and insulin sensitivity. An additional focus included fasting levels and insulin suppressibility of circulating FFAs because elevated FFAs have been implicated in glucocorticoid-induced insulin resistance (34,35), and the reduction in FFAs with troglitazone has been linked to the enhancement in insulin sensitivity (19–21,25). Finally, we examined potential interaction in the regulation of leptin because glucocorticoids have been found to increase (36) and troglitazone to decrease (37,38) leptin levels when these drugs are administered in isolation.

### TABLE 1
Baseline clinical characteristics of the study subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.1 ± 10.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.1 ± 6.1</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>36.3 ± 12.5</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>71.4 ± 9.9</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>5.17 ± 0.216</td>
</tr>
<tr>
<td>Fasting insulin level (pmol/l)</td>
<td>42.0 ± 7.8</td>
</tr>
<tr>
<td>GDR (mg · kg LBM⁻¹ · min⁻¹)</td>
<td>12.1 ± 2.4</td>
</tr>
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</table>

Data are means ± SD. LBM, lean body mass.

### RESEARCH DESIGN AND METHODS

We studied 10 healthy subjects (4 men, 6 women) with normal glucose tolerance. The clinical characteristics of the study group are listed in Table 1. Subjects were metabolically characterized as inpatients at the General Clinical Research Center, Medical University of South Carolina, Charleston, SC, on four sequential occasions: 1) baseline; 2) after dexamethasone at 2 mg b.i.d. per os for 4 days; 3) after the dexamethasone was discontinued, and the subjects were then restudied after troglitazone was given for 4–6 weeks at 400 mg/day (7 of 10 subjects were treated for 4 weeks, 2 for 5 weeks, and 1 for 6 weeks); and 4) after another period of dexamethasone administration (2 mg b.i.d. for 4 days) as troglitazone therapy was continued. Before the study, subjects were equilibrated on a weight maintenance diet (28–32 kcal · kg⁻¹ · day⁻¹) consisting of 50% carbohydrates, 30% fat, and 20% protein. The isocaloric diet was maintained throughout, and subjects were instructed to not make any changes in their usual levels of activity. None of the study subjects engaged in regular exercise. Percent body fat, regional percent body fat, and lean body mass were measured by dual-energy X-ray absorptiometry (DEXA; Lunar Radiation, Madison, WI) upon entry into the study, as previously described (39,40). None of the subjects had cardiovascular, renal, thyroid, or liver diseases and were not ingesting any medications that might affect substrate or energy metabolism. Liver function tests (alkaline phosphatase, total bilirubin, aspartate aminotransferase, and alanine aminotransferase) were checked every 1–2 weeks in all subjects. Protocols were approved by the Medical University of South Carolina institutional review board, and informed consent was obtained from every subject.

#### Glucose metabolism.

At each of the four study periods, standard 75-g oral glucose tolerance tests (OGTTs) were performed after a 12-h overnight fast. Glucose and insulin were measured at 0, 30, 60, 90, 120, and 180 min. In vivo insulin sensitivity, when assessed using the euglycemic-hyperinsulinic glucose clamp technique as previously described (30,41–43). After a 12-h fast, a catheter was inserted into the brachial vein to administer insulin, glucose, and KPO₄. A dorsal hand vein was cannulated in a retrograde manner and kept in a warming device (65°C) to provide arterialized venous blood for sampling. To maximally stimulate glucose uptake and suppress hepatic glucose production, regular insulin (Humulin, Eli Lilly, Indianapolis, IN) was administered at a rate of 200 mU · m⁻² · min⁻¹, producing a mean steady-state insulin concentration of 3,480 ± 138 pmol/l, which is maximally effective for stimulating glucose uptake into skeletal muscle (43). Serum glucose was clamped at 5.0 mmol/l for at least 3 h, and maximal glucose uptake for each individual was calculated from the mean glucose infusion rate over the final three 20-min intervals. Whole-body glucose uptake was calculated based on the glucose infusion rate calculated for changes in the glucose pool size, assuming a distribution volume of 19% body weight and a pool fraction of 0.65. Glucose uptake was normalized per kilogram lean body mass (excluding bone mass) determined by DEXA to yield the GDR per kilogram of lean body mass.

The OGTT was performed the day before the hyperinsulinemic-euglycemic clamp in all phases. At study phases 2 and 4, the OGTT was performed after 3 days of dexamethasone, and clamp study was carried out after 4 days of dexamethasone.

#### FFAs and leptin.

Nonesterified FFA levels were measured using an enzymatic colorimetric assay (NEFA C test kit; Wako Chemicals, Richmond, VA) (44). FFA levels were measured at baseline and 30, 60, 90, 120, and 180 min into the euglycemic-hyperinsulinemic clamp procedure to assess sensitivity of FFAs to suppression by insulin. FFA suppressibility was measured as (baseline level – 30-min level)/baseline level. Serum for leptin determination was obtained from blood drawn at 8:00–9:00 a.m. after an overnight fast. Quantification of serum leptin was determined using a radioimmunoassay and immunopurified rabbit antibodies raised against recombinant human leptin (Linco, St. Louis, MO). Methodology and characteristics of the assay have previously been described in detail (42).
TABLE 2
Effects of troglitazone and dexamethasone on glucose metabolism

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Troglitazone treatment (alone)</th>
<th>Dexamethasone treatment (alone)</th>
<th>Dexamethasone and troglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.2 ± 0.2</td>
<td>5.0 ± 0.2</td>
<td>5.9 ± 0.2*</td>
<td>5.2 ± 0.2†</td>
</tr>
<tr>
<td>2-h OGGTT glucose (mmol/l)</td>
<td>7.7 ± 0.87</td>
<td>7.5 ± 0.8</td>
<td>10.9 ± 0.9‡</td>
<td>8.8 ± 2.0†</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>42 ± 8</td>
<td>46 ± 10</td>
<td>96 ± 15‡</td>
<td>50 ± 8§</td>
</tr>
<tr>
<td>2-h OGGTT insulin (pmol/l)</td>
<td>265 ± 38</td>
<td>327 ± 92</td>
<td>1,172 ± 172‡</td>
<td>499 ± 86§</td>
</tr>
<tr>
<td>Fasting FFAs (mmol/l)</td>
<td>0.68 ± 0.12</td>
<td>0.53 ± 0.8</td>
<td>0.53 ± 0.8</td>
<td>0.68 ± 0.14</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.05 ± 0.12</td>
<td>1.00 ± 0.09</td>
<td>1.08 ± 0.12</td>
<td>0.81 ± 0.12</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.81 ± 0.29</td>
<td>2.48 ± 0.28</td>
<td>2.61 ± 0.22</td>
<td>2.59 ± 0.29</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.34 ± 0.17</td>
<td>1.39 ± 0.16</td>
<td>1.38 ± 0.17</td>
<td>1.37 ± 0.13</td>
</tr>
</tbody>
</table>

Data are means ± SE. *P < 0.05 compared with baseline; †P < 0.05 compared with after dexamethasone alone; ‡P < 0.001 compared with baseline; §P < 0.001 compared with after dexamethasone alone.

Other assays and statistical analysis. Plasma glucose was measured by the glucose oxidase method using a glucose analyzer (YSI 2300; Yellow Springs Instruments, Yellow Springs, OH). Serum insulin levels were measured using a microparticle enzyme immunoassay kit (Abbott Diagnostics, Chicago, IL). LDL cholesterol was calculated using the Friedewald equation from the total and HDL cholesterol levels measured by a colorimetric oxidase technique, and triglycerides were measured by a colorimetric glycerophosphate technique, using Vitos autoanalyzers (Johnson and Johnson, Rochester, NY).

Data analysis was performed using Statistica for Windows, version 5.1, 1997 edition (Statsoft, Tulsa, OK) and the SAS program version 6.10 (SAS Institute, Cary, NC). Data are expressed as means ± SE except as indicated in Table 1. Statistical significance was detected using repeated-measures ANOVA, and Tukey’s analysis was used to assess post hoc for group-by-group differences. Differences were accepted as significant at P < 0.05.

RESULTS
Effects on glucose tolerance and insulin sensitivity. Administration of high-dose dexamethasone (2 mg b.i.d.) for 3–4 days had dramatic effects to diminish both glucose tolerance and insulin sensitivity. In the presence of dexamethasone, fasting and 2-h glucose and insulin levels after a 75-g oral glucose challenge were significantly increased (Table 2), as were the areas under the respective glucose and insulin curves (Figs. 1A and 1B) when compared with the baseline study. Of the 10 subjects, 4 fulfilled diagnostic criteria for diabetes, and an additional 5 showed evidence of impaired glucose tolerance, while taking dexamethasone. One reason for these effects on glucose tolerance was a significant 34% reduction in maximal insulin-stimulated GDR in dexamethasone-treated individuals compared with baseline values (Fig. 2).

Individuals were treated with troglitazone alone (400 mg/day) for 4–6 weeks, and the metabolic effects of the thiazolidinediones are also shown in Table 2. Insulin and glucose levels after oral glucose challenge did not change significantly from baseline after troglitazone alone. Even so, troglitazone increased sensitivity as manifested by a 20% increase in GDR over baseline (P < 0.001), as depicted in Fig. 2. Subjects gained an average of 1.7 kg during the 4–6 weeks while taking this medication. There were no other untoward effects, and no elevations in hepatic transaminases were noted.

After studies were completed following 4–6 weeks of troglitazone, dexamethasone was reintroduced (2 mg b.i.d. for 4 days) while the thiazolidinedione was continued. When data in subjects treated with the combination of dexamethasone and troglitazone was compared with dexamethasone alone, troglitazone pretreatment was found to dramatically block the deleterious effects of dexamethasone on glucose tolerance (Fig. 1, Table 2). Furthermore, troglitazone completely prevented glucocorticoid-induced insulin resistance, since maximal GDRs in subjects treated with the combination of dexamethasone and troglitazone were similar to baseline values (Fig. 2). However, the mean GDR was not increased above baseline in subjects taking both drugs, as was observed with troglitazone alone.

Effects on FFAs. No significant changes in fasting FFA levels, triglyceride levels, or lipid panels were detected (Table 2). However, significant effects were observed in the suppression of FFAs during the hyperinsulinemic-euglycemic clamp, an index of insulin’s antilipolytic effect.
on adipose tissue. FFA suppression by insulin was decreased 22% by dexamethasone and did not change significantly with troglitazone alone, when compared with baseline values. However, troglitazone completely prevented dexamethasone from impairing FFA suppressibility, as shown in Fig. 3.

We found no correlation between fasting FFA levels and either GDR within treatment subgroups or the changes in GDR induced by dexamethasone and troglitazone (data not shown). However, when data were analyzed before and after treatment with dexamethasone, we found that the effect of this drug on glucose uptake was in proportion to its influence on FFA suppressibility (Fig. 4A). In contrast, the ability of troglitazone to increase glucose disposal above baseline was not correlated with FFA suppressibility effects (Fig. 4B). Even so, the improvement in GDR from subjects treated with troglitazone plus dexamethasone over dexamethasone alone was highly correlated with changes in FFA suppressibility (Fig. 4C). Thus, the pattern of alterations in FFA suppressibility was related to the level of glucocorticoid-induced insulin resistance and its reversal by troglitazone, but it was unrelated to the increase in insulin sensitivity resulting from the thiazolidinedione per se.

**Effects on leptin.** Fasting leptin levels were increased 2.2-fold by dexamethasone and were not altered by troglitazone alone, when compared with baseline values (Fig. 5). Troglitazone pretreatment, however, blocked the doubling of leptin values by dexamethasone and returned values to baseline. Fasting leptin levels were not correlated with GDR, fasting or 2-h OGTT glucose or insulin levels (data not shown).

**DISCUSSION**

We have assessed the effects of the glucocorticoid dexamethasone and the thiazolidinedione troglitazone and for the first time examined interaction between these drugs with respect to multiple metabolic parameters in humans. Our findings provide confirmation of previous studies demonstrating that glucocorticoids induce peripheral insulin resistance (2–4) in healthy humans, and they show a pronounced effect of steroids to decrease maximal insulin responsiveness, which was not clearly evident in a previous report (2). This reflects impaired stimulation of glucose uptake in skeletal muscle, which has been shown to result from defects in the recruitment of GLUT4 glucose transporters to the cell surface in animal (12,13) and cell (14–17) models. Peripheral insulin resistance, together with insulin resistance at the level of the liver (2–4), leads to impaired glucose tolerance, as manifested in the current data by higher glucose and insulin concentrations after an oral glucose challenge. Glucocorticoids can also increase lipolysis and circulating FFA concentrations, and previous
authors have implicated this effect in the pathogenesis of glucocorticoid-induced insulin resistance in skeletal muscle (5,34,35). Our data support this idea, since dexamethasone decreased insulin’s ability to suppress FFA levels, and this effect was well correlated with the reduction in maximally stimulated glucose uptake rates. Although dexamethasone did not alter fasting FFA levels in our subjects, the impairment in FFA suppressibility would predictably result in increased FFA concentrations after meals. Thus, chronic elevations in postprandial FFA profiles could contribute to insulin resistance in skeletal muscle (27–29). A relationship between insulin’s ability to suppress FFA and to stimulate muscle glucose uptake has been previously demonstrated by Reaven and colleagues (45,46) in a sample of healthy individuals.

Troglitazone, the first available antidiabetic medication in the thiazolidinedione class, has been shown to enhance peripheral insulin sensitivity in both genetic and acquired models of insulin resistance in rodents (18,47,48), and in diabetic (19,49,50) and obese nondiabetic individuals (21). In the current study, troglitazone similarly led to a significant increase in insulin-stimulated glucose uptake rates. However, we did not observe significant alterations in glucose tolerance or post–glucose challenge insulin concentrations compared with baseline. Clinical trials with troglitazone (19,20) and other thiazolidinediones have demonstrated that up to 3 months of treatment is necessary to achieve the full therapeutic effects of the drug. Our subjects were treated for 4–6 weeks with a submaximal dose (400 mg/day as opposed to 600 mg/day), and the majority received 4 weeks of treatment. Thus, it is likely that a longer course of treatment would have resulted in more pronounced effects on insulin sensitivity and a reduction in insulin concentrations during OGTTs (21). In addition, troglitazone did not alter fasting FFA levels or FFA suppressibility in the current study. Therefore, unlike dexamethasone, the effect of troglitazone on insulin sensitivity was not related to any alteration in FFA suppressibility or fasting FFA levels, suggesting that FFAs were not involved in the enhancement of insulin action in muscle. Thus, our data do not support a common notion that troglitazone’s insulin-sensitizing effect on muscle is entirely dependent on an antilipolytic effect in adipose tissue that lowers circulating FFA concentrations. This notion is based on the observations that troglitazone is generally found to decrease circulating FFA concentrations (21) and that FFA infusions induce insulin resistance (27–29). However, troglitazone has been shown to increase muscle insulin action in transgenic mice without adipose tissue (33). Furthermore, our data are in agreement with Maggs et al. (20), who found that troglitazone administration at doses of 200 and 400 mg/day increased insulin sensitivity without any effects on fasting FFA levels. Thus, the current data and these previous results indicate that troglitazone can increase insulin sensitivity independent of an effect in adipose tissue that lowers circulating FFA. By inference, troglitazone could have direct effects to enhance insulin action in muscle.

This study is the first to examine interactions between glucocorticoids and thiazolidinediones in humans. The data demonstrate that troglitazone is able to completely reverse glucocorticoid-induced changes in glucose tolerance, insulin sensitivity, and FFA suppressibility. Dexamethasone led to marked elevations in glucose and insulin concentrations, and these values were returned to baseline levels when individuals were pretreated with troglitazone. Additionally, troglitazone normalized maximally stimulated GDR in subjects receiving dexamethasone; however, the mean value in subjects treated with both drugs was similar to baseline, in contrast to the increase

FIG. 4. The relationship between FFA suppressibility and insulin sensitivity in subjects treated with dexamethasone and/or troglitazone. FFA suppressibility was assessed in response to insulin during hyperinsulinemic-euglycemic clamps and represents the decrease in FFA from baseline at the 30-min time point divided by the baseline value. Insulin sensitivity was measured as the maximally stimulated GDR during a hyperinsulinemic-euglycemic clamp study, and was normalized by kilograms of lean body mass (LBM) assessed by DEXA. The correlation between FFA suppressibility and GDR is shown in subjects at baseline (●) and after treatment with troglitazone alone (400 mg/day) for 4–6 weeks (●) in A; in subjects at baseline (●) and after treatment with dexamethasone (2 mg b.i.d.) administration (△) in B; in subjects after 4 days of dexamethasone (2 mg b.i.d.) administration (△) and after treatment with both troglitazone (400 mg/day) for 4–6 weeks and dexamethasone (2 mg b.i.d.) over the last 4 days (Dex+Trog; ▲) in C. The solid lines represent linear regression of the data in 10 subjects.
above baseline observed in subjects treated with troglitazone alone. The decline in FFA suppressibility induced by dexamethasone was also completely prevented by troglitazone. Furthermore, the increase in FFA suppressibility in subjects given both drugs compared with dexamethasone alone was correlated with the increment in maximal GDR. Thus, changes in FFA suppressibility are related to both the induction of insulin resistance by dexamethasone and its reversal by troglitazone. The data suggest that although troglitazone can increase insulin sensitivity independent of any effects on FFA as discussed above, its ability to reverse glucocorticoid-induced insulin resistance may be linked to an antilipolytic effect that would lower postprandial FFA levels. There have been several publications in animal models that are in agreement with the current data. First, thiazolidinediones have been shown to ameliorate glucocorticoid-induced insulin resistance in rats (51) and mice (52). Second, Mokuda and Sakamoto (35) have shown that glucocorticoid-induced insulin resistance in rat hindquarter is dependent on FFAs and that troglitazone improves insulin sensitivity by antagonizing these FFA effects.

Interaction between dexamethasone and troglitazone was also observed in the regulation of fasting leptin levels. Dexamethasone increased leptin above baseline, and although troglitazone alone had no effect, the thiazolidinedione was able to completely block the glucocorticoid-induced rise in leptin. Glucocorticoids are known to increase leptin levels (36,54), which has led to speculation that glucocorticoids produce leptin resistance (55). In contrast, troglitazone has been reported to decrease leptin in rats (38,56); however, the current and previous data (57,58) demonstrate the absence of an effect in humans. The interaction between glucocorticoids and thiazolidinediones is a novel observation with respect to leptin and is analogous to effects of insulin and IGF-1 to antagonize glucocorticoid-induced increments in leptin secretion in cultured rat adipose tissue (59). It is unlikely that modulation of leptin by dexamethasone and troglitazone directly mediates changes in glucose tolerance or insulin sensitivity, because leptin levels showed no correlation with GDR, fasting or 2-h OGTT glucose or insulin levels, or FFA levels.

The mechanism underlying antagonism between thiazolidinediones and glucocorticoids for these multiple metabolic parameters remains unknown. Because both drugs are ligands for nuclear receptors, it is reasonable to speculate that the antagonism probably occurs at the level of regulated gene transcription. Consistent with this hypothesis, glucocorticoids have also been shown to have potent effects on the PPAR system of nuclear receptors (60). Thiazolidinediones have also been found to antagonize other glucocorticoid actions in cultured cells, including regulation of phosphoenolpyruvate carboxykinase expression (61), gene expression in osteoblasts (62), and downregulation of insulin receptor substrate-1 (63). Regardless of the underlying mechanism, the most immediate significance of the current data translates into the clinical management of diabetic patients with endogenous or exogenous hypercortisolism. Control of hyperglycemia in these patients is extremely problematic and cannot be achieved even with very high insulin doses. By reversing glucocorticoid-induced insulin resistance, the use of troglitazone or other thiazolidinediones could allow clinicians to achieve acceptable therapeutic targets for glycemia. This hypothesis is worthy of further study.

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REFERENCES


FIG. 5. The effects of dexamethasone and troglitazone on serum leptin. Subjects were studied at baseline, after 4 days of dexamethasone (2 mg b.i.d.) administration (Dex), after treatment with troglitazone alone (400 mg/day) for 4–6 weeks (Trog), and after treatment with both troglitazone (400 mg/day) for 4–6 weeks and dexamethasone (2 mg b.i.d.) over the last 4 days (Dex+Trog). The data represent fasting (8:00–9:00 A.M) serum leptin concentrations. Data are means ± SE for 10 subjects. *P < 0.05 vs. baseline.


