The effect of PPARδ agonists (HS00098) on serum lipid profiles in diet-induced obese rhesus monkeys[*]

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ABSTRACT

Aim: Activation of peroxisome proliferator-activated receptor δ (PPARδ) subtypes increases expression of genes involved in fatty acid transport and oxidation and alters adiposity in animal models of obesity and type-2 diabetes. We aim to explore the effects of peroxisome proliferator-activated receptor δ (PPARδ) subtypes on serum lipid profiles in obese rhesus monkey, especially evaluate the efficacy of investigational new drug (HS00098). Methods: First, a prototype of obese rhesus monkey was established by continuously feeding test animals a high fat diet for 2 months. Fifteen obese rhesus monkeys were randomly divided into 3 groups, and the 2 test groups were treated with GW 501516 and HS00098. The test groups were administered doses of 0.3 mg/kg for 1 month, then with 1 mg/kg for 1 month, and finally with 3 mg/kg for 1 month. The control group received placebo treatment. In each experiment, the body weight of each animal was measured and recorded initially and prior to changing the dose of the drug each month. The total cholesterol, blood glucose, triglyceride, high density lipoprotein cholesterol, low-density lipoprotein cholesterol, serum Apo-A1, Apo-B100 and insulin were tested. Results: The average body weight gain of the GW501516 and HS00098 groups was significantly lower than that of the control group. The group receiving the HS00098 treatment had a higher signify- cant increase in high density lipoprotein and apo-A1 ($P < 0.05$) than the control monkeys, while the total cholesterol, triglycerides, low density lipoproteins, apo-B100, and insulin ($P < 0.05$ or $P < 0.01$) were sig- nificantly decreased. Compared with GW50-1516, the effects of HS00098 on serum lipid profiles in diet-in- duced obese rhesus monkeys are more obvious. Con- clusion: These results suggested that the investiga- tional drug (HS00098) can effectively reduce body weight, blood lipid and blood sugar levels of diet-in- duced obese rhesus monkeys.**

Keywords: PPARδ Agonists; HS00098; Serum Lipid Profiles; Obese; Rhesus Monkey

1. INTRODUCTION

Obesity has risen to epidemic proportions worldwide and is one of the most visible, yet often neglected public health issues. It is now prevalent in virtually all age and socioeconomic groups in both developed and developing nations [1]. Obesity is a complex, multi-factorial condi- tion produced by genetic, social, and psychological fac- tors, the most significant being a high-fat diet and a se- dentary life style. The health consequences of obesity range from increased risk of premature death to serious chronic conditions such as type 2 diabetes, dyslipidemia, atherosclerosis, hypertension, cardiovascular diseases, stroke, and certain forms of cancer [2-5]. Methods that reduce obesity through reductions in food intake or in- creased energy expenditure could serve as therapeutic options for the prevention of obesity and its comorbi- dities [6-8].

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that belong to the superfamily of nuclear receptors [9]. Three subtypes, designated PPARα (NR1C1), PPARδ (NR1C2), and PPARγ (NR1C3) have been identified as endogenous ligands that include fatty acids and fatty acid metabolites. PPARs form heterodimers with retinoid X receptors (RXRs) and bind to the hexanucleotidic PPAR respon- sive element (PPRE), thereby regulating the expression of target genes involved in lipid and carbohydrate me- tabolism. PPARs are found in species ranging from

Xenopus to humans [9] with each receptor having a distinct tissue expression profile. PPARα is expressed mainly in the liver, heart, and muscle. PPARγ is expressed predominantly in white and brown adipose tissue and is important in the regulation and control of adipocyte development and function [10]. PPARδ has a broad pattern of distribution and is expressed in many tissues, including muscle and kidney [11]. Recent work has suggested that PPARδ is involved in overall energy regulation and fatty acid oxidation in muscle. Activation of PPARδ has also been shown to increase high-density lipoprotein cholesterol (HDL-c) in diabetic db/db mice and obese rhesus monkeys [12]. Studies by Wang *et al.* [13] suggest that the overexpression of PPARδ in adipose tissue protects against diet-induced obesity in mice and treatment with a PPARδ selective agonist inhibits weight gain without effects on food intake in fat-fed mice [14]. A number of studies have described the effect of individual PPAR agonists in a variety of animal models or experimental paradigms [12,15-17].

This study provides a systematic 3-month evaluation of PPARδ agonist (GW501516, developed by Glaxo Smith Kline) and PPARδ agonist (HS00098) in a single model of chronic diet-induced obesity. This report evaluates the efficacy of the investigational drug (HS00098) on serum lipid profiles in obese rhesus monkeys.

2. MATERIALS AND METHODS

2.1. Equipment and Reagent

The Medonic CA620 fully automatic hematology analyzer, the ACL100 coagulation analyzer, the Beckman Synchron CX4 Pro clinical chemistry analyzer, the Bio-Rad enzyme immunoassay analyzer, monkey Apo-A1, Apo-B100, and Insulin ELISA kits (Uscnlife Science & Technology CO., LTD, E0604Mo, E0603Mo, E0448Mo) were used in this experiment. GW501516 capsules (Lot Number: 0701) and HS00098 capsules (Lot Number: 20070412) were provided by Zhejiang Hisun Pharmaceutical Co. Ltd. The chemical structural formula of HS00098 is shown in **Figure 1**.
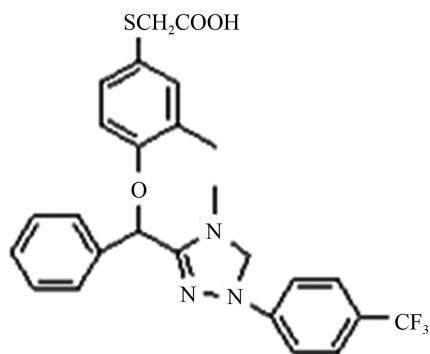
Figure 1. The chemical structural formula of HS00098.

2.2. Animal Selection and High Fat Diet

The experimental procedures were in accordance with the Guidance Suggestions for the Care and Use of Laboratory Animals, the Ministry of Science and Technology of China [18]. Animals were housed at 22°C and 50% relative humidity with a 12-hour light and dark cycle.

Fifty 7-13 year old male rhesus monkeys with a body mass index (BMI) greater than 35, weighing 9 kg or more, were obtained from the National (Sichuan) Experimental Rhesus Monkey Resources Base (Certificate Number: 22). The animals were quarantined and domesticated for 30 days before the experiment. Animal quarantine procedures included physical examinations, *Mycobacterium tuberculosis* tests (twice), and tests for parasites, *Salmonella*, *Shigella*, and B virus. Only monkeys that passed the quarantine and met the national criteria were used for this study. Monkeys were kept under controlled conditions of temperature (20°C - 28°C) and humidity (40% - 70%). A 12-h day and night cycle was maintained in the animal house. The monkeys were housed one per standard stainless steel cage with free food and water. A high fat diet (main ingredients for 18% protein, 60% carbohydrate, 8% fat）was provided to each animal (available ad libitum) in the morning, and an equally nutritious apple or vegetable was provided around 4 pm.

2.3. Establishment of Obese Rhesus Monkeys

The monkeys were continuously fed with a high fat diet for 2 months. On the final day of each month, a terminal blood sample (1 mL) was obtained via the femoral vein of the posterior limb. Routine blood tests mainly included total cholesterol (T-CHO), glucose, triglyceride (TG), high density lipoprotein cholesterol (HDLc), low density lipoprotein cholesterol (LDLc) [19-22]. At the same time, the level of serum insulin was tested by using the monkey insulin ELISA kit. When a stable increase of TC, TG, LDLc levels and a decrease in HDLc was accompanied by increased blood glucose levels and insulin levels for 2 consecutive tests, the models of obese animal were considered a success.

2.4. Grouping and Administration of Obese Rhesus Monkeys

Fifteen obese rhesus monkeys were selected according to their relatively approximate body weight and stable serum TC, TG, LDLc levels, and randomly divided into 3 groups, each with five animals. One group of animals was dosed with PPARδ agonist (GW501516 capsule) and another group was administered the investigational drug (HS00098 capsule) for 3 months, and the control group was administered oral placebo. All animals were fed 200 g of food in a high-fat diet daily. The GW501516 animals (numbers: 0141, 0375, 0997, 1003, 0047) and

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HS00098 group animals (numbers: 0851, 0483, 0869, 0379, 1029) were treatment with tris-dosage, first were treated with 0.3 mg/kg G for 1 month, then treated with 1 mg/kg GW501516 for 1 month, finally treated with 3 mg/kg GW501516 for 1 month, and one week withdrawal period between the two doses. At the end of each month after administration, test related data. The control group animals (numbers: 1011, 0901, 0099, 0441, 0095) were simulated oral administration and the other treatment like the above.

2.5. Assessment during the Experiment

In each experiment, the body weight (BW) of each animal was measured and recorded initially, and then after the first, second, and third month throughout the experiment.

Hematology and biochemical analyses, including total cholesterol (T-CHO), blood glucose (BG), triglyceride (TG), high density lipoprotein cholesterol (HDLc), and low density lipoprotein cholesterol (LDLc), were performed before and after the administration at the end of each month.

Before the administration and at the end of each month after each administration, the levels of serum Apo-A1, Apo-B100 and insulin were tested using the monkey Apo-A1, Apo-B100, and the Insulin ELISA kit to monitor the levels of serum lipids and serum glucose during the drug trial.

2.6. Data Statistical Analysis

All data are expressed as the value of individual data and mean (SD). Each individual's data was analyzed for changes after their treatment with the experimental drugs (including T-CHO, BG, TG, HDLc, LDLc, Apo-A1, Apo-B100 and insulin). Then the differences between the groups were analyzed using the two-way analysis of variance with repeated measures model (ANOVA) followed by Dunnett's post hoc test. The values were considered to be significant when a value of $P < 0.05$ was achieved.

3. RESULTS

3.1. Body Weight Changes after Treatment with HS00098 and GW501516

According to **Table 1**, after successive treatment for 3 months, the results were as follows: the mean weight gain of the GW501516 and HS00098 groups was significantly lower than that of the control group, and the mean weight gain of the HS00098 group was lower than that of the GW501516 group. According to the individual weight data, 1 monkey lost weight with GW 501516 and 3 monkeys lost weight with HS00098, but 4 monkeys gained weight in the control group. However, the food intake of the HS00098 animals decreased, whereas the food intake for the GW501516 animals changed little.

Table 1. Individual data of body weight changes in obese rhesus monkeys after treatment with HS00098 and GW501516 (kg).

Group	Pre-administration	0.3 mg/kg (first month)	1 mg/kg (second month)	3 mg/kg (third month)	Value of third month subtract pre-administration	Mean weight gain
	8.70	8.50	9.10	9.00	0.30	
	8.40	8.70	8.50	8.80	0.40	
GW501516	11.60	11.40	12.00	12.00	0.40	−0.08
	13.20	12.50	12.50	11.80	(1.40)	
	8.20	7.70	8.30	8.40	0.20	
	7.40	6.70	7.20	7.10	(0.30)	
	9.60	9.40	9.60	9.40	(0.20)	
HS00098	7.20	6.80	7.50	7.20	0.00	−0.18
	11.20	10.80	11.90	12.20	1.00	
	13.00	12.50	12.80	11.60	(1.40)	
	13.90	11.80	13.50	13.70	(0.20)	
	8.20	8.00	8.70	9.20	1.00	
Control group	9.30	8.90	9.10	9.70	0.40	0.56
	10.10	10.10	10.80	10.80	0.70	
	7.60	7.50	8.00	8.50	0.90	

The values in brackets are the decreased values.

3.2. Effects of PPARδ on the Serum Lipid Profiles

According to **Tables 2-4** and **Figures 2(a)-2(d)**, **2(g)**, **2(h)**, after 3 consecutive months of treatment, the results were as follows: The T-CHO values in the GW501516 and HS00098 groups were lower than that in the control group, but it was not considered significant (P > 0.05). The T-CHO value for the HS00098 group was lower than the value for the GW501516 group. Compared to the control and GW501516 groups, the HDLc, Apo-A1 and insulin levels of HS00098 group were significantly increased, while the level of LDLc and Apo-B100 were significantly decreased. The TG levels of the GW501516 and HS00098 groups were obviously lower than that of the control group, especially when treated with 3 mg/kg. According to the data analysis (**Tables 2-4**), the general trends were as follows: After 3 months of treatment, the animals with rising HDLc levels had significantly increased as the dosage increased. At the same time, the animals with falling T-CHO and LDLc levels decreased further as the dosage increased. The increasing/decreasing trends were more pronounced with the HS00098 animals than with the GW501516 animals at the same dosage.

3.3. Effects of PPARδ on BG and Insulin

According to **Figures 2(e)**, **2(f)**, after 3 months of treat-ment, the insulin levels showed an increasing trend. The insulin level of GW501516 group gradually increased to 0.3 at the 1 mg/kg dosage and slightly decreased at 3 mg/kg dosage, while that of HS00098 group increased significantly at the 0.3 mg/kg dosage and then decreased. At the same time, the insulin level of control group re-mained higher as time went on and was significantly higher than the other 2 groups. It was observed that the rate of increase was similar in both GW501516 and HS00098 groups. In addition, the BG level changed little in each group and dosage.

4. DISCUSSION

Recently, the antidiabetic GLP-1 agonist exenatide (Byetta) was shown to significantly reduce mean body weight (−4.7%) after 2 years of treatment [23]. In addition, recent studies have shown that peroxisome proliferator-acti-vated receptor (PPAR) delta agonists could induce weight loss by increasing energy expenditure and fatty acid oxidation [13]. In fact, PPARδ agonism either alone or in combination with agonisms of PPARα and/or PPARγ could not only induce body weight loss but could also potentially improve other metabolic parameters, including insulin sensitivity and lipid profiles. Our re-sults discovered that the mean weight gain of the GW501516 and HS00098 groups was significantly lower than that of the control group, thereby suggesting that

Table 2. Individual data of cholesterol changes in obese rhesus monkeys after treatment with HS00098 and GW501516 (unit: mol/L).

Group	Animal numbers	Pre-administration	0.3 mg/kg (first month)	1 mg/kg (second month)	3 mg/kg (third month)	Change in the third month subtract pre-administration		Change in the third month subtract first month		Change in the second month subtract first month		Change in the first month subtract pre-administration	
						Change value	Change rate (%)	Change value	Change rate (%)	Change value	Change rate (%)	Change value	Change rate (%)
GW501516	0141	14.62	13.90	10.57	8.59	6.03	41.24	1.98	18.73	3.33	23.96	0.72	4.92
	0375	13.61	11.46	10.83	10.86	2.75	20.21	(0.03)	(0.28)	0.63	5.50	2.15	15.80
	0997	12.50	9.94	11.53	11.83	0.67	5.36	(0.30)	(2.60)	(1.59)	(16.00)	2.56	20.48
	1003	13.43	11.43	12.78	12.54	0.89	6.63	0.24	1.88	(1.35)	(11.81)	2.00	14.89
	0047	21.30	18.75	17.90	19.97	1.33	6.24	(2.07)	(11.56)	0.85	4.53	2.55	11.97
	0851	16.17	12.92	11.84	9.51	6.66	41.19	2.33	19.68	1.08	8.36	5.25	20.10
HS00098	0483	16.92	12.57	9.13	7.50	9.42	55.67	1.63	17.85	3.44	27.37	4.35	25.71
	0869	14.55	11.14	9.13	6.44	8.11	55.74	2.69	29.46	2.01	18.04	3.41	23.44
	0379	14.20	12.75	11.02	11.56	2.64	18.59	(0.54)	(4.90)	1.73	13.57	1.45	10.21
	1029	12.92	11.54	10.17	7.40	5.52	42.72	2.77	27.24	1.37	11.87	1.38	10.68
	1011	11.84	8.48	9.09	9.81	2.03	17.15	(0.72)	(7.92)	(0.61)	(7.19)	3.36	28.38
	0901	12.54	10.12	9.54	9.96	2.58	20.57	(0.42)	(4.40)	0.58	5.73	2.42	19.30
Control group	0441	14.70	15.98	13.27	15.38	(0.68)	(4.63)	(2.11)	(15.90)	2.71	16.96	(1.28)	(8.71)
	0099	13.39	11.86	11.82	13.15	0.24	1.79	(1.33)	(11.25)	0.04	0.34	1.53	11.43
	0095	16.93	16.92	15.16	16.72	0.21	1.24	(1.56)	(10.29)	1.76	10.40	0.01	0.06

The normal reference value of serum cholesterol of 6-10 year-old male rhesus monkeys in our laboratory: 3.12 ± 0.64 mol/L (n = 100); the values in brackets are the increased value and rate.

Table 3. Individual data of HDL changes in obese rhesus monkeys after treatment with HS00098 and GW501516 (unit: mol/L).

Group	Animal numbers	Pre-administration	0.3 mg/kg (first month)	1 mg/kg (second month)	3 mg/kg (third month)	Change in the third month subtract pre-administration		Change in the third month subtract first month		Change in the second month subtract first month		Change in the first month subtract pre-administration	
						Change value	Change rate (%)	Change value	Change rate (%)	Change value	Change rate (%)	Change value	Change rate (%)
GW501516	0141	1.390	1.260	1.450	1.760	0.370	26.619	0.310	21.379	0.190	15.079	(0.130)	(9.35)
	0375	1.720	2.090	1.920	2.860	1.140	66.279	0.940	48.958	(0.170)	(8.134)	0.370	21.51
	0997	1.890	1.840	1.780	1.830	(0.060)	(3.175)	0.050	2.809	(0.060)	(3.261)	(0.050)	(2.65)
	1003	2.140	1.910	2.210	2.000	(0.140)	(6.542)	(0.210)	(9.502)	0.300	15.707	(0.230)	(10.75)
	0047	1.570	1.340	1.260	1.460	(0.110)	(7.006)	0.200	15.873	(0.080)	(5.970)	(0.230)	(14.65)
	0851	1.160	1.160	1.500	1.830	0.670	57.759	0.330	22.000	0.340	29.310	0.000	0.00
HS00098	0483	0.950	1.100	1.480	1.870	0.920	96.842	0.390	26.351	0.380	34.545	0.150	15.79
	0869	1.440	1.550	2.380	2.570	1.130	78.472	0.190	7.983	0.830	53.548	0.110	7.64
	0379	1.010	1.050	1.360	1.720	0.710	70.297	0.360	26.471	0.310	29.524	0.040	3.96
	1029	1.020	1.060	1.130	1.210	0.190	18.627	0.080	7.080	0.070	6.604	0.040	3.92
	1011	1.770	1.860	1.920	1.790	0.020	1.130	(0.130)	(6.771)	0.060	3.226	0.090	5.08
	0901	0.800	0.880	0.920	1.160	0.360	45.000	0.240	26.087	0.040	4.545	0.080	10.00
Control group	0441	1.040	0.960	1.210	1.260	0.220	21.154	0.050	4.132	0.250	26.042	(0.080)	(7.69)
	0099	1.230	1.040	1.120	1.200	(0.030)	(2.439)	0.080	7.143	0.080	7.692	(0.190)	(15.45)
	0095	0.900	1.440	1.660	0.920	0.020	2.222	(0.740)	(44.578)	0.220	15.278	0.540	60.00

The normal reference value of HDL of 6-10 year-old male rhesus monkeys in our laboratory: 1.92 ± 0.34 mol/L (n = 100); the values in brackets are the decreased value and rate.

Table 4. individual data of LDL changes in obese rhesus monkeys after treatment with HS00098 and GW501516 (unit: mol/L).

Group	Animal numbers	Pre-administration	0.3 mg/kg (first month)	1 mg/kg (second month)	3 mg/kg (third month)	Changes in the third month subtract pre-administration		Changes in the third month subtract first month		Changes in the second month subtract first month		Changes in the first month subtract pre-administration	
						Change value	Change rate (%)	Change value	Change rate (%)	Change value	Change rate (%)	Change value	Change rate (%)
GW501516	0141	7.720	7.620	8.010	6.210	1.510	19.560	1.800	22.472	(0.390)	(5.118)	0.100	1.295
	0375	6.750	6.420	7.120	6.020	0.730	10.815	1.100	15.449	(0.700)	(10.903)	0.330	4.889
	0997	6.960	6.020	10.060	9.910	(2.950)	(42.385)	0.150	1.491	(4.040)	(67.110)	0.940	13.506
	1003	7.790	6.980	11.040	9.470	(1.680)	(21.566)	1.570	14.221	(4.060)	(58.166)	0.810	10.398
	0047	10.210	9.250	13.190	14.980	(4.770)	(46.719)	(1.790)	(13.571)	(3.940)	(42.595)	0.960	9.403
	0851	11.500	10.010	10.990	6.890	4.610	40.087	4.100	37.307	(0.980)	(9.790)	1.490	12.957
HS00098	0483	10.000	8.840	8.220	5.560	4.440	44.400	2.660	32.360	0.620	7.014	1.160	11.600
	0869	8.480	6.860	6.770	3.750	4.730	55.778	3.020	44.609	0.090	1.312	1.620	19.104
	0379	8.030	7.090	9.570	9.540	(1.510)	(18.804)	0.030	0.313	(2.480)	(34.979)	0.940	11.706
	1029	8.350	7.850	9.840	5.780	2.570	30.778	4.060	41.260	(1.990)	(25.350)	0.500	5.988
	1011	7.250	4.970	7.380	6.750	0.500	6.897	0.630	8.537	(2.410)	(48.491)	2.280	31.448
	0901	7.650	6.740	8.860	7.290	0.360	4.706	1.570	17.720	(2.120)	(31.454)	0.910	11.895
Control group	0441	8.630	7.850	5.820	4.680	3.950	45.771	1.140	19.588	2.030	25.860	0.780	9.038
	0099	9.450	10.520	11.460	12.970	(3.520)	(37.249)	(1.510)	(13.176)	(0.940)	(8.935)	(1.070)	(11.323)
	0095	6.030	5.420	2.790	8.550	(2.520)	(41.791)	(5.760)	(206.452)	2.630	48.524	0.610	10.116

The normal reference value of LDL of 6-10 year-old male rhesus monkeys in our laboratory: 2.34 ± 0.54 mol/L (n = 100); the values in brackets are the increased value and rate.
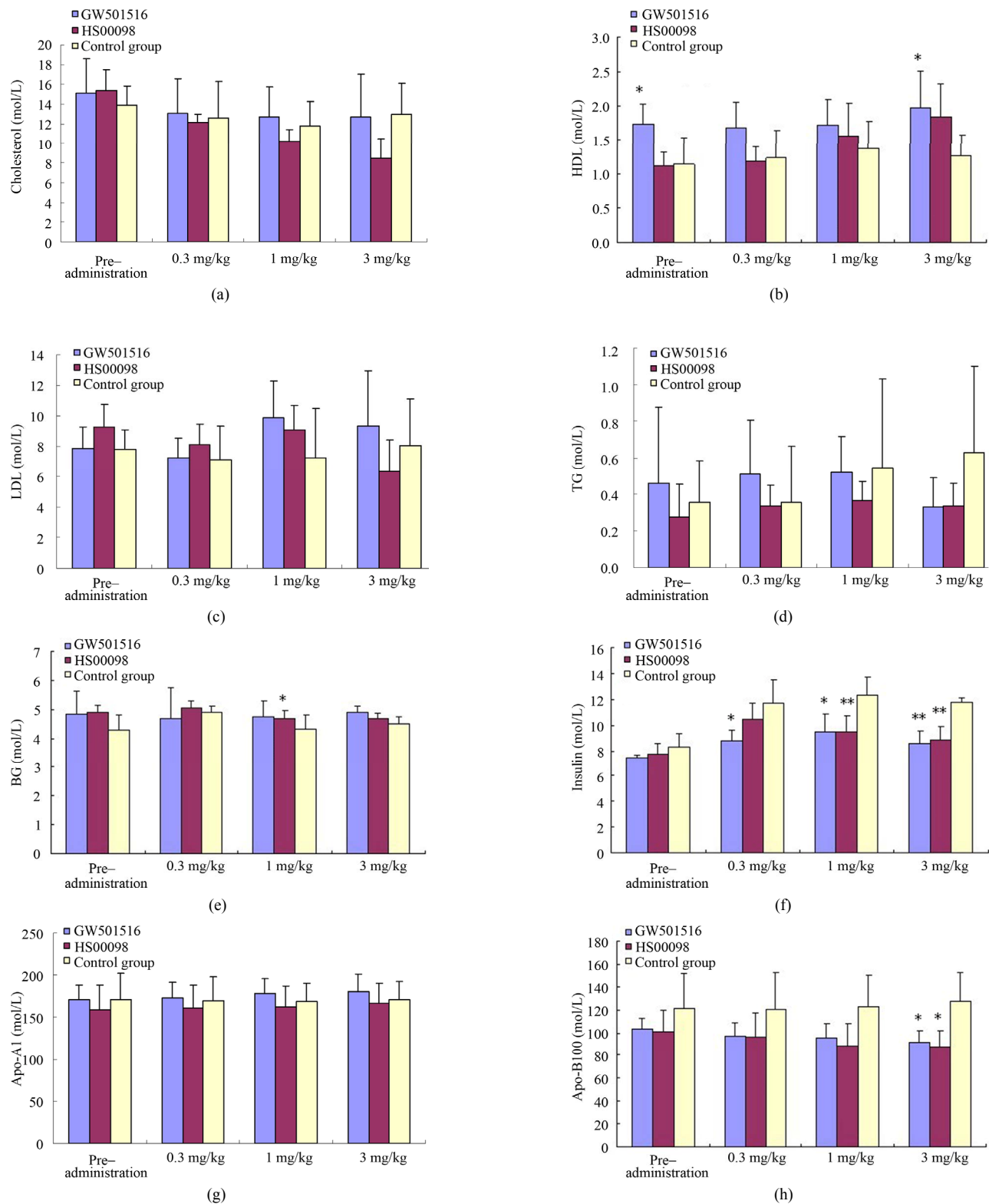
Figure 2. Effect of treatment with selective PPARδ agonists (GW501516 and HS00098) on serum cholesterol (CHO) (a); High density lipoprotein cholesterol (HDLc) (b); Low density lipoprotein cholesterol (LDLc) (c); Triglyceride (TG) (d); Blood glucose (BG) (e); Insulin (f); Apo-A1 (g); and Apo-B100 (h) in diet-induced obese rhesus monkeys. All data are expressed as mean (SD). Each dose was administered for 1 month. Initially and at the end of each month after drug treatment, the data were compared with the control group and analyzed by ANOVA with repeated measures followed by Dunnett's post hoc test. The values were considered to be significant (*) when a value of $P < 0.05$ was achieved. N = 5 animals/group.

both drugs could induce weight loss. Although the weight gain of the HS00098 subjects was lower than that of the GW501516 group, it is difficult to determine the cause considering the decreased food intake of the HS00098 animals.

Studies have revealed that PPARδ controls an array of metabolic genes involved in glucose homeostasis and fatty acid synthesis/storage, and mobilization and catabolism in a tissue-specific manner. A number of studies have also shown that PPARδ agonists regulate food intake, body weight, insulin sensitivity, and adiposity [8,24-30]. Transgenic mice, in which constitutively active PPARδ is expressed in muscle, are highly resistant to high-fat, diet-induced obesity [13]. Several synthetic ligands, namely GW501516, GW7042 and L165041, have also been developed, each exhibiting different efficacies in ameliorating symptoms of metabolic disorders [12,29,31,32]. GW501516, a selective PPARδ agonist, promotes fatty acid oxidation and utilization, and reduces lipid accumulation in adipocytes, skeletal muscle, and in the liver in diet-induced obese ob/ob [30], and db/db mice [29]. In fact, GW501516, a high affinity synthetic agonist, has been shown to reduce weight gain and decrease circulating TGs in mice fed a high fat diet or ob/ob mice [14,33]. The results from the GW501516 group in this study and also in a similar report proved that HS00098 (an investigational drug and a PPARδ agonist) had an even stronger effect than the GW501516.

In humans, lipid homeostasis is a delicate balance among dietary intake, de novo synthesis, and catabolism. The increased incidence of cardiovascular disease in Westernized nations has been linked to dyslipidemias associated with changes in the fat content of the diet [34]. Obesity, insulin resistance, and hypertension are comorbidities with these lipid disorders; these together are known as the metabolic syndrome X [35]. Individuals with this condition have high serum triglycerides and abnormally low levels of HDLc [35,36]. This lipid profile is accompanied by an increase in the proportion of small-dense LDL particles, which tend to accumulate in the arterial wall leading to the formation of atherosclerotic cholesterol-laden foam cells [37]. HDL plays a protective role through the process of reverse cholesterol transport whereby cholesterol is removed from the peripheral cells, including the macrophage-derived foam cells, and re-turned to the liver [38]. Agents that raise the levels of HDL through reverse cholesterol transport could provide a new therapeutic option for the prevention of atherosclerotic cardiovascular disease [2]. Our data showed that both GW501516 and HS00098 reduced circulating TG, T-CHO, Apo-B100, and LDLc and prevented the decline of HDLc, apoA-1, and insulin levels, thereby suggesting that GW 501516 and HS00098 regulated the lipid homeostasis. The data from the test group

HS00098 were more pronounced than those from the test group GW501516, thereby suggesting that the effect of HS00098 on serum profiles was stronger than the effect of GW501516. This implied that HS00098 played an important role in ameliorating the serum lipid profiles of high-fat diet-induced obese rhesus monkeys. Collectively, this data suggested that HS00098 and GW501516 increased fat combustion and may provide a means to regulate adiposity.

The effect of GW501516 on glucose homeostasis has been studied in several mouse models of insulin resistance/ type II diabetes. In C57BL/6 mice fed a high fat diet, co-administration of this PPARδ agonist at 3 mg·kg^{-1}·day^{-1} for 2 months increased the metabolic rate, reduced fatty liver, and decreased lipid accumulation and increased mitochondrial biogenesis in muscle. The circulating insulin levels also declined, whereas the improvement in glucose tolerance and insulin sensitivity determined by the glucose and insulin tolerant test (GTT and ITT) was moderate [33]. The effect appeared to be dose-dependent at 10 mg·kg^{-1}·day^{-1}, wherein the ability of GW501516 to lower blood glucose levels and enhance glucose tolerance became apparent [14]. Interestingly, in addition to improving glucose homeostasis, GW501516 treatment normalized pancreatic islet hypertrophy and increased glucose-stimulated insulin secretion in ob/ob mice [33]. GW501516 did not induce insulin release in isolated islets [39], thereby suggesting that the increased insulin secretion was secondary to improved islet function. Our investigation shows that HS00098 and GW501516 played a role in maintaining blood glucose level stabilization, while it was unstable in the control group. At the same time, compared with the control group, the ascending amplitude of GW501516 and HS00098 group was significantly lower, and the ascending/declining amplitude was similar. The results suggested that GW501516 and HS00098, as PPARδ agonists, played an important role in reducing the insulin level in obese rhesus monkeys and that the two drugs functioned in synergistic competition with insulin. In addition, the results showed that the 2 drugs regulated the insulin level depending on the concentration of drugs, and it can be seen that HS00098 regulated the insulin level at the 1 mg/kg dosage but GW501516 was effective at the 3 mg/kg dosage. This also suggested that high levels of HS00098 (1 mg/kg) activated PPARδ expression and then synergistically competed with insulin, thereby leading to a lower level of insulin. However, according to the previous report that PPARδ can increase insulin sensitivity [30], HS00098 also had a similar role.

In summary, the above results suggested that the investigational drug (HS00098) can effectively reduce blood lipids and maintain the blood glucose levels of diet-induced obese rhesus monkeys depending on the dose.

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5. ACKNOWLEDGEMENTS

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