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Low-Dose Rosiglitazone Exerts an Antiinflammatory Effect with an Increase in Adiponectin Independently of Free Fatty Acid Fall and Insulin Sensitization in Obese Type 2 Diabetics

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Background: We have previously demonstrated an early and potent antiinflammatory effect of troglitazone and rosiglitazone.

Hypothesis: Because inflammatory mediators interfere with insulin signal transduction, we have now hypothesized that rosiglitazone exerts an initial antiinflammatory effect independently of its metabolic actions including the suppression of the plasma concentration of free fatty acids (FFAs), insulin, and glucose after which insulin sensitization occurs.

Patient and Methods: Fourteen patients with type 2 diabetes were included in the study. Eight patients were given 2 mg daily of rosiglitazone for 6 wk, whereas the other six patients were given a placebo for the same period.

Results: After a 2-mg dose of rosiglitazone, plasma FFAs, insulin, and glucose concentrations and homeostasis model assessment of insulin resistance did not change. Plasma C-reactive protein, serum amyloid A, and matrix metalloproteinase concentrations fell significantly at wk 1 and continued to be significantly lower than the baseline levels by 25, 29, and 24%, respectively, at wk 6. Leukocyte count was significantly lower at wk 6 after rosiglitazone, whereas there was no change in the control group. Plasma adiponectin concentrations increased significantly at wk 2 and continued to increase during the treatment period with rosiglitazone. Resistin concentrations fell significantly by 10% at wk 6 only. There were no changes in any of these indices in the placebo group.

Conclusions: A low dose of rosiglitazone exerts an early and potent antiinflammatory effect with an increase in adiponectin and a fall in resistin concentrations without causing any metabolic changes (fall in plasma glucose, FFAs, and insulin concentrations) over a 6-wk period. The increase in adiponectin and the decrease in resistin after rosiglitazone are thus related primarily to its antiinflammatory effects rather than its metabolic actions. These observations have implications in relation to the mode of action of this drug as an insulin-sensitizing agent and also its use as a potential antiinflammatory and antiatherogenic drug in the future. **(*J Clin Endocrinol Metab* 91: 3553–3558, 2006)**

OUR RECENT WORK has shown that insulin exerts a potent and rapid antioxidant and antiinflammatory effect (1, 2) and that insulin sensitizers of the thiazolidinedione (TZD) class also exert a similar effect in humans *in vivo* (3–7). This effect of TZDs was first observed with troglitazone and has now been confirmed with rosiglitazone (6, 7) and pioglitazone (8, 9). In addition, we noted that it is consistently observed early during treatment with TZDs. Thus, it was observed at 7 d with troglitazone 400 mg daily (4, 5) and at 3 d with rosiglitazone 4 mg daily in both obese and type 2 diabetic patients (7). Whereas evidence of antiinflammatory action and insulin sensitization (fall in insulin concentration) occurred at 7 d of treatment with 400 mg troglitazone, 4 mg rosiglitazone induced an antiinflammatory effect between 3 and 7 d with insulin sensitization occurring much later. These data suggested that the antiinflammatory effects may be independent of the metabolic effects that are usually observed several days or weeks later. The antiinflammatory effect of TZDs is also observed, *in vitro*, in the absence of insulin (10–12).

Plasma concentrations of adiponectin have been shown to be lower in diabetic subjects, whereas TZD treatment increases its levels (13–15). On the other hand, resistin levels are higher in diabetic patients and are suppressed with TZD treatment (16–18). Both of these adipokines (resistin is secreted mainly by the macrophage in the human) have been shown to be related to inflammation, but the exact relationship in terms of TZD effects is not yet defined. As with the other inflammatory mediators, TZD effects on resistin and adiponectin in previous studies have been shown to be associated with the metabolic effects.

Because in all of the previous studies on TZD, a fall in either insulin and glucose (if they were diabetic) was observed, we hypothesized that a small dose (2 mg daily) of rosiglitazone would produce an antiinflammatory effect without a change in the metabolic variables of plasma insulin, glucose, and free fatty acid (FFA) concentrations. This

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Abbreviations: BMI, Body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; FFA, free fatty acid; HOMA-IR, homeostasis model assessment of insulin resistance; MMP, matrix metalloproteinase; RMANOVA, repeated-measures ANOVA; SAA, serum amyloid A; TWRMANOVA, two-way RMANOVA; TZD, thiazolidinedione.

would allow us to conclude that a smaller dose had an antiinflammatory effect including an effect on plasma adiponectin and resistin concentration and that it could occur independently of the metabolic effect. Such data would allow us to probe further into the early mechanism(s) underlying the insulin-sensitizing action of TZDs because inflammatory mechanisms may mediate insulin resistance through interference with insulin signal transduction.

Subjects and Methods

Subjects

Eight obese diabetic patients [five females and three males; body mass index (BMI) 44.9 ± 4.5 kg/m^2] were included in the study (Table 1). All patients were given 2 mg of rosiglitazone daily for 6 wk. Fasting blood samples were obtained at 0, 1, 2, 4, 6, and 12 wk. Six obese diabetic subjects (three females and three males; BMI 43.2 ± 5.6 kg/m^2) were also included in the study as a control group and were given placebo for 6 wk. Fasting blood samples were obtained from the control group at 0, 1, 2, 4, and 6 wk only. Fasting blood samples at wk 0 and 6 were sent to Kaleida Health clinical laboratory for leukocyte count. All the patients and controls were taking either metformin or sulfonylureas as antidiabetic medications. None of the patients was under TZDs or insulin treatment (Table 1). The subjects were advised to continue their usual eating and exercise habits and other concomitant medications. The patients' body weight did not change during the period of the study (Table 1). All patients gave their written, informed consent, and the study protocol was approved by the Institutional Review Board of the State University of New York at Buffalo.

Plasma FFAs, insulin, and glucose measurements

FFA levels were measured in plasma containing EDTA and lipoprotein lipase inhibitor Paraoxon (diethyl-*p*-nitrophenyl-phosphate, 0.275 mg/ml blood; Sigma, St. Louis, MO) by a colorimetric assay (Roche, Richmond, VA). Insulin levels were determined using an ELISA kit from Diagnostic Systems Laboratories Inc. (Webster, TX). Glucose levels were measured in plasma by a 2300 STAT Plus glucose analyzer (YSI, Yellow Springs, OH).

Plasma adipokines and inflammatory mediators measurement

Plasma matrix metalloproteinase (MMP)-9, IL-6, TNFα, adiponectin, and resistin were assayed with ELISA kits from R&D Systems (Minneapolis, MN). CRP ELISA kit was purchased from Alpha Diagnostic International (Webster, TX), and serum amyloid A (SAA) was analyzed by an ELISA kit from Biosource International (Camarillo, CA).

Statistical analysis

Statistical analysis was carried out using SigmaStat software (SPSS Inc., Chicago, IL). All data in the figures are expressed as mean ± SE. Analysis of the changes from baseline was carried out with Holm-Sidak one-way, repeated-measures ANOVA (RMANOVA). Holm-Sidak two-way RMANOVA (TWRMANOVA) method was used for all multiple comparisons between the control and rosiglitazone-treated groups. When interaction between factors was significant, *t* test comparisons were performed to determine significance between the groups. Resistin levels were compared between the groups by *t* test, and leukocyte count, insulin, FFAs, and glucose concentrations were analyzed by paired *t* test at time 0 and 6 wk.

Results

Plasma glucose insulin and FFA concentrations

The plasma concentrations of glucose, insulin, and FFAs did not change significantly after either 2 mg/d rosiglitazone or placebo for 6 wk (Table 1). Homeostasis model assessment of insulin resistance (HOMA-IR) did not change.

Leukocyte count and C-reactive protein (CRP), SAA, and MMP-9 concentrations

Total leukocyte count was significantly lower (9.1 *vs.* 8.0 10^9/liter, $P < 0.05$) at wk 6 after rosiglitazone treatment (Table 1), whereas there was no change in the control group. The fall in leukocyte count was not attributable to a fall in any particular leukocytic type. Plasma concentrations of CRP fell

TABLE 1. Demographic and other data before and 6 wk after either placebo or 2 mg/d rosiglitazone intake in obese diabetic patients

Marker	Placebo controls		Rosiglitazone 2 mg	
	wk 0	wk 6	wk 0	wk 6
Age (yr)	52 ± 11		54 ± 9	
History of diabetes (yr)	3.4 ± 2.1		4.6 ± 2.7	
BMI (kg/m^2)	42.2 ± 14.8	43.0 ± 14.2	44.9 ± 12.8	45.5 ± 12.7
Weight (kg)	110.9 ± 24.5	112.7 ± 24.9	113.4 ± 28.7	114.7 ± 28.3
HbA1c	6.96 ± 1.05	6.94 ± 1.17	7.25 ± 0.63	7.01 ± 0.71
Glucose (mg/dl)	120 ± 31	111 ± 31	113 ± 18	112 ± 17
Insulin (μIU/ml)	24.3 ± 15.2	25.5 ± 18.0	16.9 ± 12.0	18.0 ± 13.5
HOMA-IR	5.58 ± 3.41	5.74 ± 3.71	5.13 ± 4.31	5.31 ± 4.70
Medications (n)	Metformin (4), sulfonylureas (3), aspirin 81 mg (2), statins (1), β-blockers (2), ACE inhibitors (2), vitamins (3)		Metformin (6), sulfonylureas (5), aspirin 81 mg (3), statins (2), β-blockers (2), ACE inhibitors (2), vitamins (4)	
Blood pressure	130/81	134/84	136/79	123/75
Cholesterol (mg/dl)	250 ± 42	241 ± 58	228 ± 33	236 ± 41
Triglycerides (mg/dl)	122 ± 33	116 ± 28	112 ± 20	111 ± 20
FFA (mM)	0.621 ± 0.416	0.649 ± 0.512	0.667 ± 0.303	0.742 ± 0.660
WBC count (10^9/liter)	8.7 ± 3.7	8.9 ± 3.1	9.1 ± 3.3	8.0 ± 2.5[a]
MNC-NFκB (% Change)	100	124 ± 51	100	106 ± 77
MNC-IκB-α (% Change)	100	102 ± 29	100	116 ± 86
TNFα (pg/ml)	2.21 ± 0.77	2.07 ± 0.70	1.89 ± 0.31	1.92 ± 0.40
IL-6 (pg/ml)	1.65 ± 0.39	1.75 ± 0.53	1.39 ± 0.42	1.38 ± 0.77

Values are reported as mean ± SD. WBC, White blood cell; MNC-NFκB, mononuclear cell nuclear factor κB; MNC-IκB-α, mononuclear cell inhibitor of κB.

[a] $P < 0.05$ (paired *t* test).

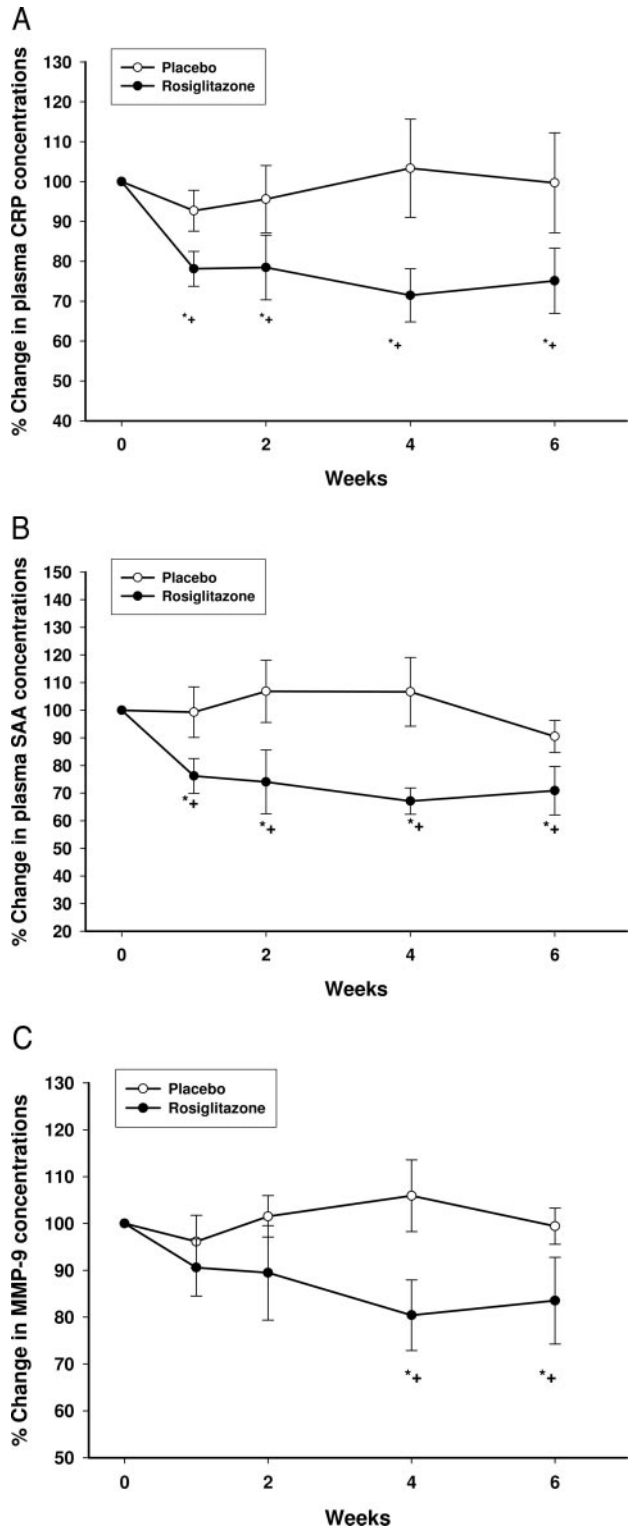

FIG. 1. A, Percent change in plasma CRP concentrations after rosiglitazone or placebo intake for 6 wk in obese, diabetic subjects. Plasma CRP decreased significantly after 6 wk of 2 mg/d rosiglitazone (from 8.47 ± 1.04 to 6.57 ± 1.23 μg/ml) and did not change after placebo (4.73 ± 0.85 *vs.* 4.51 ± 0.95 μg/ml). The results are presented as mean ± SE. *, $P < 0.05$ by Holm-Sidak test when compared with baseline (RMANOVA); +, $P < 0.05$ when compared with the control (TWRMANOVA). B, Percent change in SAA concentrations after rosiglitazone or placebo intake for 6 wk in obese, diabetic subjects. SAA concentrations decreased significantly after 6 wk of 2 mg/d rosiglitazone (from 16.51 ± 1.98 to 11.14 ± 1.24 μg/ml) and did not change after placebo (14.8 ± 2.5 *vs.* 14.1 ± 2.3 μg/ml). The results are presented as mean ± SE. *, $P < 0.05$ by Holm-Sidak test when compared with the baseline (RMANOVA); +, $P < 0.05$ when compared with the control (TWRMANOVA). C, Percent change in MMP-9 concentrations after rosiglitazone or placebo intake for 6 wk in obese, diabetic subjects. MMP-9 concentrations decreased significantly after 6 wk of 2 mg/d rosiglitazone (from 522 ± 64 to 389 ± 49 ng/ml) and did not change after placebo (473 ± 58 *vs.* 470 ± 50 ng/ml). The results are presented as mean ± SE. *, $P < 0.05$ by Holm-Sidak test when compared with baseline (RMANOVA); +, $P < 0.01$ when compared with the control (TWRMANOVA).

to 75 ± 8% (from 8.47 ± 1.04 to 6.57 ± 1.23 μg/ml, RMANOVA $P < 0.01$, Fig. 1A), SAA to 71 ± 9% (from 16.51 ± 1.98 to 11.14 ± 1.24 μg/ml, RMANOVA $P = 0.017$, Fig. 1B), and MMP-9 to 76 ± 6% (from 522 ± 64 to 389 ± 49 ng/ml, RMANOVA $P < 0.01$, Fig. 1C) of the baseline levels at 6 wk after 2 mg/d rosiglitazone. In the placebo group, CRP, SAA, and MMP-9 concentrations did not change significantly (4.73 ± 0.85 *vs.* 4.51 ± 0.95 μg/ml, 14.8 ± 2.5 *vs.* 14.1 ± 2.3 μg/ml, and 473 ± 58 *vs.* 470 ± 50 ng/ml, respectively). After 6 wk of treatment cessation, CRP and SAA concentrations increased to levels closer to baseline values (7.15 ± 1.45 and 14.21 ± 0.90 μg/ml, respectively). MMP-9 concentrations were significantly lower, compared with baseline values, even 6 wk after rosiglitazone treatment cessation (384 ± 50 ng/ml, $P < 0.01$). The change in CRP, SAA, and MMP-9 concentrations was statistically significant when compared with changes in the control group by TWRMANOVA ($P = 0.035$, 0.011, and 0.006, respectively). The difference in CRP and SAA concentrations between the treatment groups was not dependent on time, whereas the difference in MMP-9 concentrations was ($P = 0.049$ for interaction). When compared by *t* test, MMP-9 concentrations were different between the two groups at 2, 4, and 6 wk ($P < 0.05$ for all). The concentrations of TNFα and IL-6 did not change after either rosiglitazone or placebo treatments (Table 1).

Plasma adiponectin and resistin concentrations

The concentration of the adipose tissue-specific adipokine, adiponectin, increased gradually and significantly to 49 ± 21% over baseline (from 8.25 ± 1.22 to 11.63 ± 1.57 μg/ml; $P < 0.001$ RMANOVA, Fig. 2A) at wk 6. The difference in adiponectin concentrations between the treatment groups was time dependent ($P = 0.006$ for interaction). When compared by *t* test, adiponectin concentrations were different between the two groups at 4 and 6 wk ($P < 0.05$ for both). Resistin concentrations fell significantly to 90 ± 4% of the baseline levels (from 13.26 ± 1.57 to 11.67 ± 1.09 ng/ml, $P < 0.05$, RMANOVA, Fig. 2A) at 6 wk after 2 mg/d rosiglitazone. This modest but significant change at wk 6 was also statistically significant when compared with the control group by *t* test ($P < 0.05$, Fig. 2B). In the placebo group, adiponectin and resistin concentrations did not change significantly (7.84 ± 1.45 *vs.* 8.52 ± 2.06 μg/ml and 13.22 ± 1.47 *vs.* 13.46 ± 1.17 ng/ml, respectively). Six weeks after stopping rosiglitazone treatment, adiponectin and resistin concentrations returned to baseline levels (8.14 ± 1.36 μg/ml, 12.16 ± 0.87 ng/ml, respectively).

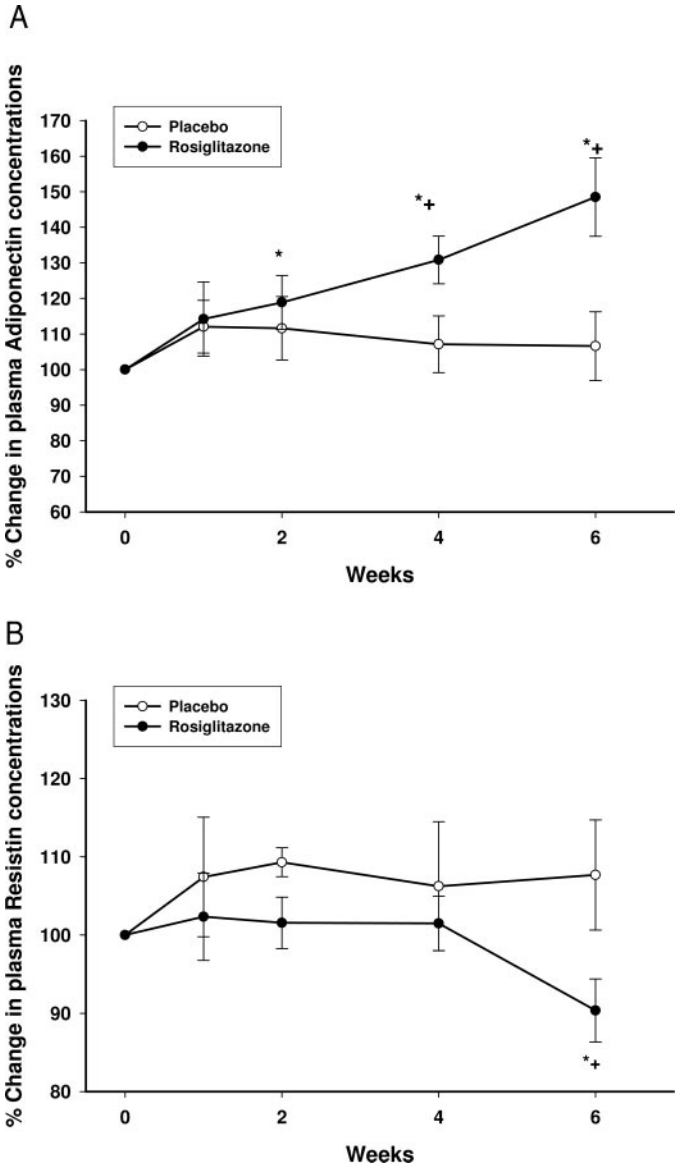

FIG. 2. A, Percent change in plasma adiponectin concentrations after rosiglitazone or placebo intake for 6 wk in obese, diabetic subjects. Adiponectin concentrations increased significantly after 6 wk of 2 mg/d rosiglitazone (from 8.25 ± 1.22 to 11.63 ± 1.57 μg/ml) and did not change after placebo (7.84 ± 1.45 *vs.* 8.52 ± 2.06 μg/ml). The results are presented as mean ± SE. *, $P < 0.05$ by Holm-Sidak test when compared with the baseline (RMANOVA); +, $P < 0.05$ when compared with the control (TWRMANOVA). B, Percent change in plasma resistin concentrations after rosiglitazone or placebo intake for 6 wk in obese, diabetic subjects. Plasma resistin decreased significantly after 6 wk of 2 mg/d rosiglitazone (from 13.26 ± 1.57 to 11.67 ± 1.09 ng/ml) and did not change after placebo (13.22 ± 1.47 *vs.* 13.46 ± 1.17 ng/ml). The results are presented as mean ± SE. *, $P < 0.05$ by Holm-Sidak test when compared with baseline (RMANOVA); +, $P < 0.05$ when compared with the control (*t* test).

Discussion

Our data show clearly that a 2-mg dose of rosiglitazone suppresses the plasma concentration of major indices of systemic inflammation including leukocyte count, CRP, SAA, and MMP-9. Even at this small dose, this effect is evident after 1 wk of administration of rosiglitazone in patients with type 2 diabetes. The fall in MMP-9 was observed at 4 wk. However, at this dose, no change in FFA concentration, insulin, or glucose was observed over the entire 6-wk period. Clearly, therefore, the antiinflammatory effect of rosiglitazone is independent of FFA concentration, insulin sensitization, or a fall in plasma glucose.

The antiinflammatory effects of low-dose rosiglitazone thus include several mediators of inflammation, which might indicate a reduced cardiovascular disease (CVD) risk. Total leukocyte count, a marker of inflammation, is an independent predictor of CVD (19–21). Although the total leukocytes count fell significantly at 6 wk, there was no significant reduction in any specific cell type. CRP and SAA are among the most sensitive markers and mediators of inflammation, and high CRP concentration is the most commonly recognized inflammatory risk factor for CVD (22, 23). The antiinflammatory effects observed in our study also included a time-dependent suppression of circulating levels of MMP-9, an important metalloproteinase that may be involved in plaque rupture (24, 25).

Our data are also consistent with the concept that insulin sensitization and the glucose-lowering effect of rosiglitazone may be due to the antiinflamamtory action of TZDs because insulin signal transduction is interfered with by inflammatory mediators like TNFα and IL-6 because on the basis of that concept, an antiinflammatory effect would have to precede insulin sensitization. Interestingly, plasma TNFα and IL-6 concentrations did not change during this treatment period and possibly occur later. TNFα induces serine phosphorylation of insulin receptor substrate-1, which in turn causes serine phosphorylation of insulin resistance in fat cells (26, 27). Both suppress tyrosine phosphorylation, which is essential for normal insulin signal transduction. TNFα has also been shown to inhibit tyrosine phosphorylation of insulin receptor and insulin receptor expression in human aortic endothelial cells (28). It is possible that the process of suppression of the inflammatory mediators has to lead to a significant fall in the interference of insulin signal transduction before insulin sensitization and a fall in plasma glucose occur. Indeed, we previously demonstrated that both troglitazone (400 mg daily) and rosiglitazone (4 mg daily) cause a fall in plasma TNFα concentrations in obese subjects (4, 7).

A significant increase in adiponectin concentrations from the baseline was observed at wk 2 after rosiglitazone and persisted to increase in a time-dependent fashion into wk 6. Clearly, therefore, adiponectin increase occurs early during treatment with even a low dose of rosiglitazone. This increase is associated with antiinflammatory effects of this drug rather than the metabolic changes, which occur subsequently as reflected in a fall in plasma FFA, insulin, and glucose concentrations. The increase in adiponectin may contribute subsequently to insulin sensitization. Further studies are required to elucidate the role of peroxisomal proliferator-activated receptor-γ and other transcription factors in the execution of these effects.

Plasma resistin concentrations fell by a small but significant amount at wk 6. Resistin is secreted primarily by the macrophage in the human rather than the adipocyte as in rodents. Its secretion is modulated by proinflammatory cytokines, and therefore, it is of interest that even with a small

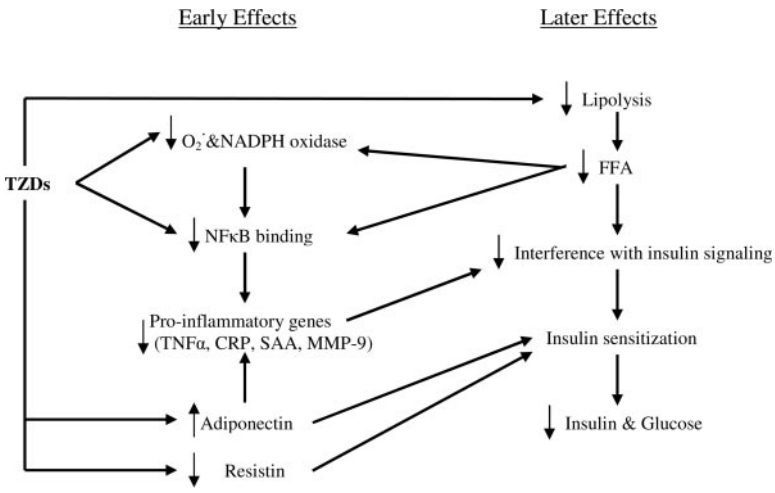

FIG. 3. Schematic diagram showing the multiple levels at which TZDs affect oxidative stress, inflammation, adiponectin, lipolysis, and insulin sensitivity. The antiinflammatory effect and an increase in adiponectin occur earlier, whereas the antilipolytic and insulin sensitization (metabolic effect) follow later. Resistin induces insulin resistance in experimental animals but not in the human. NADPH, Nicotinamide adenine dinucleotide phosphate reduced; NFκB, nuclear factor-κB.

dose of rosiglitazone, there was a reduction in resistin before insulin sensitization and other metabolic changes. It is noteworthy that the suppression of resistin took longer than the increase in adiponectin concentrations.

Our previous data on the effect of 4 mg rosiglitazone also suggested that this drug exerts an early antiinflammatory effect within 1 wk but that insulin sensitization and glucose-lowering effects occur over the next few weeks. Thus, it appears that the antiinflammatory effect of this drug is the earliest among the functions known to be affected by it. It is therefore possible that in the future, rosiglitazone and other TZDs may be used as antiinflammatory and antiatherogenic drugs because atherosclerosis is a chronic inflammation of the arterial wall. It is also likely that the antiinflammatory effect contributes eventually to insulin sensitization and glucose lowering. It is possible that it may coincide with the fall in TNFα and IL-6, two cytokines that have been shown to interfere with insulin signal transduction. The precise molecular mechanisms involved need to be investigated.

The antiinflammatory effect of TZD is probably a direct one on inflammatory cells because this effect has also been demonstrated *in vitro* (10–12). Once this drug causes insulin sensitization *in vivo* in type 2 diabetics, it is possible that the reactive oxygen species suppression and antiinflammatory effect of insulin (1, 2) come into play, as may the loss of the prooxidant (29) and proinflammatory effect of hyperglycemia (30) after the restoration of normoglycemia. Thus, the antiinflammatory effect of rosiglitazone and other TZDs may be exerted at various levels: the initial, direct inhibitory effect on reactive oxygen species generation and nicotinamide adenine dinucleotide phosphate reduced oxidase expression and nuclear factor-κB suppression with the suppression of proinflammatory genes; the restoration of the antiinflammatory effect of endogenous insulin; and finally the restoration of euglycemia.

The data on the antiinflammatory effect of 2 mg of rosiglitazone have a potential for the use of this dose in an antiinflammatory and potentially antiatherogenic regimen in nondiabetic patients with the metabolic syndrome. However, clinical outcomes based on this dose would be required for such use. This dose may also be used in investigating the mode of action of rosiglitazone and the sequence of mechanisms involved in the evolution of the insulin-sensitizing and other metabolic effects of TZDs, independently of the induction of any metabolic changes. The recently described effect of rosiglitazone on fat clearance should also be investigated at this dose (31).

Our current data along with previous evidence indicate that there are two distinct phases of TZDs action: an initial antiinflammatory phase including an increase in adiponectin concentration, and a latter metabolic effect during which antilipolysis and insulin sensitization occurs. These phases are separated distinctly with a low dose of rosiglitazone (Fig. 3).

We conclude that a small dose of rosiglitazone exerts a rapid and comprehensive antiinflammatory effect along with an increase in adiponectin and a decrease in resistin concentrations, independently of the metabolic effects of insulin sensitization and glucose and FFA lowering. This effect may well be the primary effect of this drug, which then contributes to the subsequent metabolic effects. The low dose (2 mg) of this drug may be potentially useful in the treatment of the metabolic syndrome and type 2 diabetes aimed at the prevention of atherosclerosis. Such a consistent early antiinflammatory action of rosiglitazone also raises the possibility of its use in other inflammatory conditions.

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