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Voluntary exercise prevents colonic inflammation in high-fat diet-induced obese mice by up-regulating PPAR-γ activity

Wei-Xin Liu [a, *], Ting Wang [a], Feng Zhou [a], Ying Wang [a], Jun-Wei Xing [a], Shen Zhang [a], Shou-Zhi Gu [b], Li-Xuan Sang [c], Cong Dai [a], Hai-Lan Wang [d]

[a] Department of Gastroenterology, First Affiliated Hospital of China Medical University, Shenyang 110001, Liaoning, China
[b] Department of Anatomy, Seirei Christopher College, Hamamatsu 433-8558, Japan
[c] Department of Cadre Ward II, First Affiliated Hospital of China Medical University, Shenyang 110001, Liaoning, China
[d] Guangdong Province Hospital for Occupational Disease Prevention and Treatment, Guangzhou 510300, Guangdong, China

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ABSTRACT

Obesity is associated with increased colonic inflammation, which elevates the risk of colon cancer. Although exercise exerts anti-inflammatory actions in multiple chronic diseases associated with inflammation, it is unknown whether this strategy prevents colonic inflammation in obesity. We hypothesized that voluntary exercise would suppress colonic inflammation in high-fat diet (HFD)-induced obesity by modulation of peroxisome proliferator-activated receptor (PPAR)-γ. Male C57Bl/6J mice fed either a control diet (6.5% fat, CON) or a high-fat diet (24% fat, HFD) were divided into sedentary, voluntary exercise or voluntary exercise with PPAR-γ antagonist GW9662 (10 mg/kg/day). All interventions took place for 12 weeks. Compared with CON-sedentary group, HFD-sedentary mice gained significantly more body weight and exhibited metabolic disorders. Molecular studies revealed that HFD-sedentary mice had increased expression of inflammatory mediators and activation of nuclear factor (NF)-κB in the colons, which were associated with decreased expression and activity of PPAR-γ. Voluntary exercise markedly attenuated body weight gain, improved metabolic disorders, and normalized the expression of inflammatory mediators and activation of NF-κB in the colons in HFD-mice while having no effects in CON-animals. Moreover, voluntary exercise significantly increased expression and activity of PPAR-γ in the colons in both HFD- and CON-animals. However, all of these beneficial effects induced by voluntary exercise were abolished by GW9662, which inhibited expression and activity of PPAR-γ. The results suggest that decreased PPAR-γ activity in the colon of HFD-induced obesity may facilitate the inflammatory response and colon carcinogenesis. Voluntary exercise prevents colonic inflammation in HFD-induced obesity by up-regulating PPAR-γ activity.

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1. Introduction

The prevalence of overweight and obesity has increased alarmingly over the past several decades throughout the world. Although genetics play an important role in the regulation of body weight homeostasis, consumption of a high-fat diet (HFD) and physical inactivity are also important environmental contributors to overweight and obesity [1]. Experimental and epidemiological studies have revealed that obesity is a robust risk factor of many types of cancer, and the data are particularly compelling for colon cancer [2]. It is now widely accepted that inflammation plays a crucial role in the cancer development [3]. Obesity is associated with a state of chronic, low-grade inflammation [4] and recent study showed that increased expression of inflammatory mediators in the colons of obese animals led to activation of important pro-carcinogenic signaling pathways, contributing to the development of colon cancer [5]. A prevention strategy that targets inflammation could, therefore, be important for preventing the colon cancer in these high-risk populations.

Numerous studies have demonstrated that regular exercise provides protection against, and may be useful as a treatment for a wide variety of chronic diseases associated with low-grade inflammation [6,7]. Recent studies reported that exercise training

* Corresponding author. Department of Gastroenterology, First Affiliated Hospital of China Medical University, 155 North Nanjing Street, Heping District, Shenyang 110001, Liaoning Province, China. Fax: +86 24 83282208.
E-mail address: weixinliu@yahoo.com (W.-X. Liu).

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attenuated elevated inflammatory mediators in the intestinal tract in healthy aged mice [8], and inhibited colon inflammation and cell proliferation in rats with dimethylhydrazine-induced colon carcinogenesis [9]. However, it is unknown whether exercise training prevents elevated inflammatory mediators in the colons in obesity, especially induced by HFD.

In animal models, forced exercise on treadmills may be problematic, as they are stressful. It was recently reported that forced treadmill exercise training exacerbated colon inflammation and led to mortality while voluntary exercise training was protective in a mouse model of colitis [10], suggesting that voluntary exercise may be a better model. Indeed, voluntary exercise training has been shown to protect against inflammatory gene expression in adipose tissue and improve insulin sensitivity in HFD-induced obese mice [11].

Hence, the aim of the present study was to examine the effects of voluntary exercise on obesity-associated inflammation in the colons, and to explore possible molecular mechanism underlying these effects in HFD-induced mice model of obesity, which closely mimics human characteristics of obesity [12]. For the mechanism involved, we focused on the expression and activity of peroxisome proliferator-activated receptor (PPAR)-γ, a nuclear receptor that has been shown to play a key role in the regulation of colonic inflammation in response to HFD [13] and is recently known to be modulated by exercise in the skeletal muscle [14] and in monocytes [15].

2. Methods

2.1. Animals

Ten week old male C57BL/6J mice were obtained from Shanghai Laboratory Animal Centre (Shanghai, China). All animal experiments were performed in accordance with the guidelines of the Institutional Animal Care and Use Committee (IACUC) at China Medical University. The research protocols and procedures were approved by IACUC of China Medical University.

The animals were randomly divided into six groups (n = 8 for each group): control diet and sedentary (CON + SED); control diet and voluntary exercise (CON + EXE); control diet and voluntary exercise with GW9662 (a selective PPAR-γ antagonist, Sigma–Aldrich, Inc, St. Louis, MO, USA) (CON + EXE + GW); HFD and sedentary (HFD + SED); HFD and voluntary exercise (HFD + EXE); HFD and voluntary exercise with GW9662 (HFD + EXE + GW). GW9662 (10 mg/kg/day) was given by gastric gavage once a day as previously described [16]. Animals began the diet and voluntary exercise training with or without GW9662 concomitantly. These treatments took place for 12 weeks. Control diet contains 6.5% fat by weight and has 16.7% total calories from fat. HFD contains 24% fat by weight and has 45% calories from fat. Animals were individually housed in cages fitted with running wheels (14-cm diameter, 6-cm width, Melquest Ltd., Toyama, Japan), which were locked for the sedentary groups. Running distance was monitored daily. Animals in all groups were reared at 25 °C with a 12-h light/dark cycle and had ad libitum access to food and water. Food and body weights were recorded weekly.

2.2. Glucose tolerance test (GTT)

GTT was performed one week before the end of the protocol. Running wheels were locked in the evening before metabolic testing. Animals were fasted overnight (17:00–08:00) and were subsequently injected with glucose (2 g/kg body weight, ip) as previously described [11]. Tail blood was collected at 0, 30, 60, and 120 min. Blood glucose concentrations were measured by a glucometer (Roche, Mannheim, Germany).

2.3. Plasma insulin, leptin and adiponectin

Fasting plasma insulin, leptin and adiponectin concentrations were measured by commercially available mice ELISA kit (Invitrogen, Camarillo, CA) according to manufacturers' instructions.

2.4. Analysis of protein levels for inflammatory mediators and PPAR isoforms in the colon

At the termination of the study, animals were sacrificed and colons were quickly isolated for molecular studies. Protein levels of inflammatory mediators and PPAR isoforms (PPAR-α, PPAR-β and PPAR-γ) in the colons were measured with Western blot, using primary antibody to IL-1β, TNF-α, IL-6, COX-2, PPAR-α, PPAR-β, PPAR-γ and β-actin (Santa Cruz Biotechnology Inc, Santa Cruz, CA). The density of the bands was quantified with NIH ImageJ software (Bethesda, MD, USA) and all data were corrected by β-actin.

2.5. Analysis of NF-κB and PPAR isoform activity in the colon

Nuclear and cytoplasmic extracts were prepared from the colon tissues using a Nuclear Extract Kit (Active Motif, Carlsbad, CA, USA). NF-κB p65, PPAR-α, PPAR-β and PPAR-γ DNA binding activity were measured by Transcription Factor Assay Kits (Abcam, Cambridge, MA and Active Motif, Carlsbad, CA, USA) following the manufacturer's instructions. Cytoplasmic IκBα level was measured with Western blotting as described above, using a polyclonal antibody to IκBα (Santa Cruz Biotechnology).

2.6. Statistical analysis

Data are presented as mean ± SD. Statistical analysis was performed using the ANOVA test followed by the Newman–Keuls multiple-comparison post-hoc test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Voluntary exercise reduces HFD-induced obesity

Mice that had access to running wheels ran a total of 7842 ± 750 m during the 12 h of the dark cycle (19:00–7:00) and 240 ± 96 m during the 12 h of the light cycle. Compared with control-sedentary group, HFD-sedentary mice gained substantially more body weight from 3 weeks until the end of the experiment at 12 weeks (Fig. 1A). Exercise significantly attenuated body weight gain in both control and HFD mice compared with their respective sedentary animals. GW9662 did not affect exercise-induced weight loss in both groups.

Cumulative food intake was increased in HFD-sedentary mice as compared to control-sedentary group (Fig. 1B). Neither exercise nor GW9662 had effect on cumulative food intake in both animals.

3.2. Voluntary exercise ameliorates metabolic disorders in HFD-induced obese mice

At the end of the study, fasting blood glucose levels at baseline (0 min) were similar among the six experimental groups (Fig. 1C). However, GTT showed that compared with control-sedentary group, HFD-sedentary mice had significantly worse glucose tolerance as evidenced by delayed glucose clearance with higher glucose levels at 60 and 120 min after glucose injection. Exercise

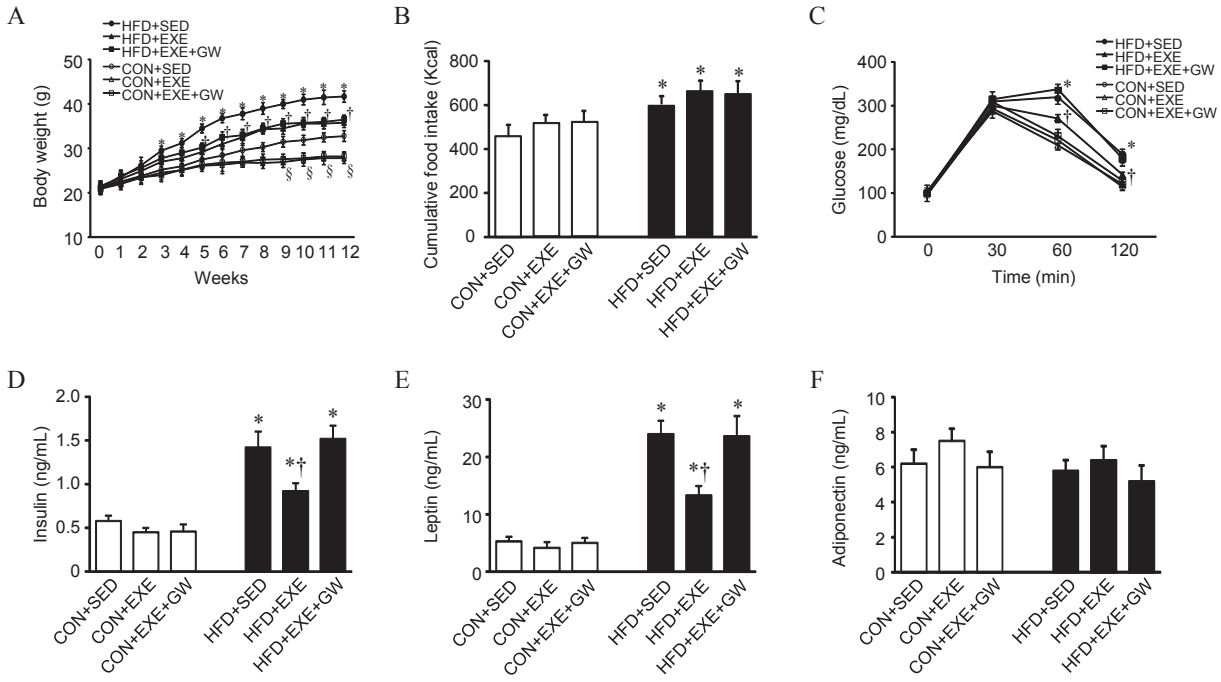

Fig. 1. Effects of voluntary exercise (EXE) on body weight (A), cumulative food intake (B), glucose tolerance test (C), plasma insulin (D), leptin (E) and adiponectin (F) levels in mice fed a control diet (CON) or a high-fat diet (HFD) for 12 weeks. SED: sedentary; GW: PPAR-γ antagonist GW9662. For A and B: *P < 0.05 vs. CON + SED; †P < 0.05, HFD + EXE or HFD + EXE + GW vs. HFD + SED; §P < 0.05, CON + EXE or CON + EXE + GW vs. CON + SED. For C–F: *P < 0.05 vs. CON + SED; †P < 0.05, HFD + EXE vs. HFD + SED or HFD + EXE + GW.

training did not alter glucose tolerance in control animals, but it significantly improved glucose tolerance in HFD animals. Fasting plasma insulin and leptin levels were markedly higher in HFD-sedentary mice than in control-sedentary group (Fig. 1D and E). Exercise significantly reduced the levels of both parameters in HFD mice, whereas it had no effects in control animals. Of note, GW9662 completely inhibited the effects of exercise on all these parameters in HFD animals. No significant differences in plasma adiponectin levels were observed among the experimental groups (Fig. 1F).

3.3. Voluntary exercise prevents colonic inflammation in HFD-induced obese mice

As shown in Fig. 2, HFD-sedentary mice had significantly increased protein expression of TNF-α, IL-1β and COX-2 in the colon as compared to control-sedentary animals. Exercise completely inhibited the increases in all these parameters and GW9662 abolished these inhibitory effects in HFD mice. In contrast, exercise alone or combination of exercise with GW9662 did not alter expression of these inflammatory mediators in control animals. There were no differences in IL-6 expression across the six experimental groups.

3.4. Voluntary exercise suppresses colonic NF-κB activity in HFD-induced obese mice

NF-κB, which is known to be controlled upstream by the cytoplasmic IκBα, is a key regulator of tissue inflammation. HFD-induced colonic inflammation has been shown to be mediated by activation of NF-κB, which stimulates synthesis and releases of multiple inflammatory mediators. These inflammatory mediators may in turn facilitate activation of NF-κB, thus inducing intestinal inflammatory state [17]. We therefore examined the effect of exercise on NF-κB activity in the colons by measuring NF-κB p65 DNA binding activity in nuclear extract and its inhibitor IκBα level in cytoplasmic extract. As shown in Fig. 3, compared with control-sedentary group, HFD-sedentary mice had markedly increased NF-κB p65 DNA binding activity, which was associated with a reduction of IκBα protein expression in the colons. Exercise completely inhibited NF-κB p65 DNA binding activity and reversed IκBα protein expression, whereas GW9662 abrogated these beneficial effects of exercise in HFD-animals. Notably, neither NF-κB p65 DNA binding activity nor IκBα protein expression was changed by exercise alone or combination of exercise with GW9662 in control animals.

3.5. Voluntary exercise selectively elevates colonic PPAR-γ activity in both control and HFD-induced obese mice

To examine whether exercise inhibited colonic NF-κB activity and prevented the expression of inflammatory mediators in HFD-induced obesity by increasing colonic PPAR-γ activity, we next evaluated the effects of exercise on colonic PPAR-γ expression and activity. As shown in Fig. 4, PPAR-γ protein expression and its DNA binding activity in the colon were significantly decreased in HFD-sedentary mice compared with control-sedentary group. Importantly, exercise markedly increased PPAR-γ expression and its activity in both control and HFD animals, whereas these increases were completely abolished by GW9662. Interestingly, there were no significant differences in expression and activity of PPAR isoforms PPAR-α or PPAR-β across the experimental groups.

4. Discussion

The present study demonstrates for the first time that HFD-induced obesity down-regulates colonic PPAR-γ activity, and voluntary exercise training prevents inflammation in the colons in HFD-induced obesity by modulation of colonic PPAR-γ activity.

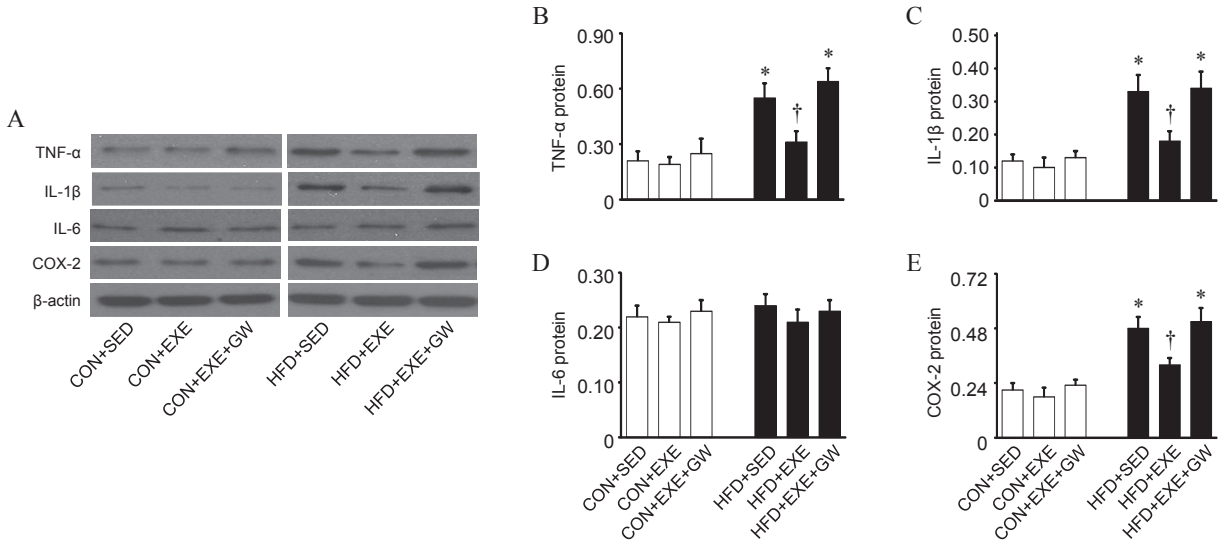

Fig. 2. Representative Western blots (A) and quantitative comparison of protein levels for proinflammatory cytokines TNF-α (B), IL-1β (C), IL-6 (D) and COX-2 (E) in the colons. *P < 0.05 vs. CON + SED; †P < 0.05, HFD + EXE vs. HFD + SED or HFD + EXE + GW.

We found that 12 weeks of voluntary exercise was associated with a partial reduction in body weight gain, a concomitant improvement in glucose tolerance, insulin sensitivity and leptin resistance in mice with diet-induced obesity, although increased total food intake was unchanged by exercise. These observations are in agreement with the results of a previous study [11], suggesting that voluntary exercise effectively attenuates obesity and improves metabolic disorders induced by HFD.

It is widely accepted that obesity and the metabolic syndrome are associated with low-grade systemic inflammation, despite the fact that the molecular origin of the inflammation is unclear [18]. Although adipose tissue is considered as a major source of inflammation in the development of obesity, emerging evidence suggests that a HFD promotes inflammation in the gastrointestinal tract which is thought to be another potential source of inflammation associated with HFD-induced obesity [19]. It has been suggested that intestinal inflammation is an early response to HFD and may play an important role in the onset of HFD-induced obesity and obesity-related metabolic disorders [20]. In addition, obesity-induced intestinal inflammation is conspicuously associated with colon cancer [5]. The present findings of decreased cytoplasmic IκBα expression and increased NF-κB p65 DNA binding activity in the colon of obese mice indicates activation of this pro-inflammatory transcription factor signaling pathway in response to HFD-induced obesity. Degradation of IκBα may lead to disinhibition of NF-κB in the cytosol with subsequent phosphorylation and translocation of NF-κB subunits p65 and p50 to the nucleus, inducing transcription and expression of several inflammatory cytokines in the colon and overall promotion of a pro-inflammatory state. The results of the present study showing increases in expression of the inflammatory cytokines TNF-α and IL-1β as well as COX-2 in the colons of obese mice are consistent with this process. These observations are in agreement with previous reports in both obese human subjects [21] and animal models of obesity [17].

A number of studies have shown that exercise exerts some of its beneficial health effects by inducing anti-inflammatory actions [6]. Cross-sectional studies reveal an association between physical inactivity and low-grade systemic inflammation in elderly people [22,23] and in patients with intermittent claudication [24]. Moreover, the finding in longitudinal studies that regular exercise training leads to a reduction in CRP level suggests that the exercise as such may suppress systemic low-grade inflammation [6]. Several

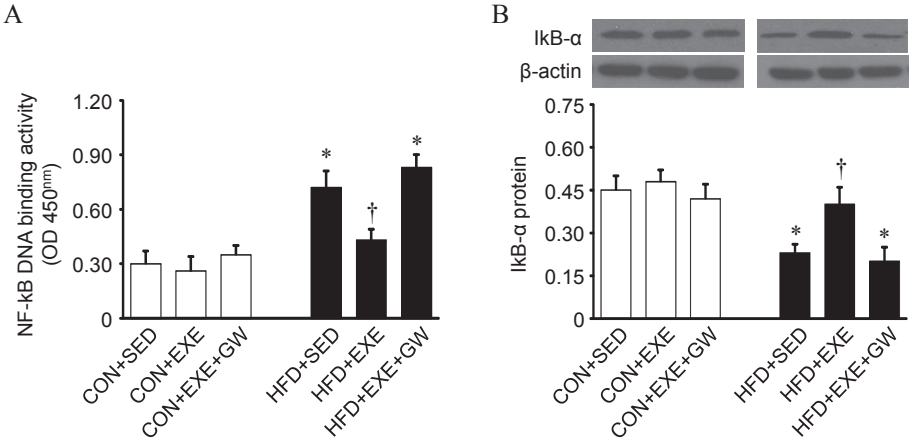

Fig. 3. NF-κB p65 DNA binding activity (A) and its inhibitory protein IκBα expression (B) in the colons. *P < 0.05 vs. CON + SED; †P < 0.05, HFD + EXE vs. HFD + SED or HFD + EXE + GW.

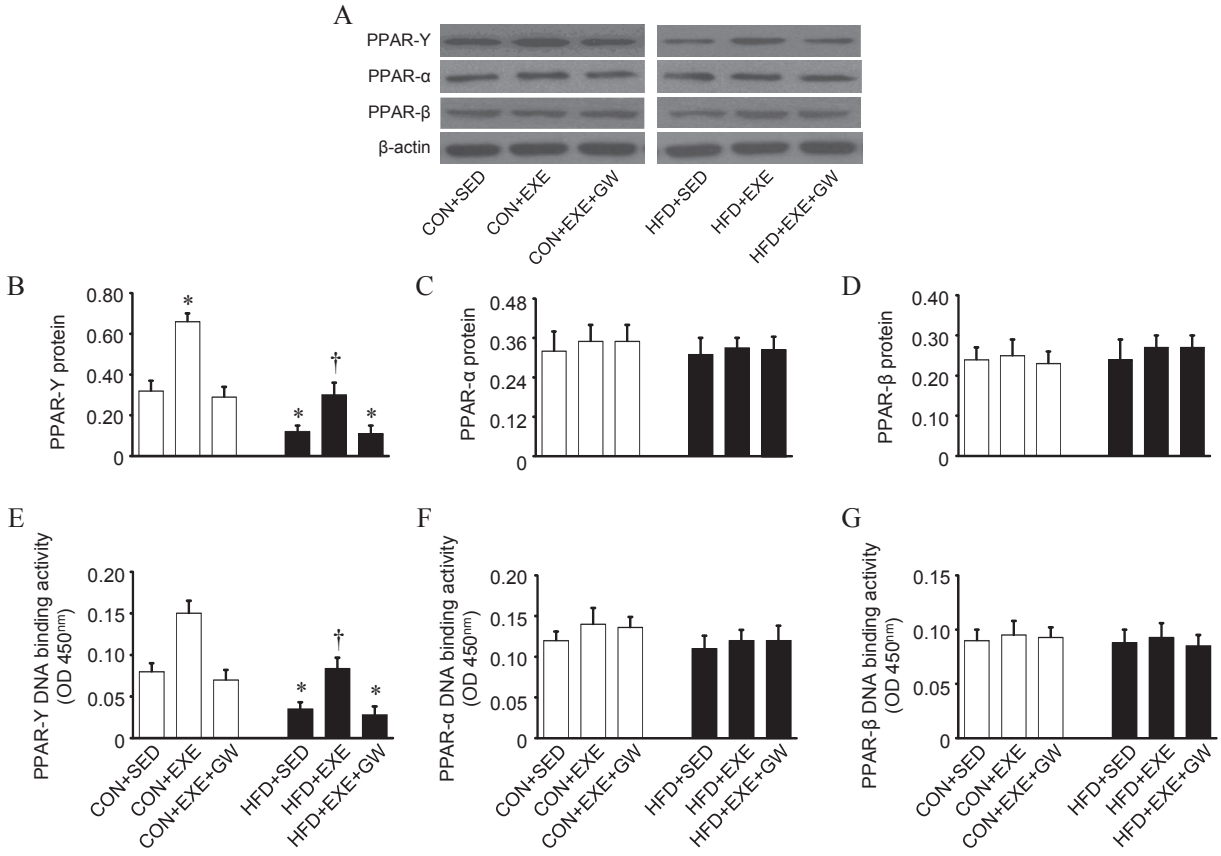

Fig. 4. Effects of EXE on protein levels (A–D) and DNA binding activity (E–G) of PPAR-γ, PPAR-α and PPAR-β in the colons. *P < 0.05 vs. CON + SED or CON + EXE + GW; †P < 0.05, HFD + EXE vs. HFD + SED or HFD + EXE + GW.

studies have recently reported that voluntary exercise attenuates obesity-associated inflammation in adipose tissue in obese animal models [11,25]. However, to our knowledge there is no direct evidence that voluntary exercise can prevent inflammation in the colons in obesity. Our study extends these prior findings by showing that voluntary exercise exerts potent anti-inflammatory actions in the colons in HFD-induced obesity, including inhibition of NF-κB activation and reductions in expression of inflammatory mediators to levels similar to those observed in control group.

To explore the possible mechanism by which voluntary exercise attenuates colonic inflammation, we examined the expression and activity of PPAR-γ in the colons. PPAR-γ is a member of the nuclear receptor superfamily of transcription factors that play an important role in regulating lipid metabolism and insulin resistance [26]. In addition, PPAR-γ is a key regulator of the inflammatory response [26]. It has been demonstrated that PPAR-γ plays a pivotal role in the regulation of inflammatory signaling pathways by acting on transcription factors, including NF-κB [27,28]. Activation of PPAR-γ suppresses activation of mucosal NF-κB, thus inhibiting production of multiple pro-inflammatory cytokines, such as IL-1β, TNF-α [27]. The colon is a major tissue highly expressing PPAR-γ in epithelial cells, macrophages and lymphocytes [29]. Numerous studies have shown that activation of PPAR-γ in the colons by synthetic PPAR-γ agonists inhibit inflammation and reduce disease severity in various experimental models of colitis [27,28]. In contrast, disruption of PPAR-γ expression in mouse colonic epithelial cells increases susceptibility to dextran sulfate sodium-induced inflammation and ulcerative colitis [30]. In current study, we found that expression and activity of PPAR-γ, but not PPAR isoform PPAR-α and PPAR-β, were significantly decreased in the colons of HFD-induce obese mice. This result confirms a previous report [13], indicating that down-regulation of colonic PPAR-γ in obesity is selective; PPAR-γ rather than PPAR-α and PPAR-β may be implicated in obesity-associated inflammation in the colons. We speculate that decreased PPAR-γ activity in the colons may facilitate the inflammatory response and colon carcinogenesis in obesity. The mechanism and signaling pathways responsible for down-regulation of colonic PPAR-γ in obesity remain to be elucidated in the future.

Exercise is known to upregulate PPAR-γ expression and activity within skeletal muscle to promote mitochondrial biogenesis, aerobic respiration, and other exercise-triggered benefits [14]. In addition, recent study reported that exercise led to generation of PPAR-γ ligands in the plasma that activated PPAR-γ signaling within circulating monocytes, contributing to anti-inflammatory effects [15]. In the present study, we found that 12 weeks of voluntary exercise significantly increased PPAR-γ expression and activity in the colons in both control and HFD animals, thus providing the direct evidence that exercise is associated with increased PPAR-γ activity in the colons. More importantly, we observed that exercise-induced beneficial effects in metabolic disorders and decreases in the expression of colonic inflammatory mediators were completely abrogated by concomitant treatment with a specific PPAR-γ antagonist GW9662, which inhibited exercise-induced increases in colonic PPAR-γ expression and activity. These findings indicate that improved metabolic disorders and reduced inflammation by voluntary exercise are mediated by activation of colonic PPAR-γ. Interestingly, exercise increased PPAR-γ expression and activity but did not alter inflammatory mediator expression in the colons in control group, because no differences in expression of inflammatory mediators were observed between

exercise control and sedentary control animals, suggesting that changes in colonic PPAR-γ expression may not influence inflammatory mediator expression under normal conditions.

In conclusion, the present study demonstrates that decreased PPAR-γ activity in the colons of HFD-induced obesity may facilitate the inflammatory response and colon carcinogenesis. Voluntary exercise prevents colonic inflammation in HFD-induced obesity by up-regulating PPAR-γ activity. The results from this study indicate a potential role of colonic PPAR-γ in mediating the protective effects that voluntary exercise has on colon tissue when presented with an inflammatory insult. Moreover, this study may also provide new insights into the mechanisms by which voluntary exercise exerts beneficial effects on preventing the obesity-associated colon cancer in these high-risk populations.

Conflict of interest

None.

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