Insulin Resistance in Lipoatrophic A-ZIP/F-1 Mice*

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WY14,643, a Peroxisome Proliferator-activated Receptor α (PPARα) Agonist, Improves Hepatic and Muscle Steatosis and Reverses Insulin Resistance in Lipoatrophic A-ZIP/F-1 Mice*

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WY14,643 is a specific peroxisome proliferator-activated receptor α (PPARα) agonist with strong hypolipidemic effects. Here we have examined the effect of WY14,643 in the A-ZIP/F-1 mouse, a model of severe lipoatrophic diabetes. With 1 week of treatment, all doses of WY14,643 that were tested normalized serum triglyceride and fatty acid levels. Glucose and insulin levels also improved but only with high doses and longer treatment duration. WY14,643 reduced liver and muscle triglyceride content and increased levels of mRNA encoding fatty acid oxidation enzymes. In liver, the elevated lipogenic mRNA profile (including PPARγ) in A-ZIP/F-1 mice remained unchanged. These results suggest that WY14,643 acts by increasing β-oxidation rather than decreasing lipogenesis or lipid uptake. Hyperinsulinemic euglycemic clamp studies indicated that WY14,643 treatment improved liver more than muscle insulin sensitivity and that hepatic mRNA levels of glucogenic enzymes were reduced. Combination treatment with both WY14,643 and a PPARγ ligand, rosiglitazone, did not lower glucose levels more effectively than did treatment with WY14,643 alone. These data support the hypothesis that reducing intracellular triglycerides in non-adipose tissues improves insulin sensitivity and suggest that further investigation of the role of PPARα agonists in the treatment of lipoatrophic diabetes is warranted.

Severe adipose tissue deficiency or lipoatrophy causes a metabolic syndrome known as lipoatrophic diabetes with insulin resistance, hypertriglyceridemia, and hepatic steatosis (1, 2). Lipoatrophic diabetes is intriguing because it is typically obesity, an excess of triglyceride in adipocytes, and not a deficiency of adipose tissue that causes insulin resistance. Here we have studied the A-ZIP/F-1 mouse, which closely mimics the severe human lipoatrophic phenotype, with a near complete lack of fat, insulin resistance, diabetes, hypoleptinemia, increased appetite, hypertriglyceridemia, and hepatic steatosis (3). The A-ZIP/F-1 mouse was produced by the expression of a dominant negative protein (A-ZIP/F) selectively in adipose tissue. The A-ZIP/F molecule heterodimerizes with and inactivates certain bZIP transcription factors, including C/EBP family members. The lack of adipose tissue causes the metabolic phenotype, because fat ablation by other methods gives a similar phenotype (4–6) and because adipose tissue transplantation reverses it (7, 8).

Treatment of lipoatrophy, whether mouse or human, has been difficult. Insulin and insulin secretagogues and dietary restriction (9) are only partially effective. Modest success has been achieved with insulin-sensitizing agents, the thiazolidinediones (5, 10, 11) and metformin (12). Recent experiments replacing the adipose hormone leptin show great promise (13, 14).

Attempts at treatment of lipoatrophic diabetes can also yield insights into the causes and mechanisms underlying the metabolic complications. A number of lines of evidence point to elevated tissue triglyceride content in non-adipose tissue as a correlate, and possibly a cause, of insulin resistance (15). WY14,643 is a PPARα1 (peroxisome proliferator-activated receptor α) activator that increases fatty acid oxidation by increasing transcription of genes encoding peroxisomal and mitochondrial fatty acid β-oxidation enzymes (16). Here we have tested the hypothesis that WY14,643 will decrease insulin resistance in A-ZIP/F-1 mice.

EXPERIMENTAL PROCEDURES

Animals—Animal handling followed National Institutes of Health guidelines, and experimental procedures were approved by the NIDDK animal care and use committee. All A-ZIP/F-1 mice were 8–12-week-old hemizygous males on the FVB/N background. Wild type controls were matched for age and sex. Mice were typically housed 2–4 per cage, kept on a 12-hour light/dark cycle (0600–1800), and fed NIH-07 rodent chow (12.9 kcal % fat, Zeigler Brothers Inc., Gardiners, PA) and water ad libitum. The treatment diet was powdered AIN-93G (Dyets, Bethlehem, PA) (17) with or without WY14,643 (ChemSyn Laboratories, Lenexa, KS) prepared daily using a coffee grinder. Mice were sacrificed in the non-fasted state between 0900 and 1200. Tissue was fixed in neutral buffered formalin. Glucose levels were measured using a Glucometer Elite (Bayer Corp., Elkhart, IN). Fatty acid (no. 1383175, Roche Diagnostics), triglyceride and β-hydroxybutyrate (no. 339-11 and no. 310-A, respectively, Sigma), and insulin (no. SRI-13K, Linco Research Inc., St. Louis, MO) were measured using appropriate kits.

Serum samples were prepared from tail (weeks 0 and 1, awake) or retro-orbital (week 2, anesthetized) blood in non-fasting mice between 0900 and 1200. Glucose levels were measured using a Gluco-Meter Elite (Bayer Corp., Elkhart, IN). Fatty acid (no. 1383175, Roche Diagnostics), triglyceride and β-hydroxybutyrate (no. 339-11 and no. 310-A, respectively, Sigma), and insulin (no. SRI-13K, Linco Research Inc., St. Louis, MO) were measured using appropriate kits.

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1 The abbreviations used are: PPAR, peroxisome proliferator-activated receptor; GLUT4, glucose transporter 4; GS, glycogen synthase; ACC, acetyl-CoA carboxylase; EGP, endogenous glucose production; FAS, fatty acid synthase; CPT-1, carnitine palmitoyltransferase 1; AOX, acyl-CoA oxidase; IRS-2, insulin receptor substrate 2; SREBP-1, sterol response element binding protein 1; ANOVA, analysis of variance; WAT, white adipose tissue; G6P, glucose 6-phosphatase; NS, not significant.
Charles, MO) were assayed according to the manufacturers’ instructions.

Tissue Triglyceride Assay—Extraction of tissue triglycerides with chloroform/methanol was modified from Burant et al. (5). After hydrolysis with base, triglycerides were measured radiometrically using a glycolaldehyde kinase assay (18).

Northern Blotting—Total RNA from liver and skeletal muscle was isolated using TRIzol reagent (Invitrogen) and assayed as previously described (11). Additional probes include glucose-6-phosphatase (19). PCR was used to prepare the following additional probes: glucose transporter 4 (GLUT4; 5’-primer, 5’-CTCAGCAAGTGACTGGGAC-3’ and 3’-primer, 5’-CCCTGCGCCCAATGAGG-3’; glycogen synthase (GS; 5’-primer, 5’-CGGAGGAGGCAATTTATTACCC-3’ and 3’-primer, 5’-CAGTGTTCCACAGCGTCCCG-3’; and acetyl-CoA carboxylase (ACC; 5’-primer, 5’-GGGACTTCATGAATTGCTGATTCTCAGTT-3’ and 3’-primer, 5’-GTCATTACCATCTCATTACCTCAATC-3’).

Euglycemic Hyperinsulinemic Clamp—The clamp protocols are based on those of Jason Kim and Gerald Shulman2 and were performed as described (20).

Statistical Analysis—Data are expressed as means ± S.E. Statistical significance between the groups was determined with SigmaStat (SPSS, Inc., Chicago, IL) using Student’s t test or two-way ANOVA.

RESULTS

WY14,643 Lowers Serum Triglyceride, Fatty Acid, and Glucose Levels in A-ZIP/F-1 Mice in a Dose- and Time-dependent Manner—A-ZIP/F-1 mice were treated for 2 weeks with the PPARα agonist WY14,643 (Fig. 1). WY14,643 reduced the glucose levels slightly after 1 week and to nearly wild type levels after 2 weeks. The greatly elevated insulin levels remained unchanged. In contrast to the slow and partial glucose reduction, 1 week of WY14,643 treatment normalized the triglyceride and fatty acid levels in the A-ZIP/F-1 mice. In wild type FVB/N mice, WY14,643 affected only the triglyceride levels, which were reduced by 70% at both 1 and 2 weeks of treatment.

In an independent experiment, A-ZIP/F-1 mice were treated for 2 weeks with different doses (control, 0.01%, 0.03%, and 0.1% of diet) of WY14,643. The highest dose gave results nearly identical to those in Fig. 1, except that the glucose levels were actually normal by 2 weeks of treatment (data not shown). Insulin levels did not change. Only when treatment was extended to 4 weeks did insulin levels fall (see below and Fig. 6). In marked contrast to the glucose and insulin levels, 1 week of treatment, even at the lowest dose, completely normalized the triglyceride and fatty acid levels. Thus, PPARα agonist treatment rapidly improves the lipid levels of A-ZIP/F-1 mice, but the reduction in glucose and insulin levels requires a higher dose and occurs with a slower time course.

WY14,643 Decreases Liver and Muscle Triglyceride Content—WY14,643 treatment changed body and liver weights (Fig. 2). In wild type mice, WY14,643 reduced body weight, probably because of reduced adipose tissue weight. The control A-ZIP/F-1 group lost weight, possibly because of worsened diabetes due to the diabetogenic nature of the powdered AIN-93G control diet.2 In wild type mice and A-ZIP/F-1 mice, WY14,643 treatment increased liver weight, a known effect of the hepatocyte hypertrophy and hyperplasia caused by PPARα agonists in mice (21). The increase in A-ZIP/F-1 body weight was quantitatively accounted for by the increase in liver weight.

Histologically, hepatocyte hypertrophy was caused by WY14,643 in both A-ZIP/F-1 and wild type mice (Fig. 3A). The WY14,643-treated A-ZIP/F-1 livers also showed decreased vacuolization, suggestive of reduced hepatic triglyceride levels. Indeed, liver triglyceride levels were reduced by 40% in the A-ZIP/F-1 mice and 41% in the wild type controls (Fig. 3B).

Muscle triglyceride levels were measured in quadriceps muscle. The levels in wild type muscle are problematic due to interspersed adipose tissue (5),3 but the lack of WAT in the A-ZIP/F-1 mouse allows accurate measurement of intramyocellular triglyceride. WY14,643 treatment of the A-ZIP/F-1 mice reduced the muscle triglyceride levels by 44% (Fig. 3C).

Hyperinsulinemic Euglycemic Clamp Analysis of WY14,643 Treatment—Liver and muscle both contribute to the insulin resistance of the A-ZIP/F-1 mouse (8). We used the hyperinsulinemic euglycemic clamp to investigate the improvement caused by WY14,643 treatment. The basal pre-clamp glucose values (after a ~13-hour fast) were elevated in the control A-ZIP/F-1 mice but were reduced to normal in the WY14,643-treated A-ZIP/F-1 mice (Table 1). The base-line insulin levels
were similar between wild type and A-ZIP/F-1 mice despite their high glucose levels.

Base-line EGP was slightly increased in the WY14,643-treated wild type mice (Fig. 4A), possibly because of the increased liver size (Fig. 2). In untreated A-ZIP/F-1 mice, basal EGP was high, as expected for their diabetes. Base-line EGP in the WY14,643-treated A-ZIP/F-1 mice was reduced. WY14,643 treatment caused increased insulin suppression of EGP in both wild type and A-ZIP/F-1 mice during the clamp (Fig. 4B). Clamp EGP in the WY14,643-treated A-ZIP/F-1 mice was similar to that of the untreated wild type mice, reflecting the improvement in insulin sensitivity. WY14,643 treatment tended to increase whole body glucose uptake, a measure of muscle insulin sensitivity (Fig. 4C). However, this was quantitatively small, suggesting that the A-ZIP/F-1 muscle remained quite insulin-resistant. Taken together, these data show that WY14,643 treatment reduces liver insulin resistance more than muscle insulin resistance.

Liver Gene Expression Changes Caused by WY14,643 Treatment—A possible explanation for the reduced tissue triglyceride levels is increased fatty acid oxidation, a known effect of PPARα agonists achieved via increased transcription of peroxisomal and mitochondrial β-oxidation genes (22). WY14,643 treatment increased liver CPT-1 and AOX mRNA levels about 1.5- and 7-fold, respectively, in both wild type and A-ZIP/F-1 mice (Fig. 5). Small but significant increases in AOX mRNA levels were observed in muscle (Fig. 5). The data suggest that increased liver, and possibly muscle, β-oxidation contributes to the lowered tissue triglyceride levels. In A-ZIP/F-1 mice, WY14,643 also reduced the liver mRNA levels of the gluconeogenic enzymes, phosphoenolpyruvate carboxykinase, and glucose-6-phosphatase (Fig. 5). A-ZIP/F-1 mice have an increased lipogenic mRNA profile (Fig. 5, PPARγ, ACC, FAS) (11), and this was not changed by WY14,643 treatment. WY14,643 increased the lipogenic mRNA in the wild type mice. WY14,643 did not affect the liver mRNA levels of two genes important for insulin signaling, IRS-2 and SREBP-1, or of glycogen synthase or of muscle GLUT4 (Fig. 5).

Combined Rosiglitazone and WY14,643 Treatment of A-ZIP/F-1 Mice—Rosiglitazone treatment of FVB/N A-ZIP/F-1 mice has little effect on serum glucose and insulin levels (11), the net result of decreased liver and improved muscle insulin sensitivity.4 We reasoned that adding a PPARα agonist would treat the liver insulin resistance and might prove synergistic to the PPARγ agonist. However, treatment with both rosiglitazone and WY14,643 did not lower glucose, insulin, triglyceride, or

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4 J. K. Kim and G. I. Shulman, unpublished observations.
fatty acid levels more than did treatment with WY14,643 alone, even when extended to a period of 4 weeks (Fig. 6). WY14,643 treatment decreased liver triglyceride content, whereas rosiglitazone treatment increased it. Treatment with both rosiglitazone and WY14,643 caused a 2.1-fold increase ($p = ns$) in liver triglyceride as compared with WY14,643 alone and a 43% decrease ($p = ns$) in muscle triglyceride levels (Fig. 7).

DISCUSSION

We have shown that the PPARα agonist WY14,643 greatly improves the metabolic phenotype of lipoatrophic A-ZIP/F-1 mice. The circulating triglyceride levels are normalized by a low dose and by short treatment durations. In contrast, the improvement in blood glucose levels required a higher dose and prolonged treatment. Clamp studies indicate that the improvement in the diabetes is mostly due to improved insulin sensitivity in liver, whereas muscle remained relatively resistant.

The mechanisms by which the lack of adipose tissue causes insulin resistance and hyperlipidemia are partially understood. Leptin deficiency is a major component, causing insulin resistance and increased food intake (13, 14, 23, 24). Deficiency of other adipose hormones such as adiponectin/Acrp30 may also contribute (25). It is not known how the WAT-deficient status is communicated to the liver, but the result is abnormal metabolic regulation. This includes resistance to insulin-mediated suppression of glucose production but preservation of the insulin-mediated stimulation of lipogenesis and suppression of ketogenesis. It has been proposed that reduced hepatic IRS-2 levels mediates hyperinsulinemia (26). Livers of lipoatrophic mice also have elevated levels of PPARα (11), which contributes to the hepatic triglyceride accumulation.

There is evidence that excess accumulation of triglyceride in non-adipose tissue causes the tissue to be insulin-resistant. Muscle overexpression of lipoprotein lipase increases muscle triglyceride content and decreases muscle insulin sensitivity (27, 28). Similarly, liver overexpression of lipoprotein lipase increases liver triglyceride content and decreases liver insulin sensitivity (27). The correlation between muscle triglyceride levels and insulin resistance has also been documented in lipoatrophic humans (29) and exists for the lipoatrophic mice. Several manipulations of the A-ZIP/F-1 mouse increase hepatic and reduce circulating/muscle triglyceride levels while decreasing liver and increasing muscle insulin sensitivity. The manipulations are rosiglitazone treatment, switching the genetic

**TABLE I**

Euglycemic-hyperinsulinemic clamp measurements

| Statistics                  | WTc   | WTwy | AZIPc | AZIPwy |
|-----------------------------|-------|------|-------|--------|
| Basal insulin (ng/ml)       | 0.80  | 0.80 | 0.80  | 0.80   |
| Basal glucose (mg/dl)       | 89    | 89   | 89    | 89     |
| Basal EGP (μmol/kg BW/min)  | 110   | 110  | 110   | 110    |
| Clamp insulin (ng/ml)       | 4.2   | 4.2  | 4.2   | 4.2    |
| Glucose infusion rate (μmol/kg BW/min) | 201  | 201  | 201   | 201    |
| Whole body glycolysis (μmol/kg BW/min) | 200 | 200 | 200   | 200    |
| Whole body glycogen synthesis (μmol/kg BW/min) | 29   | 29   | 29    | 29     |
| Clamp EGP (μmol/kg BW/min)  | 0.05  | 0.05 | 0.05  | 0.05   |

* , WY14,643 versus untreated.

**, interaction between transgene status and WY14,643 treatment.

, A-ZIP/F-1 versus wild type.

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3 Colombo, C., Cutson, J. J., Yamauchi, T., Vinson, C., Kadowaki, T., Gavriloa, O., and Reitman, M. L. (2002) *Diabetes* 51, in press.
PPARα agonists such as WY14,643 increase fatty acid oxidation, particularly in the liver but also to a lesser degree in other tissues (30). Mice lacking PPARα develop hepatic steatosis upon fasting, confirming that PPARα is important for β-oxidation (31, 32). Although better studied for their lipid-lowering effects, PPARα ligands also lower glucose and insulin levels (33). Our results extend this observation to lipoatrophic diabetes, confirming evidence from one patient (34).

The phenotype of the WY14,643-treated mice provides some clues to the mechanisms underlying the physiology of lipoatrophic diabetes. The slow kinetics of the improvement in insulin sensitivity compared with the more rapid hypolipidemic effect is consistent with the hypothesis that insulin sensitization is due to a reduction in tissue triglyceride levels, a slow step that may take weeks to completely reach a new steady state. The mechanism by which adipose deficiency is signaled to the liver to cause increased lipogenesis is unknown (but is reversed by adipose transplantation or leptin infusion). Although WY14,643 treatment reduces liver triglyceride content and insulin resistance, it does not reduce hepatic PPARγ, ACC, or FAS mRNA levels, suggesting that WY14,643 does not interfere with the sensing of the low WAT signal by the liver.

Addition of rosiglitazone treatment did not significantly improve the insulin sensitivity of WY14,643-treated mice. As expected, rosiglitazone did lower muscle and increase liver triglyceride levels compared with mice treated with WY14,643 alone. The lack of measured improvement in insulin sensitivity may be due to the relatively crude measurement used (glucose and insulin levels, as opposed to clamps) or the high degree of improvement already seen with this dose of WY14,643 by itself.

In conclusion, PPARα agonist treatment normalized the dyslipidemia and improved the insulin resistance of A-ZIP/F-1 mice. It is likely that the improvement was caused by increased

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**Fig. 5. Effect of WY14,643 treatment on liver and quadriceps muscle mRNA levels.** Tissues were taken from the mice described in the legends to Figs. 1 and 2. Filled bars indicate untreated mice and open bars, WY14,643-treated mice. * indicates a WY14,643 effect within genotype at \( p < 0.05 \); ** indicates \( p < 0.005 \). Results are presented using an arbitrary scale with levels in control wild type mice set to 100. Data are mean ± S.E., \( n = 6 \) group.

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6 C. Colombo, M. Haluzik, J. J. Cutson, K. R. Dietz, B. Marcus-Samuels, C. Vinson, O. Gavrilova, and M. L. Reitman, manuscript in preparation.
fatty acid oxidation. This caused decreased non-adipose triglyceride levels, thus secondarily improving insulin sensitivity.

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REFERENCES

1. Reitman, M. L., Arioglu, E., Gavrilova, O., and Taylor, S. I. (2000) Trends Endocrinol. Metab. 11, 410–416
2. Garg, A. (2000) Am. J. Med. 108, 143–152
3. Muitra, J., Mason, M. M., Olive, M., Krylov, D., Gavrilova, O., Marcus-Samuels, B., Pei, D., Lee, E., Aoyama, T., Eckhaus, M., Reitman, M. L., and Vinson, C. (1998) Genes Dev. 12, 3168–3181
4. Ross, S. R., Graves, R. A., and Spiegelman, B. M. (1993) Genes Dev. 7, 1318–1324
5. Burant, C. F., Sreenan, S., Hirano, K., Tai, T. A., Lohmiller, J., Lukens, J., Davidson, N. O., Ross, S., and Graves, R. A. (1997) J. Clin. Invest. 100, 2900–2908
6. Shimomura, I., Hammer, R. E., Richardson, J. A., Ikemoto, S., Bashmakov, Y., Goldstein, J. L., and Brown, M. S. (1998) Genes Dev. 12, 3182–3194
7. Gavrilova, O., Marcus-Samuels, B., Graham, D., Kim, J. K., Shulman, G. I., Castle, A. L., Vinson, C., Eckhaus, M., and Reitman, M. L. (2000) J. Clin. Invest. 105, 273–278
8. Kim, J. K., Gavrilova, O., Chen, Y., Reitman, M. L., and Shulman, G. I. (2000) J. Biol. Chem. 275, 8456–8460
9. Robbins, D. C., Danforth, E. Jr., Horton, E. S., Burse, R. L., Goldman, R. F., and Sims, E. A. (1997) Metabolism 46, 306–316
10. Arioglu, E., Duncan-Morin, J., Sebring, N., Feigenbaum, L., Lee, E., Aoyama, T., Eckhaus, M., Reitman, M. L., and Vinson, C. (1999) Ann. Intern. Med. 133, 263–274
11. Chao, L., Marcus-Samuels, B., Mason, M. M., Muitra, J., Vinson, C., Arioglu, E., Gavrilova, O., and Reitman, M. L. (2000) J. Clin. Invest. 106, 1221–1228
12. Vantyghem, M. C., Vigouroux, C., Magre, J., Desheu-Mouthon, C., Pattou, F., Lebeuf, J., and Capeau, J. (1999) Diabetes Care 22, 1374–1376
13. Shimomura, I., Hammer, R. E., Ikemoto, S., Brown, M. S., and Goldstein, J. L. (1999) Nature 401, 73–76
14. Oral, E. A., Simha, V., Ruiz, E., Andewelt, A., Premkumar, A., Snell, P., Wagner, A. J., DelPoioli, A. M., Reitman, M. L., Taylor, S. I., Gordon, P., and Garg, A. (2002) N. Engl. J. Med. 346, 570–578
15. Simhan, G. I. (2000) J. Clin. Invest. 106, 171–176
16. Aoyama, T., Peters, J. M., Iritani, N., Nakajima, T., Furihata, K., Hashimoto, T., and Gonzalez, F. J. (1998) J. Biol. Chem. 273, 5678–5684
17. Reeves, P. G., Nielsen, F. H., and Fahey, G. C., Jr. (1993) J. Nutr. 123, 1939–1951
18. Gavrilova, O., Leon, L. R., Marcus-Samuels, B., Mason, M. M., Castle, A. L., Reffettof, S., Vinson, C., and Reitman, M. L. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 14623–14628
19. Shelly, L. L., Lei, K. J., Pan, C. J., Sakata, S. F., Ruppert, S., Schutz, G., and Chou, J. Y. (1993) J. Biol. Chem. 268, 21482–21485
20. Kim, J. K., Michael, M. D., Previs, S. F., Peroni, O. D., Maurais-Jarvis, F., Neschen, S., Kahn, B. B., Kahn, C. R., and Shulman, G. I. (2000) J. Clin. Invest. 105, 1791–1797
21. Graaso, P. (1993) in Peroxisomes: Biology and Importance in Toxicology and Medicine (Gibson, G., and Lake, B., eds), pp. 639–652, Taylor and Francis, London
22. Minnich, A., Tian, M., Byan, L., and Bilder, G. (2001) Am. J. Physiol. Endocrinol. Metab. 280, E279–E279
23. Gavrilova, O., Marcus-Samuels, B., Leon, L. R., Vinson, C., and Reitman, M. L. (2000) Nature 403, 850
24. Ebihara, K., Ogawa, Y., Masuzaki, H., Shintani, M., Miyagawa, F., Aizawa-Abe, M., Hayashi, T., Hossada, K., Inoue, G., Yoshimasa, Y., Gavrilova, O., Reitman, M. L., and Nakao, K. (2001) Diabetes 50, 1440–1448
25. Yamauchi, T., Kamon, J., Waki, H., Nishimura, K., Hara, K., Mori, Y., Ide, T., Murakami, K., Tsuneyama-Kasao, N., Eraki, O., Akanuma, Y., Gavrilova, O., Vinson, C., Reitman, M. L., Kagechika, H., Shudo, K., Yoda, M., Nakano, Y., Toke, T., Nagai, R., Kimura, S., Tomita, M., Fugel, P., and Kadowaki, T. (2001) Nature Med. 7, 941–946
26. Shimomura, I., Matsuda, M., Hammer, R. E., Bashmakov, Y., Brown, M. S., and Goldstein, J. L. (2000) Mol. Cell 6, 71–86
27. Kim, J. K., Fillmore, J. J., Chen, Y., Yu, C., Moore, I. K., Pypaert, M., Lutz, E. P., Kako, Y., Velez-Carrasco, W., Goldberg, I. J., Breslow, J. L., and Goldstein, J. L. (2000) J. Biol. Chem. 275, 1498–1505
28. Ferreira, L. D., Pulawa, L. K., Jensen, D. R., and Eckel, R. H. (2001) Diabetes 50, 1064–1068
29. Szczepaniak, L. S., Babcock, E. E., Schick, F., Robbins, D. L., Garg, A., Burns, D. K., McGarry, J. D., and Stein, D. T. (1999) Am. J. Physiol. 276, E977–E985
30. Cook, W. S., Yeldandi, A. V., Rao, M. S., Hashimoto, T., and Reddy, J. K. (2000) Biochem. Biophys. Res. Commun. 278, 250–257
31. Kersten, S., Seydoux, J., Peters, J. M., Gonzalez, F. J., Desvergne, B., and Wahli, W. (1999) J. Biol. Chem. 274, 1489–1496
32. Hashimoto, T., Cook, W. S., Qi, C., Yeldandi, A. V., Reddy, J. K., and Rao, M. S. (2000) J. Biol. Chem. 275, 28928–28932
33. Guerre-Millo, M., Gervois, P., Raspe, E., Madsen, L., Poulain, P., Derudas, B., Herbert, J. M., Winegar, D. A., Wilsson, T. M., Fruchtat, J. C., Berge, R. K., and Staels, B. (2000) J. Biol. Chem. 275, 16638–16642
34. Panz, V. R., Wring, J. R., Raal, F. J., Redda, M. A., and Joffe, B. I. (1997) Clin. Endocrinol. 46, 365–368

**Fig. 6.** Effects of combined rosiglitazone plus WY14,643 on serum glucose, insulin, triglyceride, and fatty acid levels in A-ZIP/F-1 mice. Male mice (6 weeks old) were placed on a powdered AIN-93G diet with no drug (□), rosiglitazone only (■), WY14,643 only (▲), or both rosiglitazone and WY14,643 (▶). WY14,643 was given at 0.1% and rosiglitazone at 3 mg/kg (0.012 mg/g diet). Data are mean ± S.E., n = 4–6/group.

**Fig. 7.** Liver and muscle triglyceride levels after 4 weeks of treatment with WY14,643 and rosiglitazone. Data are mean ± S.E., n = 4–6/group. For liver, all pairwise comparisons are significant (ANOVA with post hoc Tukey test) at p < 0.05, except for control versus rosiglitazone (rosi) and WY14,643 (wy) versus WY14,643 plus rosiglitazone (wy+rosi). For muscle, of all pairwise comparisons, only the control versus WY14,643 plus rosiglitazone was significant (ANOVA with post hoc Tukey test).
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