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Original Article

Berberine improves metabolic syndrome insulin resistance by inducing macrophage M2 polarization

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Abstract: Objective: To study the therapeutic effect of berberine (BBR) on metabolic syndrome insulin resistance and the impact on macrophage M2 polarization, and to investigate the mechanism of action of BBR. Method: Ten SD rats were in the normal group. The other 40 rats were used to establish the metabolic syndrome model, and were randomly divided into the model group (n=20) and the treatment group (n=20). Rats were fasted overnight, and serum was tested for mRNA levels of M2 marker genes, Mrc1, Ym1, Fizz1, and Arg1. Fasting blood-glucose (FBG) and fasting insulin (FINS) levels were also obtained, and the insulin resistance index (HOMA-IR) was calculated. Results: After treatment, the FBG and FINS levels and the HOMA-IR of rats in treatment group decreased compared with those of the rats in the same group before treatment ($P<0.05$), and were also significantly lower than those of the rats in the model group ($P<0.05$). The FBG and FINS levels and HOMA-IR of rats in the treatment group decreased following implementation of the high-fat diet ($P<0.05$). Moreover, after treatment, mRNA levels of Mrc1, Ym1, Fizz1, and Arg1 of rats in the treatment group increased compared with those before treatment ($P<0.05$), and also compared with those in the model group ($P<0.05$). Arg1 was higher in the treatment group than in the normal group ($P<0.05$), Ym1 and Fizz1 were lower than that in the normal group ($P<0.05$). Conclusions: BBR improves metabolic syndrome insulin resistance by inducing M2 tissue macrophage polarization.

Keywords: BBR, tissue macrophage, M2 polarization, metabolic syndrome, insulin resistance

Introduction

Metabolic syndrome is a group of complicated metabolic disorders, such as abnormal glucose tolerance and hyperuricemia, which are important factors in the onset of diabetes mellitus as well as cardiovascular and cerebrovascular diseases [1, 2]. Obesity is the main cause of metabolic syndrome. Due to social development and changes in dietary structure, the prevalence of obesity is increasing yearly [3]. A 2016 study reported that the worldwide obese population has increased to 600 million in recent years, with male and female obesity rates increasing by three- and two-fold, respectively [4]. The worldwide prevalence of morbid obesity is estimated to be between 0.64% and 1.6%.

The core of metabolic syndrome is insulin resistance [5]. Berberine (BBR) is a component of the coptis chinensis extract, and has anti-inflammatory and hypoglycemic effects similar to that of coptis chinensis [6]. A study has reported that BBR can reduce body weight and improve insulin resistance by multiple mechanisms. However, its specific mechanism of action has not been elucidated [7]. Obesity is associated with low-grade inflammation and an imbalance of cytokine levels which eventually leads to progression of insulin resistance and other related diseases [8, 9]. The macrophage is a component of body's innate immune system [10]. In recent years, studies have found that macrophages not only participate in the specific induction and immunoregulation of immune responses, but also in the regulation of the body's metabolic function. Macrophages become polarized by cues in their environment and this polarization causes a functional change in their behavior. Two main subsets of polar-

Table 1. Primer series

	Forward primer	Reverse primer
Mrc1	AGGGACCTGGATGGATGACA	TGTACCGCACCCTCCATCTA
Ym1	AACACGGCAGTGGCTTTAAC	GTCAGTCCCTGGCTTATGGTT
Fizz1	CATGAGCAAGACTTGCGTGAC	GGTCCAAACTTCCATCCTCCA
Arg1	CCCTGCTGGGATGACTGCTA	TGCAAGTATCTCCACTCTGGA
Actin	GGTCATCACTATTGGCAACGR	ACGGATGTCAACGTCACACT

ized macrophages have been described. M1, or "classically activated" macrophages, are pro-inflammatory and M2, or "alternatively activated" macrophages, are anti-inflammatory [11]. Macrophage M2 polarization is an important form of anti-inflammation [12]. Hussaarts L, et al. reported that promoting macrophage M2 polarization can improve insulin sensitivity in obese mice [13]. The current study aimed to investigate the effect of BBR on rat macrophage M2 polarization and insulin resistance, and study the mechanism of BBR in improving insulin resistance by treating rats with metabolic syndrome with BBR.

Materials and methods

Laboratory animal and feeding

All SD rats in healthy and mature period were purchased from Changzhou Cavens Laboratory Animal Co., Ltd., and fed with Shuke Beita SPF-level fodder (purchased from Jiangsu Xietong Medical Bioengineering Co. Ltd.). SD rats were aged 10~12 weeks with body weight of 210-240 g, and fed in a room with a temperature of 23.5±2.4°C. The ammonia concentration was not more than 20 ppm, airflow velocity was (18.2±5.1) cm/s, ventilation rate was (13±2) times/h, humidity was 40-50%, and fluorescent lamp provided illumination. All rats were allowed to freely eat and drink (sterile water). The feed box was changed 1-2 times per week, and the water bottle was changed 3-4 times per week.

Establishment of metabolic syndrome model

After 1 week of environmental adaptation feed, 50 SD rats were divided into two groups in accordance with the random number table. Specifically, 10 rats were in normal rat group, and fed with fundamental feed (purchased from Keao Xieli Company), and the other 40 rats were used to establish the metabolic syndrome model by feeding with high-fat diet (purchased from Keao Xieli Company) for 8 weeks.

Treatment method of rats

Rats in the treatment group were given BBR (manufactured by Shanghai Shifeng Biotechnology Co., Ltd. with national drug approval number of H51020855) by intraperitoneal injection at 5 mg/kg of body weight per day starting at the 9th week, and the rats in the normal and model groups were given an equal of normal saline by intraperitoneal injection for 2 weeks starting at the 9th week.

Observation index

Rats were fasted overnight, and blood was collected. The insulin resistance index (HOMA-IR) was calculated (HOMA-IR = FPG (mmol/L) × FINS (mIU/L)/22.5). Both the blood glucose and insulin levels of the rats were tested by ELISA kits (Shanghai Guangrui Biotechnology Co., Ltd.) according to the manufacturer's instructions.

Extraction of total mRNA in serum

TRIzol reagent (purchased from Shanghai Mingjin Biotechnology Co., Ltd.) was used to extract the total RNA in serum according to the manufacturer's instructions. A micro-ultraviolet spectrophotometer MD1000 (purchased from Thmorgan Biotechnology Co., Ltd.) was used to analyze the concentration and purity of RNA extracted, and agarose gel electrophoresis (AGE) (the gel electrophoresis suit was purchased from Shanghai Jkinlight Chemical Technology Co., ltd.) in a 3% gel was used to analyze the integrity of RNA.

qRT-PCR analysis of mRNA levels

Reverse transcription of total RNA and PCR analysis of cDNA was carried out using fluorescent quantitative PCR kit according to the manufacturer's instructions (Thermo Fisher Scientific (China) Co., Ltd.). cDNA synthesis was performed for 45 min at 37°C, and 5 min at 95°C. The amplification reaction for the cDNA was in a total volume of 20 uL in total, denatured for 10 min at 95°C, followed by 40 cycles consisting of: denaturation for 10 seconds at

Table 2. Weight changes before and after rat model establishment (g)

	Normal rats	Modeling group	Treatment group	F	*p*-value
Before the modeling	226.3±8.4	225.4±12.2	225.8±12.4	0.020	0.980
After modeling	481.4±14.3*	521.4±21.1$^{*,\&}$	522.8±21.9$^{*,\&}$	16.07	<0.001
Post-treatment	502.4±17.5$^{\#}$	541.7±24.5$^{\#,\&}$	500.4±18.5$^{\#,\Delta}$	22.56	<0.001

Note: *, *vs.* before model establishment, P<0.05; #, *vs.* after remodeling, P<0.05; &, *vs.* Normal group, P<0.05; Δ, *vs.* Modeling group, P<0.05.

Table 3. Rat model establishment and FBG changes before and after treatment (mmol/L)

	Normal rats	Modeling group	Treatment group	F	*p*-value
Before the modeling	7.32±1.33	7.34±1.94	7.52±1.92	0.045	0.956
After modeling	7.33±1.25	22.3±5.41$^{*,\&}$	22.5±5.32$^{*,\&}$	38.55	<0.001
Post-treatment	7.33±1.28	17.2±4.13$^{\&,\#}$	9.3±2.74$^{\#,\Delta}$	44.15	<0.001

Note: *, vs. before model establishment, P<0.05; #, vs. after remodeling, P<0.05; &, vs. Normal group, P<0.05; Δ, vs. Modeling group, P<0.05.

95°C, annealing for 20 seconds at 60°C, extension for 10 seconds at 72°C, and a final extension for 5 minutes at 72°C at the completion of the cycles. Actin was used as the reaction internal reference. Each sample was plated in triplicate and results were analyzed by the $2^{-\Delta Ct}$ method. For primer sequences, see **Table 1**.

Statistical analysis

Statistical method: SPSS22.0 (Asia Analytics Formerly SPSS China) was used for statistical analysis. Measurement data are represented by $\bar{X}$±S, analysis of variance was used for comparison of measurement data among groups, paired t-test was used for comparison between two groups, and analysis of variance of repeated measures was used for comparisons among different time points within group. P<0.05 was considered statistically significant.

Results

Changes in body weight of rats before and after model establishment, as well as treatment

Forty healthy SD rats with an average weight of 225.6±12.3 g were used to establish the experimental model. After 8 weeks of model establishment, the average weights of 40 model rats and 10 normal rats were 522.1±21.5 g and 481.4±14.3 g, respectively. The weights of rats in all three groups increased significantly following establishment of the experimental model (P<0.05). Additionally, the average body weight of rats in both the model and treatment groups were higher than those in the normal rat group (P<0.05). However, there was no difference between the body weights of rats in model group and those in the treatment group (P>0.05). Following 2 weeks of treatment, the body weights of rats in treatment group decreased compared to those in the same group before treatment (P<0.05). The weights of the treatment group after 2 weeks of treatment were also reduced compared with those in the model group at the same time point (P<0.05), and were not significantly different than those in normal rat group (P>0.05). The body weights of rats in the model group was much bigger than the normal group following treatment (P<0.05) (**Table 2**).

Fasting blood-glucose (FBG) changes before and after treatment

The FBG of rats in the three groups showed no difference before establishment of the experimental model (P>0.05). After 8 weeks of a high-fat diet, the FBG of rats in the model and treatment groups was significantly increased (P<0.05). These values were also higher than those in the normal rat group (P<0.05). The FBG within the normal rat group had no significant changes (P>0.05), and the FBG of rats in the model group had no difference compared with those in the treatment group (P>0.05). After 2 weeks of treatment, the FBG of rats in the treatment group decreased compared with the same group before treatment (P<0.05), and was also lower compared with those in the model group (P<0.05), but was still higher than

Table 4. Rat model establishment and changes of fasting FINS before and after treatment (ng/ml)

	Normal rats	Modeling group	Treatment group	F	*p*-value
Before the modeling	0.45±0.12	0.44±0.17	0.46±0.18	0.073	0.930
After modeling	0.44±0.11	1.52±0.23$^{*,\&}$	1.54±0.22$^{*,\&}$	109.9	<0.001
Post-treatment	0.45±0.13	1.49±0.21$^{\&}$	0.93±0.16$^{\#,\&,\Delta}$	123.5	<0.001

Note: *, vs. before model establishment, P<0.05; #, vs. after remodeling, P<0.05; &, vs. Normal group, P<0.05; Δ, vs. Modeling group, P<0.05.

Table 5. Rat model establishment and the changes in HOMA-IR before and after treatment

	Normal rats	Modeling group	Treatment group	F	*p*-value
Before the modeling	0.15±0.01	0.14±0.01	0.15±0.02	2.712	0.077
After modeling	0.14±0.01	1.51±0.06$^{*,\&}$	1.54±0.05$^{*,\&}$	21.08	<0.001
Post-treatment	0.15±0.01	1.14±0.04$^{\#,\&}$	0.38±0.02$^{\#,\&,\Delta}$	19.67	<0.001

Note: *, vs. before model establishment, P<0.05; #, vs. after remodeling, P<0.05; &, vs. Normal group, P<0.05; Δ, vs. Modeling group, P<0.05.

the FBG values in the normal rat group (P<0.05) (**Table 3**).

Model establishment of rats and changes of fasting FINS before and after treatment

The average fasting insulin (FINS) of rats before the establishment of the experimental model was not significantly different (P>0.05). After 8 weeks of model establishment, the FINS of the rats in the model group and the treatment group were significantly elevated compared to the values before treatment (P<0.05) and compared to those in the normal rat group (P<0.05). The FINS of rats in the normal group had no significant changes (P>0.05), and the FINS of rats in the model group had no difference compared with those in the treatment group (P>0.05). After 2 weeks of treatment, the FINS values of rats in the treatment group decreased compared with those before treatment (P<0.05) and also compared with those in the model group, but were still higher than those in the normal rat group (P<0.05) (**Table 4**).

Changes in HOMA-IR before and after treatment

The HOMA-IR of rats before model establishment showed no difference (P>0.05). However, after 8 weeks of high-fat diet, the HOMA-IR of the rats was significantly elevated (P<0.05). The HOMA-IR of rats in the model and the treatment groups was higher than that in normal rat group (P<0.05), and the HOMA-IR within normal rat group had no significant changes (P>0.05). There were no differences in the HOMA-IR of rats between the model group and the treatment group (P>0.05). After 2 weeks of treatment, the HOMA-IR of rats in the treatment group decreased (P<0.05). These levels were lower than those in the model group (P<0.05), but were still higher than those in the normal rat group (P<0.05) (**Table 5**).

The change of M2 polarization genes before and after treatment

There were no significant differences in the mRNA levels of Mrc1, Ym1, Fizz1, and Arg1 of rats before the establishment of the experimental model (P>0.05). However, after 8 weeks, the mRNA levels of Mrc1, Ym1, Fizz1, and Arg1 of rats didn't change much in the normal group, but significantly decreased in the model and treatment groups (all P<0.05). The mRNA levels of Mrc1, Ym1, Fizz1, and Arg1 of rats in the model and treatment groups were significantly lower than those in the normal rat group (P<0.05). Additionally, there were no significant differences in these mRNA levels of rats in the model group compared with those of the rats in the treatment group (P>0.05). Following 2 weeks of treatment, the mRNA levels of Mrc1, Ym1, Fizz1, and Arg1 of rats in the treatment group were increased compared with those before treatment (P<0.05). Arg1 was still lower in rats in the treatment group than in rats in the normal group (P<0.05) (**Table 6**).

Discussion

Chronic obesity is often accompanied by insulin resistance [14]. In recent years, the use of BBR

Table 6. Rat model establishment and the change in M2 marker gene before and after treatment

		Normal rats	Modeling group	Treatment group	F	*p*-value
Mrc1	Before the modeling	1.44±0.12	1.44±0.16	1.46±0.15	0.162	0.851
	After modeling	1.45±0.11	0.98±0.24*	1.01±0.23*	25.38	<0.001
	Posttreatment	1.47±0.12	0.94±0.25	1.43±0.11$^{\#,\Delta}$	13.82	0.001
Ym1	Before the modeling	1.35±0.07	1.39±0.09	1.36±0.09	0.614	0.545
	After modeling	1.36±0.05	0.88±0.19$^{*,\&}$	0.89±0.21$^{*,\&}$	33.53	<0.001
	Posttreatment	1.38±0.06	0.81±0.16$^{\&}$	1.12±0.09$^{\#,\&,\Delta}$	11.81	0.003
Fizz1	Before the modeling	1.48±0.14	1.51±0.19	1.52±0.18	0.045	0.957
	After modeling	1.51±0.12	1.12±0.26$^{*,\&}$	1.13±0.27$^{*,\&}$	25.41	<0.001
	Posttreatment	1.53±0.11	1.18±0.29$^{\&}$	1.42±0.23$^{\Delta}$	39.75	<0.001
Arg1	Before the modeling	1.24±0.05	1.27±0.07	1.27±0.09	0.070	0.933
	After modeling	1.26±0.05	0.62±0.17$^{*,\&}$	0.63±0.15$^{*,\&}$	25.09	<0.001
	Posttreatment	1.28±0.04	0.54±0.11$^{\&}$	1.38±0.09$^{\#,\Delta}$	8.798	0.012

Note: *, vs. before model establishment, P<0.05; #, vs. after remodeling, P<0.05; &, vs. Normal group, P<0.05; Δ, vs. Modeling group, P<0.05.

for the treatment of insulin resistance has been studied. Chang, et al. [15] showed that BBR improves insulin resistance in cardiomyocytes via activation of 5'-adenosine monophosphate-activated protein kinase. Pérez-Rubio KG, et al. [16] found that BBR can improve insulin sensitivity and insulin secretion in patients with metabolic syndrome. However, the specific mechanism of BBR in improving insulin sensitivity has not been elucidated. Han, et al. [17] have found that macrophages can promote obesity-induced insulin resistance and inflammation by JNK expression. Therefore, the present study was intended to validate whether BBR improves insulin sensitivity by inducing M2 polarization in macrophages.

Metabolic syndrome was established in this study by feeding SD rats a high-fat diet for 8 weeks. Following the feeding period, the body weights of SD rats significantly increased, and were higher than those that of rats fed with fundamental feed. The ELISA results of FBG and FINS of rats before and after the high-fat feeding period showed a significant increase in FBG and FINS of SD rats fed with high-fat diet compared to those fed with fundamental feed. The HOMA-IR index of rats fed with high-fat diet for 8 weeks was also significantly elevated compared with rats fed with fundamental feed over the same period. These results indicate that the rats that were fed a high-fat diet developed insulin resistance. We also tested serum M2 macrophages of rats with metabolic syndrome. The RT-PCR results showed that mRNA levels of the maker genes of M2 macrophages, Mrc1, Ym1, Fizz1, and Arg1, significantly decreased in rats that were fed a high-fat diet. Although there have been only a few reports about the macrophage M2 polarization level in rats with metabolic syndrome, we speculate that obesity triggers an inflammatory reaction in rat's body which reduces macrophage M2 polarization. We administered BBR to rats with metabolic syndrome by intraperitoneal injection to evaluate its effect on insulin resistance. After 2 weeks of treatment, the body weight of rats with metabolic syndrome significantly decreased, along with FBG and FINS levels. HOMA-IR results also showed that the insulin resistance of these rats had improved, indicating that BBR can effectively improve the insulin sensitivity of rats with metabolic syndrome. These results are also consistent with the results of Pérez-Rubio KG, et al. [16]. Recently, there have been only a few reports regarding the effects of BBR on insulin resistance of rats with metabolic syndrome. Li, et al. [18] reported that BBR can also effectively improve the insulin resistance of patients with polycystic ovarian syndrome. In our study, however, the insulin resistance level of rats did not recover to the level of normal rats after 2 weeks of treatment with BBR. This result may be attributed to the dose and duration of treatment with BBR, which we plan to investigate in future studies.

We tested the mRNA levels of Mrc1, Ym1, Fizz1, and Arg1 of rats with metabolic syndrome before and after treatment, finding that the lev-

els of Mrc1, Ym1, Fizz1, and Arg1 of rats with metabolic syndrome elevated to varying degrees following treatment. This result suggests that macrophage M2 polarization level increased following treatment. In another study, Ye, et al. [19] demonstrated that BBR can improve the insulin resistance by inhibiting macrophage M1 polarization. Macrophages have two different polarization phenotypes, M1 type and M2 type. M1 macrophages promote pro-inflammatory reactions, while M2 macrophages are anti-inflammatory [20, 21]. These studies are relevant to our results, to some extent, that BBR can improve insulin resistance by attenuating the inflammatory reaction level in a patient's body.

In conclusion, BBR improves metabolic syndrome insulin resistance by inducing M2 tissue macrophage polarization.

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Disclosure of conflict of interest

None.

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