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A novel peroxisome proliferator–activated receptor α/γ dual agonist ameliorates dyslipidemia and insulin resistance in prediabetic rhesus monkeys

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Abstract

TAK-559, a newly developed non-thiazolidinedione, activates both peroxisome proliferator–activated receptors α and γ. We investigated the effects of TAK-559 on dyslipidemia and insulin resistance in nonhuman primates. Five adult male obese prediabetic rhesus monkeys were studied on vehicle and after TAK-559 treatment (0.3, 1.0, 3.0 mg/kg per day) for a total of 12 weeks. No significant changes were observed in body weight and fasting plasma glucose, total plasma cholesterol, very low-density lipoprotein–triglyceride, and low-density lipoprotein cholesterol levels. TAK-559 treatment resulted in significant elevation of circulating high-density lipoprotein (HDL) cholesterol levels, consisting of an increase in large HDL particles and a decrease in small dense HDL particles. Nuclear magnetic resonance data exhibited a less atherogenic lipoprotein profile with treatment. Plasma triglyceride and apolipoprotein B-100 levels decreased, whereas apolipoprotein A-I increased during TAK-559 treatment. Hyperinsulinemia and insulin resistance (quantitative insulin sensitivity check index and homeostasis model assessment) were significantly corrected with the highest dose of 3.0 mg/kg per day in these prediabetic monkeys. In addition, no adverse effects on representative liver function parameters were observed during the study period. These results suggest that TAK-559 had beneficial effects on lipoprotein profiles and insulin sensitivity, without any side effect on body weight, which suggests that TAK-559 may provide a potentially safe approach for delaying the onset of type 2 diabetes mellitus and may reduce the risk of cardiovascular disease. The positive effects of TAK-559 in nonhuman primates have led to further clinical trials of TAK-559 in Europe and the United States.

1. Introduction

Both insulin resistance and dyslipidemia, characterized as elevated plasma triglyceride (TG) and reduced high-density lipoprotein cholesterol (HDL-C) levels, play important roles in the development of type 2 diabetes mellitus [1-3] and usually precede impaired glucose tolerance and hyperglycemia [4,5]. Thus, ameliorating dyslipidemia and insulin resistance while still in a prediabetic status through pharmacologic intervention may delay the onset of type 2 diabetes mellitus and also may reduce the risk of cardiovascular disease [6].

Clinical trials aimed at correcting abnormal lipid profiles and insulin resistance have targeted a family of nuclear transcription factors termed *peroxisome proliferator–activated receptors* (PPARs) [7]. Three PPARs have been identified as PPARα, γ, and δ, with tissue-specific distribution and distinct physiologic roles. Peroxisome proliferator–activated receptor α controls enzymes critical to the transport and oxidation of fatty acids, whereas PPARγ regulates genes involved in fatty acid uptake and storage [8]. Peroxisome proliferator–activated receptor γ activation is associated with adipogenesis, increased adiposity, and weight gain, which limit the clinical use of these drugs [9,10]. In contrast, both human and rodent model studies indicate that activation of PPARα and PPARδ receptors is associated with enhanced lipid catabolism and loss of fat mass [11,12].

For many years, the PPARα agonists, specifically the fibrates, were used for the treatment of dyslipidemia, whereas PPARγ agonists of the thiazolidinedione (TZD) class, were used as efficient insulin sensitizers in diabetes

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Table 1
Baseline characteristics of the prediabetic rhesus study subjects compared with healthy animals from the same colony

Parameters	Healthy rhesus	Prediabetic rhesus
Age (y)	9.8 ± 1.5	16.5 ± 2.2
Body weight (kg)	11.2 ± 1.1	19.5 ± 2.7
Fasting glucose (mg/kg)	60.7 ± 1.1	76.4 ± 1.8
Fasting insulin (μU/mL)	32.4 ± 5.8	109.2 ± 24.8
TGs (mg/dL)	47.8 ± 8.0	171.2 ± 64.8

Data are presented as means ± SE for 5 rhesus monkeys. All parameters reflect study subjects at day 0 of study as compared with healthy adult rhesus monkey values described in reference [5].

treatment. Theoretically, a compound targeting both the PPARα and PPARγ receptors simultaneously might combine the insulin-sensitizing potential of TZDs with the beneficial lipid-regulating activities of fibrates. The propensity for adipogenesis resulting from PPARγ activation may be offset by PPARα activation–induced lipid catabolism, which may diminish the undesirable side effects of selective PPARγ agonists [13]. Some novel PPARα/γ dual agonists have been developed to target multiple tissues simultaneously, thereby producing complementary effects, such as TZD derivatives KRP-297 and JTT501 and non-TZDs LY465608, tesaglitazar, and ragaglitazar [14-18].

TAK-559, a novel oxyiminoalkanoic acid derivative, (*E*)-4-(4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl) methoxy]benzyloxyimino)-4-phenylbutyric acid, is a newly developed non-TZD dual PPARα/γ agonist with nearly equal EC_{50} values [19]. In various rodent models of insulin resistance and type 2 diabetes mellitus, TAK-559 showed favorable pharmacokinetic properties with good absorption and duration, and exhibited marked glucose- and lipid-lowering activities, without causing significant body weight gain [20]. TAK-559 has therefore been considered an attractive candidate for further investigation.

The present study was designed to evaluate the efficacy of TAK-559 in a group of prediabetic nonhuman primates. These rhesus monkeys spontaneously develop obesity and prediabetes, with frequently exhibited atherogenic dyslipidemia and insulin resistance [4,5]. Previous studies have demonstrated that these monkeys resemble the abnormalities often seen in human populations and are excellent models for understanding the pathogenesis of type 2 diabetes mellitus, as well as investigating therapeutic approaches [21,22]. In the current study, the primary outcomes were a beneficial lipid profile and improvement in insulin sensitivity.

2. Materials and methods

2.1. Subjects

Subjects included 5 adult male prediabetic rhesus monkeys (*Macaca mulatta*) aged 12.1 to 21.5 years at the start of the study. The baseline metabolic characteristics of each monkey are shown in Table 1. The monkeys were individually housed and cared for according to the Guide for the Care and Use of Laboratory Animals (National Research Council-Institute for Laboratory Animal Resources) [23]. All protocols were approved by the Institutional Animal Care and Use Committee at the University of Maryland, Baltimore. The monkeys were maintained on the standard Lab Diet monkey chow (17% protein, 13% fat, and 70% carbohydrate, 5038, Purina Mills, St Louis, MO), provided ad libitum together with unlimited access to fresh water. Laboratory temperature was maintained at 22°C, and lights were cycled on from 6:00 AM to 6:00 PM.

2.2. Study design

TAK-559, a non-TZD dual PPARα/γ agonist, was provided by Takeda Chemical Industries (Osaka, Japan).

The monkeys were studied during 6 consecutive treatment periods (2 weeks each) in this order: vehicle, low dose (0.3 mg/kg), washout, intermediate dose (1.0 mg/kg), washout, and high dose (3.0 mg/kg). The experimental dual PPARα/γ agonist TAK- 559 was given orally with vehicle (a standard piece of fruit) once daily each morning during the treatment phase. Food consumption was monitored daily, and the body weights were recorded weekly. Blood was drawn under light sedation (ketamine hydrochloride 10-15 mg/kg body weight) after a fasting duration of 16 hours at the end of vehicle, washout, and at each dose escalation phase. Plasma was collected, and clinical chemistry, hematology, and lipid/lipoprotein analyses were performed.

2.3. Assays

Plasma glucose was determined using the glucose oxidase method on a Beckman Autoanalyzer II (Beckman Instruments, Fullerton, CA). Plasma insulin was measured by radioimmunoassay at Linco Research Laboratories (St Louis, MO). The clinical chemistry and hematology profile was carried out by the Animal Diagnostic Laboratory (Baltimore, MD). Apolipoproteins were determined by immunoprecipitation (Medstar, Washington, DC). Lipoprotein subclass distribution was determined by proton nuclear magnetic resonance (NMR) spectroscopy (LipoScience, Raleigh, NC) on EDTA plasma samples as described by Otvos [24]. The lipoprotein subclasses were defined by NMR-determined particle size as follows: small high-density lipoprotein (HDL), 7.3 to 8.8 nm; large HDL, 8.8 to 13 nm; small low-density lipoprotein (LDL), 18.8 to 19.7 nm; medium LDL, 19.8 to 21.2 nm; large LDL, 21.3 to 23.0 nm; small very low-density lipoprotein (VLDL), 27 to 35 nm; medium VLDL, 35 to 60 nm; and large VLDL, 60 to 200 nm. The results of lipoprotein subclass analyses were used to calculate estimates of the concentrations of total cholesterol, total TG, VLDL-TG, LDL-C, and HDL-C.

2.4. Insulin sensitivity

Insulin sensitivity was estimated using the quantitative insulin sensitivity check index (QUICKI) and homeostasis

Table 2
Effects of TAK-559 on body weight, fasting plasma glucose, fasting plasma insulin, and insulin sensitivity indexes in prediabetic rhesus monkeys

TAK-559	Body weight (kg)	FPG (mg/dL)	FPI (μU/mL)	QUICKI	HOMA
Vehicle	19.5 ± 2.7	76.4 ± 1.8	109.2 ± 24.8	0.27 ± 0.02	20.3 ± 4.5
0.3 mg/kg	19.2 ± 2.6	75.4 ± 3.1	82.6 ± 20.9	0.29 ± 0.02	15.1 ± 3.8
1.0 mg/kg	19.7 ± 2.8	71.6 ± 3.6	82.4 ± 10.8	0.29 ± 0.01	14.4 ± 1.9
3.0 mg/kg	19.8 ± 2.8	72.2 ± 4.8	61.6 ± 10.7 *	0.31 ± 0.02 *	10.9 ± 1.9 *

Data are presented as means ± SE. Body weight was determined weekly and the average was used for each phase. Fasting plasma glucose (FPG) and fasting plasma insulin (FPI) were determined at the end of baseline and each dose escalation phase.

* $P < .05$, significantly different from placebo.

model assessment–estimated insulin resistance (HOMA-IR). The QUICKI is defined as 1/[log fasting insulin (μU/mL) + log fasting glucose (mg/dL)]; HOMA-IR = [fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5] [25].

2.5. Statistical analysis

Results are expressed as means ± SE. A repeated-measures analysis of variance was performed to evaluate the effect of increasing doses of TAK-559 on each outcome variable using the NCSS 2000 software (NCSS, Kaysville, UT). Paired Student *t* tests were separately performed for all pairs, although only comparison between vehicle vs dose 3 was considered primary. A *P* value of less than .05 was considered statistically significant.

3. Results

As shown in Table 2, TAK-559 treatment did not cause body weight gain. The basal glucose levels were initially between the reference range and hyperglycemia, and no significant changes were seen during the dosing period. Plasma insulin levels tended to fall in response to TAK-559 treatment. High insulin levels tended to decrease at the 2 lower doses, whereas the highest dose of TAK-559 lowered insulin levels significantly (109.2 ± 24.8 vs 61.6 ± 10.7 μU/mL, $P < .05$). This was especially true in 3 very hyperinsulinemic monkeys, where the insulin levels were decreased markedly from the baseline values of 169, 162, and 117 μU/mL to 85, 44, and 85 μU/mL at the 3.0 mg/kg dose. Insulin sensitivity was improved when comparing vehicle to the high dose, 3.0 mg/kg, as shown by significantly enhanced QUICKI values and decreased HOMA-IR values.

TAK-559 had no significant effects on levels of total cholesterol, VLDL-TG, and LDL-C throughout the study (Table 3). Repeated-measures analysis of variance showed a significant change of plasma TG concentration between vehicle administration and administrations of TAK-559 at the 0.3, 1.0, and 3.0 mg/kg per day dose levels (F ratio = 3.7, $P = .04$). The highest dose of TAK-559 decreased mean levels of TG to approximately 42% from the baseline. Nonetheless, because of the individual variance in plasma TG levels among monkeys, the decrease did not reach statistical significance (171.2 ± 64.8 vs 99.2 ± 30.4 mg/dL, $P = .057$). The change in plasma TG was accompanied by a

Table 3
Effect of TAK-559 on NMR-determined plasma lipoprotein subclass levels, estimated lipid levels, and apolipoproteins in prediabetic rhesus monkeys

Variables (mg/dL)	Vehicle	TAK-559		
		0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
TG	171.2 ± 64.8	156.4 ± 52.7	166.0 ± 61.8	99.2 ± 30.4
Total cholesterol	164.2 ± 8.3	162.6 ± 7.0	168.6 ± 10.5	164.2 ± 8.8
VLDL-TG	82.9 ± 50.2	75.1 ± 42.2	82.4 ± 45.4	40.4 ± 24.0
LDL-C	105.1 ± 10.5	105.7 ± 11.1	102.8 ± 9.9	98.8 ± 10.3
HDL-C	70.9 ± 7.5	71.5 ± 7.6	79.4 ± 8.4 **	81.0 ± 8.6 **
Large VLDL	52.6 ± 34.1	46.1 ± 24.3	45.3 ± 29.3	17.9 ± 10.1
Medium VLDL[a]	12.4 ± 12.4	13.4 ± 13.4	12.8 ± 12.8	9.7 ± 9.7
Small VLDL	18.0 ± 6.5	15.6 ± 7.2	15.4 ± 11.6	12.7 ± 7.9
Large LDL	38.5 ± 10.8	42.6 ± 11.7	50.3 ± 17.0	49.5 ± 12.9
Medium LDL	1.8 ± 1.8	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Small LDL	64.9 ± 20.6	63.2 ± 20.9	49.4 ± 22.7	49.2 ± 13.4
Large HDL	67.7 ± 6.5	67.4 ± 6.4	78.1 ± 8.6 **	78.9 ± 7.5 **
Small HDL	3.2 ± 1.2	4.2 ± 1.3	1.3 ± 0.6	2.3 ± 1.3 *
Apo A-I	123.0 ± 4.2	122.2 ± 3.5	123.4 ± 4.5	125.8 ± 4.2 *
Apo B	51.2 ± 7.6	49.2 ± 8.9	47.4 ± 8.7	44.4 ± 6.8 *

Data are presented as means ± SE for 5 rhesus monkeys. Lipoprotein composition was determined at the end of baseline and each dose escalation phase.

[a] The medium VLDL levels of 4 of 5 monkeys are zero.

* $P < .05$, significantly different from vehicle.

** $P < .01$, significantly different from vehicle.

Table 4
The changes in liver function and thyroid parameters during the treatment period

Parameters	Vehicle	TAK-559		
		0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
AST (mU/mL)	21.6 ± 3.7	19.0 ± 3.4	20.8 ± 3.7	18.4 ± 3.3
ALT(mU/mL)	80.2 ± 18.3	76.8 ± 13.1	69.2 ± 12.3	69.6 ± 17.5
AlkP (mU/mL)	149.6 ± 17.4	144.8 ± 20.9	148.0 ± 29.1	122.6 ± 23.1 *
γ-GTP (mU/mL)	72.8 ± 4.1	69.6 ± 4.3	71.6 ± 7.3	66.4 ± 5.3 *
TT3 (ng/dL)	214.6 ± 27.9	206.8 ± 24.3	151. 8 ± 22.0 **	173.0 ± 19.6 **
TT4 (μg/dL)	3.5 ± 0.6	4.0 ± 0.6	4.0 ± 0.5	3.4 ± 0.5

Data are presented as means ± SE. AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; AlkP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; TT3; total triiodothyronine; TT4, total thyroxine.

* $P < .05$, significantly different from vehicle.

** $P < .01$, significantly different from vehicle.

trend toward lower apolipoprotein (apo) B and higher apo A-I levels upon TAK-559 treatment. At the highest dose of 3.0 mg/kg, apo B levels were significantly lower than baseline values (51.2 ± 7.6 vs 44.4 ± 6.8 mg/dL, $P < .05$), and apo A-I levels were slightly but significantly higher (123.0 ± 4.2 vs 125.8 ± 4.2 mg/dL, $P < .05$).

The agent also dose-dependently increased HDL-C levels of the studied monkeys. As seen in Table 3, levels of HDL-C significantly increased during the study (F = 8.6, $P = .002$), consistent with the change in large HDL subclasses ($HDL_3 + HDL_4 + HDL_5$) assessed by the NMR spectroscopy (F = 13.1, $P = .0004$). Paired t tests showed that HDL-C increased significantly by 12% at the 1.0 mg/kg dose and 14% at the 3.0 mg/kg dose compared to vehicle. Large HDL subclasses increased in a stepwise manner during the treatment with 1.0 and 3.0 mg/kg doses (67.7 ± 6.5 vs 78.1 ± 8.6 and 78.9 ± 7.5 mg/dL, respectively; $P < .01$). However, the small HDL subclasses ($HDL_1 + HDL_2$) were observed to decrease significantly at the 3.0 mg/kg dose level (3.2 ± 1.2 vs 2.3 ± 1.3 mg/dL, $P < .05$).

Subjects with low HDL-C and high TG levels usually show an atherogenic lipoprotein composition containing high levels of small dense LDL particles and large VLDL particles. Nuclear magnetic resonance data showed that TAK-559 treatment produced a declining trend in the proportion of small and medium LDL subclasses and an increased proportion of large LDL subclasses. For VLDL, a reduction in the proportion of large VLDL and elevations in the proportion of small and medium VLDL subclasses were also observed (Table 3).

In addition to the positive effects on the lipoprotein profile and insulin sensitivity, TAK-559 proved to be well tolerated by all the monkeys during the study period. Some representative liver function and thyroid parameters are shown in Table 4. The highest dose of TAK-559 significantly decreased levels of alkaline phosphatase, γ-glutamyl transpeptidase, and total triiodothyronine. However, all values of these parameters remained well within the normal physiological range for adult nonhuman primates.

4. Discussion

Selective PPARγ agonists (TZDs) and PPARα agonists (fibrates) have been respectively used to treat dyslipidemia and type 2 diabetes mellitus for a number of years. The efficacy of PPARγ agonists is associated with improved insulin sensitivity and glucose tolerance but at the cost of increased weight gain and some other side effects, such as liver dysfunction [26] and bone loss [27]. Fibrates have shown specific efficacy on reducing the angiographic progression of coronary heart disease in type 2 diabetes mellitus, and the effect is most likely related to the correction of the atherogenic dyslipidemia. However, unlike PPARγ agonists, PPARα agonists do not cause body weight gain. Thus, targeting of PPARα and PPARγ with one compound may diminish some of these side effects and be more beneficial to correcting diabetes-related dyslipidemia.

Several previous studies have described compounds that activate both PPARα and PPARγ. Chanput et al [13] reported the effects of fenofibrate and rosiglitazone and a PPAR α/γ coactivator KRP-297 in fatty (*fa*/*fa*) Zucker rats and *db*/*db* mice. Fenofibrate and rosiglitazone both lowered serum TG levels, yet their effects on body weight gain were the opposite. However, despite a serum pharmacologic profile similar to rosiglitazone, no significant weight gain was observed with KRP-297. Shibata et al [28] reported that JTT-501, also a PPARα/γ dual agonist, prevented not only hyperglycemia but also hyperlipidemia in Zucker diabetic fatty (ZDF) rats. They reported that JTT-501 was more comprehensively effective in preventing the development of diabetic complications compared with the agonist for PPARγ alone. Another study by Etgen et al [16] reported that the novel PPAR α/γ dual agonist LY465608 dose-dependently elevated HDL-C and lowered glucose levels in ZDF rats; the long-term treatment (28 days) of ZDF rats with LY465608 did not increase food intake and resulted in significantly less fat accumulation and body weight gain compared with rats treated with BRL-49653 despite a similar level of glycemic control. Other well-investigated dual PPAR α/γ agonists, tasaglitazar and ragaglitazar, also showed potent insulin-

sensitizing and lipid-improving efficacy in various animal models and human studies [29-32].

In our laboratory, extensive information has been developed to identify the natural history of diabetes in monkeys. Dyslipidemia and insulin resistance are known to be extensively associated with prediabetic states and precede type 2 diabetes mellitus, similar to the occurrence in humans [4,33]. The present study examined the effects of a novel PPAR α/γ agonist on dyslipidemia and accompanying insulin resistance in prediabetic rhesus monkeys. No clinical adverse effects of the drug were apparent during the study period, and the monkeys maintained their body condition throughout the whole study.

Consistent with previous studies on dual PPARα/γ agonists, TAK-559 improved dyslipidemia in obese prediabetic monkeys, especially by increasing HDL-C levels and ameliorating the atherogenic particle composition. Although because of individual variation of basal TG levels and the small number of monkeys, the group comparisons did not reach significant levels, and the overall effects of TAK-559 were clearly apparent. Apolipoprotein B is the primary protein component of VLDL and LDL fractions and is involved in the transport of TG and their conversion to chylomicrons [34]. In this study, a tendency toward lower apo B levels was observed to be accompanied by decreases in plasma TG. The mechanisms for the observed decreases in TG and apo B and increases in HDL-C and apo A-I in this study are not yet clear but presumably involve an enhanced capacity for reverse cholesterol transport by HDL in treated monkeys [35].

With the advanced development of understanding on dyslipidemia, the lipoprotein distribution has attracted more attention in recent years [2,24,36]. Lipoproteins are composed of a heterogeneous spectrum of particles that differ in size, density, chemical composition, and atherogenicity and that contribute differently to the development of cardiovascular disease or diabetes. It has been reported that despite the circulating HDL-C level, large HDL particles are cardioprotective, whereas small HDL particles are thought to be associated with coronary artery disease progression. Small dense LDL particles are also more atherogenic than their larger, buoyant counterparts because they are more liable to oxidation and more readily adhere to and subsequently invade the arterial wall [36-38].

In humans and monkeys, NMR-determined lipoprotein profiles correlate well with those measured by other traditional methods and provide extensive information on the lipoprotein particle composition. Nuclear magnetic resonance data in this study specifically showed that in addition to increasing levels of HDL-C, TAK-559 treatment also significantly increased large protective HDL particle concentration while decreasing small HDL particle concentration. Although LDL-C level was not changed during dosing, a declining trend in the proportion of atherogenic small dense LDL subclasses and an increasing trend in the proportion of large LDL subclasses were observed. For VLDL, a switch towards a decrease in the amount of large particles was also seen in this study. This is the first study describing the effects of a dual PPAR α/γ agonist on the detailed lipoprotein profiles.

In addition to the amelioration of the abnormal lipoprotein profile, TAK-559 treatment also improved hyperinsulinemia in prediabetic monkeys and enhanced insulin sensitivity, without adversely affecting body weight and liver function during the study period. TAK-559 appears to be a promising agent in the treatment of prediabetes.

In summary, this study suggests that mitigation of both dyslipidemia and insulin resistance may have positive effects in postponing the development of type 2 diabetes mellitus and reducing diabetic complications. The complex mechanism by which PPARα/γ dual agonists influence lipoprotein profiles and insulin sensitivity is not yet clear. Whether these beneficial effects were mainly the result of increased production or decreased clearance of HDL-C will require further evaluation. However, this study further confirms that the rhesus monkey is an excellent model for investigating the therapeutic potential of PPARα/γ dual agonists in the treatment of diabetes-related dyslipidemia and the possible underlying mechanisms. Nonetheless, there are some limitations in this study. The study involves only 5 monkeys and only a 2-week treatment period for each dose of the drug. Although the efficacy of TAK-559 was confirmed and the drug was well tolerated in the pharmacologic dose range in all monkeys, longer treatment periods and more experimental animals are recommended in future studies for better understanding of the mechanisms of action of PPAR α/γ agonists and the long-term consequences of treatment.

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