



Sodium butyrate recovers high-fat diet-fed female Wistar rats from glucose dysmetabolism and uric acid-associated cardiac tissue damage

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Abstract

Increased global consumption of high-fat/high-calorie diet has led to higher incidence of the multifactorial cardiometabolic syndrome especially among women. The links between glucose deregulation and eventual mortal cardiac diseases are still being investigated. However, several reports have implicated elevated uric acid (UA) in the progression of metabolic disorders especially during high-fructose diet. Also, butyrate (BUT) a short-chain fatty acid is being identified with intriguing therapeutic potentials in metabolic disorders. We therefore hypothesized that high-fat diet-induced glucose deregulation and cardiac tissue damage are associated with elevated UA and attenuated by BUT in female rats. Twenty-four 10-week-old female Wistar rats with weights ranging from 135 to 150 g were treated with normal rat chow and distilled water (*po*) or sodium butyrate (200 mg/kg; *po*) or high-fat diet and distilled water (*po*) or high-fat diet and sodium butyrate. Treatments lasted for 6 weeks. Results showed that high-fat diet caused glucose dysmetabolism, elevated plasma triglyceride (TG), total cholesterol (TC), corticosterone, malondialdehyde (MDA), plasma and cardiac UA, and lactate dehydrogenase (LDH). High-fat diet also led to depressed reduced glutathione (GSH). Histological analysis of cardiac tissue showed cellular infarction, infiltration, and fibrosis in high-fat diet-fed rats. However, all these effects were ameliorated by BUT treatment. The findings here showed that high-fat diet resulted in glucose dysmetabolism and cardiac tissue damage through a UA-dependent mechanism and that BUT can protect against high-fat diet-induced cardiometabolic disorders through UA suppression and augmentation of glutathione antioxidant defenses.

Keywords High-fat diet · Sodium butyrate · Uric acid · Oxidative stress · SCFA

Introduction

High-fat diet (HFD) and obesity are considered to elicit low-grade inflammation and cardiometabolic diseases (CMD) (Johnson et al. 2012; Wellen and Hotamisligil 2005) with high incidence among women. Eventual atherosclerotic cardiovas-

cular disease is ubiquitously associated with these diseases of metabolism. Studies have shown a compelling link between insulin resistance (IR)/glucose deregulation and increased occurrence of coronary artery disease, peripheral vascular diseases, myocardial infarction, cancer, and stroke (Wang et al. 2011; WHO 2013). Interest in the study of CMD and its multifactorial nature has heightened recently based on the alarming prevalence of cardiovascular disease due to hypertension and diabetes (Hossain et al. 2007). Although the involvement of lipotoxicity, inflammation, and oxidative stress in HFD/obesity-engendered CMD is already conceded, the mechanisms involved in cardiometabolic syndrome progression to various associated mortal pathologies are poorly understood.

Nevertheless, an array of data agreeably shows that intracellular uric acid (UA) can induce deleterious inflammatory events and oxidative stress in vascular cells and adipocytes (Masuo et al. 2003; Kodama et al. 2009; Lee 2009). In addition, a range of abnormalities associated with UA are often

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regarded part of cardiometabolic syndrome (De Moura et al. 2009). UA has been shown to contribute to cardiometabolic syndrome via mechanisms including induction of gene expression of chemokines and growth factors leading to inflammatory responses (Corry et al. 2008), oxidative stress leading to cellular damage, inflammation and fibrosis (Sui et al. 2008; Chao et al. 2008; Sautin et al. 2007), and activation of arginase with consequent inhibition of nitric oxide (NO) possibly leading to IR (Feig et al. 2008).

Another increasingly proposed mechanism in the development of cardiometabolic syndrome is altered colonic formation of short-chain fatty acids (SCFAs) and variation in the composition of gut microbiome (Topping and Clifton 2001). SCFAs are products of complex carbohydrate and digestible fiber fermentation in the colon especially by anaerobic gut microbiota bacteria (Cummings and Englyst 1987). Over 90% of the SCFAs present in the colon are represented by acetate, propionate, and butyrate (BUT) (Mortensen and Clausen 1996). Recently, studies have identified alterations in the gut microbiome as a causative factor in the pathogenesis of metabolic syndrome such as obesity and diabetes (Backhed et al. 2004; Ley et al. 2006). In addition, high-fat diet has been shown to reduce the formation of BUT by the gut microbiome with an associated inflammation, and ectopic fat accumulation in the liver. These effects were also shown to be ameliorated by adding BUT-producing dietary fiber to the animal feed (Jakobsdottir et al. 2013). Also, SCFA treatment reportedly ameliorates metabolic syndrome, colitis, kidney disease, and airway disease in diet-induced obesity in mice (Maslowski et al. 2009). There is however dearth of information on the effects of SCFAs or altered microbiome on the cardiac tissue during diet-induced metabolic derangement. In the present study, high-fat diet given to female rats was used to induce glucose dysregulation and cardiac derangement. Sodium butyrate was administered to high-fat diet-fed female rats. Plasma and cardiac uric acid levels, oxidative stress/stress makers (lactate dehydrogenase (LDH) malondialdehyde (MDA), and plasma corticosterone), antioxidant defense marker (reduced glutathione (GSH)), histological analysis, and glucoregulation were considered to arbitrate high-fat diet-induced cardiometabolic syndrome. The aim was to verify the association of uric acid with high-fat diet-induced glucose deregulation and cardiac tissue damage and to examine the effect of SCFA, BUT as supplement on the established metabolic status.

Materials and methods

Animals

All experimental protocols were conducted according to the guidelines for the use and care of experimental animals and it was approved by the College Ethical Review Committee,

College of Medicine and Health Sciences, Afe Babalola University, Nigeria, in accordance with guidelines of the National Institutes of Health Guide (NIH) for the Care and Use of Laboratory Animals, and every effort was made to minimize both the number of animals used and their suffering. Twenty-four (24) adult female rats with weights ranging between 135 and 150 g were used for the study. Rats had unrestricted access to standard rat chow and tap water. After 1 week of acclimatization, the animals were randomly assigned to 4 groups of $n = 6$ each. Rats were maintained under standard environmental conditions of temperature, relative humidity, and 12-h dark/light cycle. Body weight was also monitored for all the groups.

Treatment

The control group received distilled water (vehicle; *po*) daily. The HFD group received high-fat rich diet. The BUT group received sodium butyrate (200 mg/kg body weight) daily, and the HFD + BUT group received a combination of high fat with sodium butyrate daily. The treatment lasted for 6 weeks.

Sample preparation

Finally, after 6 weeks of treatment, the rats were anesthetized with pentobarbital sodium. Blood was collected by cardiac puncture into heparinized bottles, accordingly. Blood collected in heparinized bottle was centrifuged at 3000 rpm for 5 min. Plasma was stored frozen until needed for biochemical assay.

Oral glucose tolerance test and insulin resistance

Glucose challenge test was performed 48 h before the end of the experiment. The rats were kept in fasting condition for 12 h overnight. Blood sample was collected by tail cut method before glucose load and blood glucose level are assessed by a glucometer (ONETOUCH®-Life Scan, Inc., Milpitas, CA, USA), and it was denoted as 0th time point. Glucose (2 g/kg *bw*) was administered orally (*po*) and blood glucose was assessed subsequently after 30, 60, 90 and 120 min. Glucose tolerance was expressed as a function of the area under the oral glucose tolerance test (OGTT) curve (AUC) and postload glucose responses. The IR was determined using the homeostasis model assessment for insulin resistance (HOMA-IR = fasting glucose (mmol/l) $\times$ fasting insulin (μ U/l)/22.5).

Biochemical assays

The plasma levels of corticosterone were estimated using ELISA kits (Elabscience Biotechnology Co., Ltd., Wuhan, China). Insulin was also determined using ELISA kit (Ray Biotechnology, Cruz, Canada). The biological markers of

dyslipidemia including total cholesterol (TC), triglyceride (TG), and high-density lipoprotein-cholesterol (HDL-C) were estimated by standardized enzymatic colorimetric methods using assay kit obtained from Fortress Diagnostics Ltd. Antrim, UK. The atherogenic indices (TC/HDL-C and TG/HDL-C ratios) were estimated.

Histopathology of rat's heart

The ovarian tissues were excised and fixed in 10% formalin solution immediately after removal. The specimens were dehydrated in ascending grades of alcohol, cleared in xylene, and embedded in paraffin. Serial sections were cut, stained appropriately, and examined by the light microscope for evaluation of histopathological changes. The same pathologist, who had no knowledge of the experimental data, reviewed the histological slides.

Statistical analysis

All experimental data were expressed as means $\pm$ SD. Statistical significance for measured variables was determined by one-way analysis of variance (ANOVA) for the comparison of the mean values of variables among the groups. Bonferroni's test was used to identify the significance of pairwise comparison of mean values among the groups. Statistically significant differences were accepted at $p < 0.05$. Statistical group analysis was performed with SPSS statistical software.

Results

Effect of sodium butyrate on body weight and body weight change in high-fat diet-fed rats

Body weight of all the animals increased from initial to final weight (Table 1). The body weight change (difference between final and initial body weight) was not affected by HFD or BUT treatment singly or in combination with HFD compared with control (Table 1).

Table 1 Body weight (initial and final) and fasting blood glucose

	CON	BUT	HFD	HFD + BUT
Body weight (g)				
Initial	141.1 $\pm$ 19.4	142.2 $\pm$ 17.0	141.3 $\pm$ 23.5	142.6 $\pm$ 21.1
Final	159.6 $\pm$ 18.0	157.8 $\pm$ 10.6	157.9 $\pm$ 9.8	154.9 $\pm$ 22.7
Fasting blood glucose (mmol/l)	3.0 $\pm$ 0.5	3.0 $\pm$ 0.2	3.2 $\pm$ 0.5	2.9 $\pm$ 0.5

Values are expressed as mean $\pm$ SD of 6 rats per group; * $p < 0.05$ vs control, # $p < 0.05$ vs HFD group. Data were analyzed by one-way ANOVA and Bonferroni's post hoc analysis; CON control, BUT sodium butyrate, HFD high-fat diet

Effect of sodium butyrate on postload glycaemia, AUC of OGTT, insulin, and insulin resistance in high-fat diet-fed rats

High-fat diet increased 1-h postload glycaemia, AUC of OGTT, insulin level, and HOMA-IR (Fig. 1) in high-fat-fed rats. Whereas, sodium butyrate in normal diet-fed rats did not affect the 1-h postload glycaemia, AUC of OGTT, insulin level, and HOMA-IR when compared with CON group (Fig. 1). High-fat diet-fed rats treated with sodium butyrate attenuated the high-fat diet-induced glucose dysregulation indicated by attenuated 1-h postload glycaemia, AUC of OGTT, insulin level, and HOMA-IR when compared with HFD group (Fig. 1). The results also showed that glucoregulation markers in sodium butyrate-treated high-fat diet-fed rats were comparable with the CON group (Fig. 1).

Effect of sodium butyrate on histology of the heart in high-fat diet-fed rats

The histology of the heart shows that high-fat diet disrupted cardiac tissue architecture revealing cellular infarction, infiltration, and fibrosis (Fig. 2c), whereas the sodium butyrate-treated group and control group which were given normal diet showed normal cardiac tissue architecture (Fig. 2a, b). However, sodium butyrate recovers the cardiac tissue of high-fat-fed rats from infarction and infiltration showing only mild fibrosis as seen in Fig. 2d.

Effect of sodium butyrate on plasma and cardiac lipids in high-fat diet-fed rats

High-fat diet-fed rats had increased plasma triglyceride (Fig. 3a), total cholesterol (Fig. 3b), triglyceride/high-density lipoprotein cholesterol ratio (Fig. 3c), and total cholesterol/high-density lipoprotein cholesterol ratio (Fig. 3d) compared with control. Conversely, the cardiac triglyceride (Fig. 3e), total cholesterol (Fig. 3f), triglyceride/high-density lipoprotein cholesterol ratio (Fig. 3g), and total cholesterol/high-density

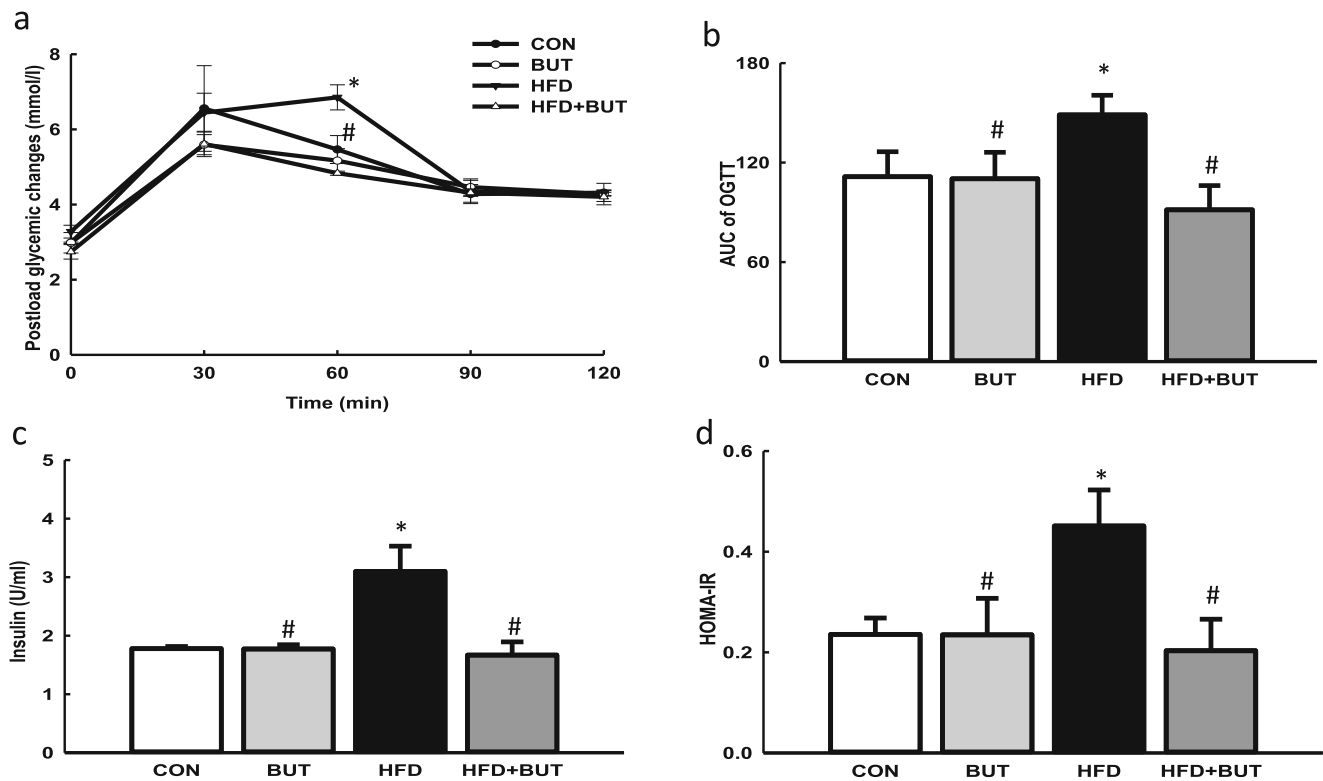


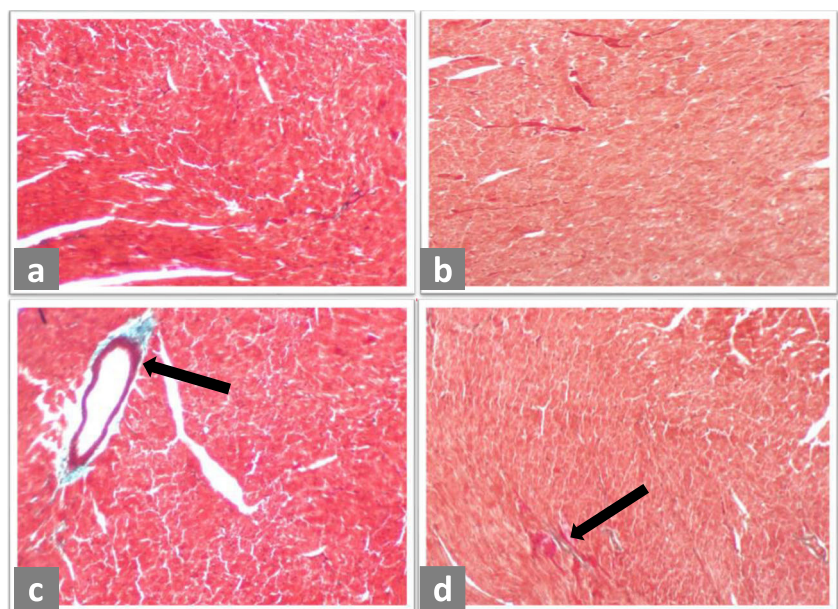
Fig. 1 BUT improves glucose homeostasis in female rats following high-fat diet for 6 weeks. BUT improved 1-h postload glycemia (**a**), area under curve of oral glucose tolerance (**b**), fasting insulin level (**c**), and HOMA-IR (**d**). Values are expressed as mean $\pm$ SD of 6 rats per group; * $p < 0.05$

vs control, # $p < 0.05$ vs HFD group. Data were analyzed by one-way ANOVA and Bonferroni's post hoc analysis; CON control, HFD high-fat diet, BUT sodium butyrate

lipoprotein cholesterol ratio (Fig. 3H) in high-fat diet-fed rats did not change compared with control. The butyrate-treated normal diet-fed rats had unaltered plasma and cardiac lipids compared with the control except for slight increase in plasma

of the lipid ratios (Fig. 2). Nevertheless, high-fat diet-fed rats treated with sodium butyrate showed attenuated plasma but unaltered cardiac triglyceride, total cholesterol, triglyceride/high-density lipoprotein cholesterol ratio, and total

Fig. 2 Photomicrographs of Masson's Trichrome staining of rat heart sections show **a** normal architecture and cardiac muscle fiber, **b** normal architecture and cardiac muscle fiber in sodium butyrate-treated rats, **c** disrupted myocardial tissue with cellular infarction, infiltration, and fibrosis in high-fat diet-treated rats, **d** and preserved cardiac muscle fiber with mild fibrosis in high-fat plus sodium butyrate-treated rat ($\times 100$, longitudinal section)



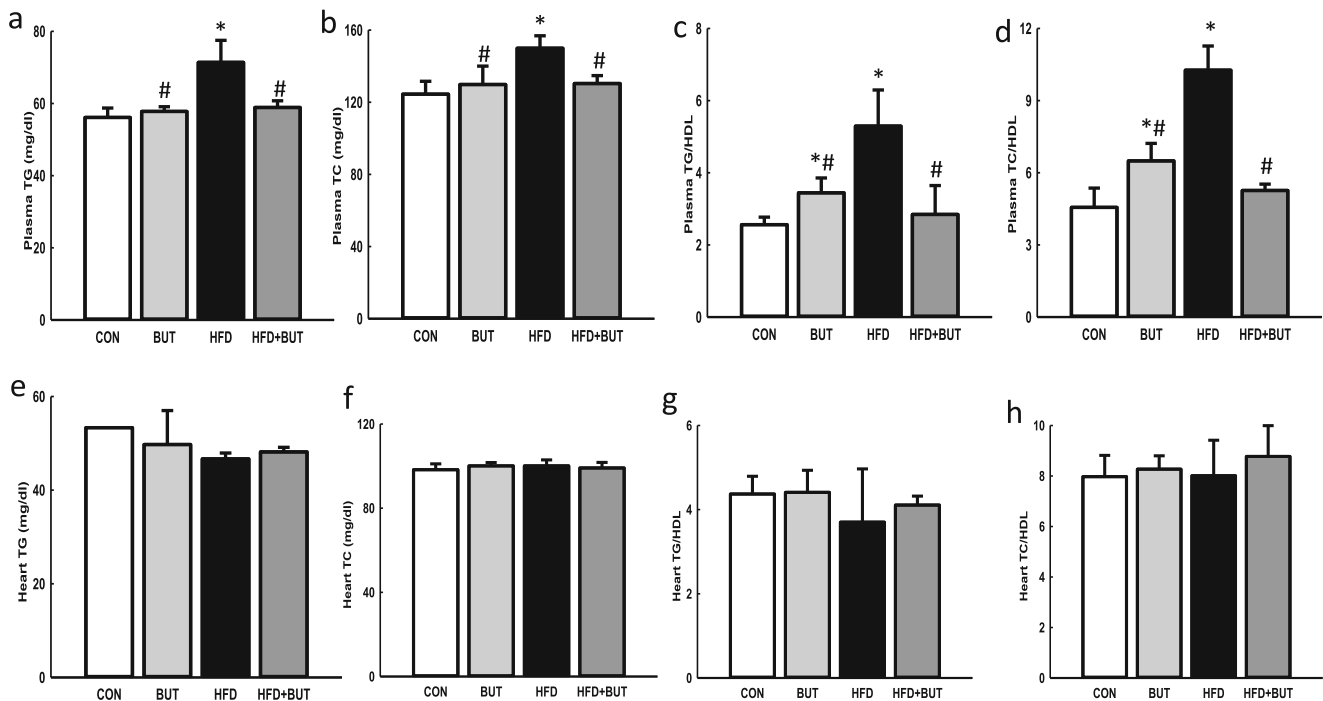


Fig. 3 BUT reduces plasma lipids but not cardiac lipids in female rats following high-fat diet for 6 weeks. BUT reduces plasma triglyceride (TG) (a), total cholesterol (TC) (b), triglyceride-high-density lipoprotein ratio (c), and total cholesterol-high-density lipoprotein ratio (d). BUT did not alter cardiac triglyceride (TG) (e), total cholesterol (TC) (f),

triglyceride-high-density lipoprotein ratio (g), and total cholesterol-high-density lipoprotein ratio (h). Values are expressed as mean $\pm$ SD of 6 rats per group; $^*p < 0.05$ vs control, $^{\#}p < 0.05$ vs HFD group. Data were analyzed by one-way ANOVA and Bonferroni's post hoc analysis; CON control, HFD high-fat diet, BUT sodium butyrate

cholesterol/high-density lipoprotein cholesterol ratio (Fig. 3) compared with high-fat diet group.

Effect of sodium butyrate on plasma and cardiac uric acid in high-fat diet-fed rats

High-fat diet increased plasma and cardiac uric acid by over twofold compared with control (Fig. 4). Butyrate treatment to both normal and high-fat diet-fed rats showed attenuated plasma and cardiac uric acid compared with the high-fat diet group without butyrate treatment, which remained unaltered compared with the control group (Fig. 4).

Effect of sodium butyrate on plasma and cardiac lactate dehydrogenase in high-fat diet-fed rats

High-fat diet increased plasma and cardiac lactate dehydrogenase compared with the control group (Fig. 5). Butyrate treatment to both normal and high-fat diet-fed rats showed attenuated plasma and cardiac lactate dehydrogenase compared with the high-fat diet group without butyrate treatment. However, plasma and cardiac lactate dehydrogenase remained unaltered in both normal and high-fat diet-fed rats treated with sodium butyrate compared with the control group (Fig. 5).

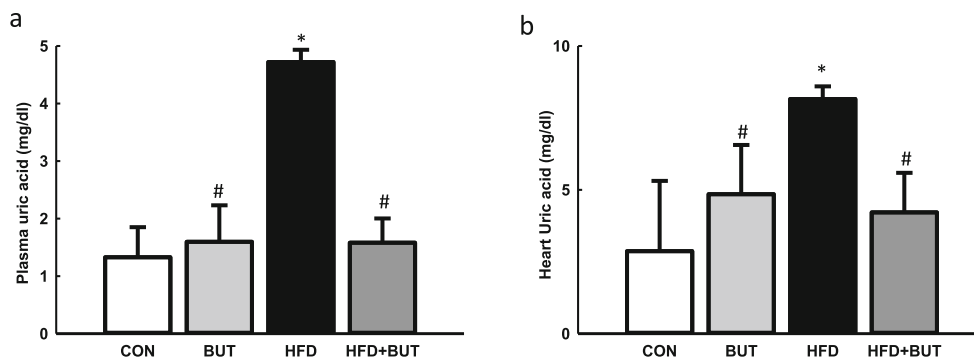


Fig. 4 BUT ameliorates plasma and cardiac uric acid in female rats following high-fat diet for 6 weeks. BUT reduces plasma uric acid (a), BUT reduces cardiac uric acid (b). Values are expressed as mean $\pm$ SD of

6 rats per group; $^*p < 0.05$ vs control, $^{\#}p < 0.05$ vs HFD group. Data were analyzed by one-way ANOVA and Bonferroni's post hoc analysis; CON control, HFD high-fat diet, BUT sodium butyrate

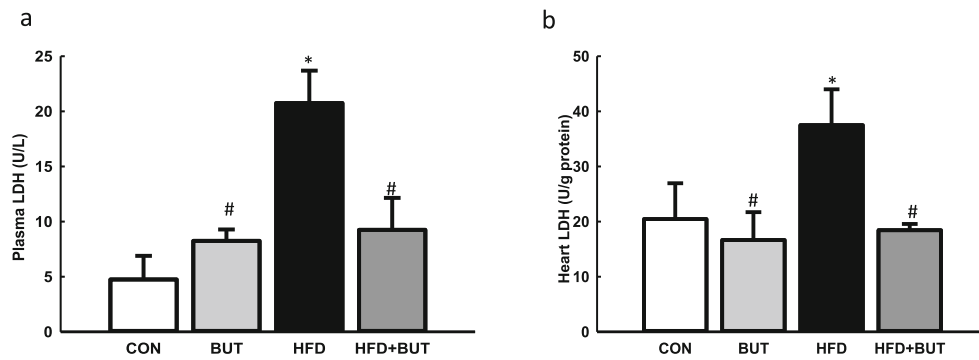


Fig. 5 BUT ameliorates lactate dehydrogenase in female rats following high-fat diet for 6 weeks. BUT reduces plasma lactate dehydrogenase (a), BUT reduces cardiac lactate dehydrogenase (b). Values are expressed as

mean $\pm$ SD of 6 rats per group; * p < 0.05 vs control, # p < 0.05 vs HFD group. Data were analyzed by one-way ANOVA and Bonferroni's post hoc analysis; CON control, HFD high-fat diet, BUT sodium butyrate

Effect of sodium butyrate on plasma and cardiac malondialdehyde and reduced glutathione in high-fat diet-fed rats

Plasma MDA but not cardiac MDA was increased in high-fat diet-fed rats compared with the control group (Fig. 6a, b). Plasma and cardiac GSH decreased in high-fat diet-fed rats compared with control. Conversely, sodium butyrate treatment in both normal diet and high-fat diet-fed rats attenuated plasma MDA compared with high-fat diet-fed rats, and augmented plasma and cardiac GSH with figures that are comparable with the control group (Fig. 6a, c and d). However, cardiac MDA was reduced in high-fat diet-fed rats treated with

butyrate compared with control and high-fat diet-fed rats without butyrate (Fig. 6b).

Effect of sodium butyrate on plasma and cardiac corticosterone in high-fat diet-fed rats

High-fat diet increased corticosterone compared with control (Fig. 7). Butyrate treatment to both normal diet and high-fat diet-fed rats attenuated plasma corticosterone compared with high-fat diet-fed rats without butyrate treatment and at levels comparable with the control group (Fig. 7).

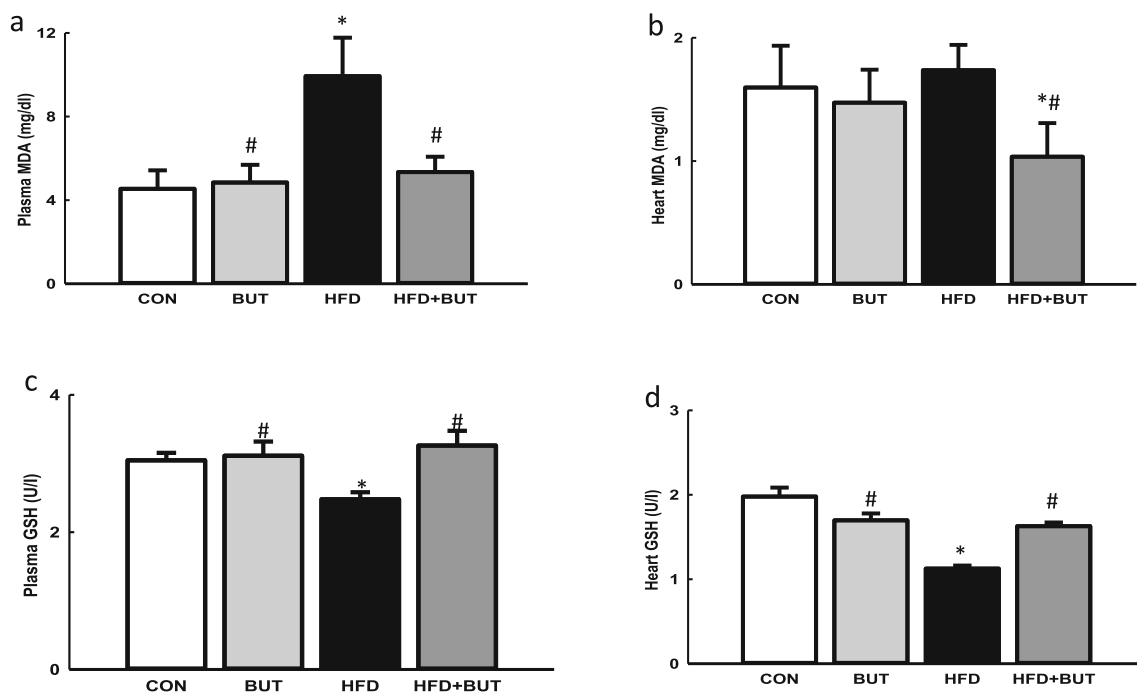


Fig. 6 BUT attenuates oxidative stress in female rats following high-fat diet for 6 weeks. BUT reduces plasma malondialdehyde (MDA) (a), cardiac malondialdehyde (MDA) (b). BUT increases plasma reduced glutathione (GSH) (c), cardiac reduced glutathione (GSH) (d). Values

are expressed as mean $\pm$ SD of 6 rats per group; * p < 0.05 vs control, # p < 0.05 vs HFD group. Data were analyzed by one-way ANOVA and Bonferroni's post hoc analysis; CTR control, HFD high-fat diet, BUT sodium butyrate

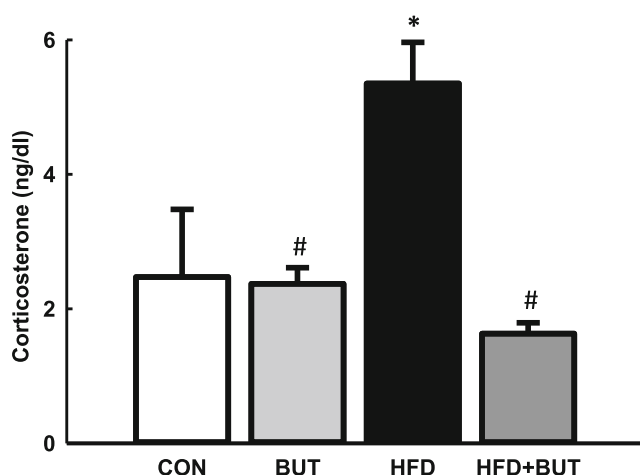


Fig. 7 BUT ameliorates corticosterone in female rats following high-fat diet for 6 weeks. BUT reduces plasma corticosterone level. Values are expressed as mean $\pm$ SD of 6 rats per group; * $p < 0.05$ vs control, # $p < 0.05$ vs HFD group. Data were analyzed by one-way ANOVA and Bonferroni's post hoc analysis; CTR control, HFD high-fat diet, BUT sodium butyrate

Discussion

The present study demonstrates that high-fat diet-induced cardiometabolic status is attended by altered uric acid production, depleted GSH, plausible oxidative stress-induced elevated corticosterone, and evidence of cardiac tissue fibrosis. The present study also shows that parallel treatment of high-fat diet-fed female rats with oral dose (200 mg/kg) of sodium butyrate for 6 weeks restored normalcy in glucoregulation, attenuated high-fat diet-induced elevated uric acid and corticosterone levels and protected cardiac tissue architecture and integrity. Hence, BUT may offer cardioprotection and play therapeutic roles in high-fat diet-induced deleterious events.

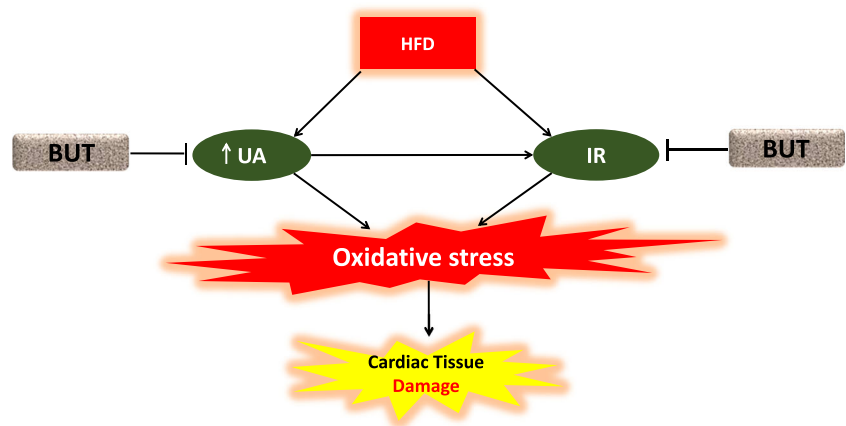
High-fat diet delivers increased fatty acids into the circulation which enters the adipocytes for storage. The excess fatty acids or spill over causes obesity-like deleterious metabolic effects through various suggested mechanisms including inhibition of mitochondrial function and biogenesis, activation of inflammatory signaling, inhibition of insulin signaling, increase in reactive oxygen species, and muscular and/or hepatic ectopic lipotoxic lipid accumulation (Martins et al. 2012). All these will lead to reduced tissue sensitivity to insulin and glucose deregulation. In line with the afore stated allusions, a 6-week high-fat diet herein caused glucose deregulation revealed by elevated 1-h postload glycemia, AUC of OGTT, plasma insulin level and HOMA-IR (Fig. 1). Researchers have conceded that insulin resistance/glucose dysmetabolism is the central event in cardiometabolic syndrome (De Fronzo 2010) and the present study has similar findings with a high-fat diet rat model of cardiometabolic syndrome. Also, decline in insulin sensitivity results in lipolysis and increased circulating FFA. This increases FFA delivery to non-adipose tissues (muscles and liver especially) leading to intracellular lipid accumulation and lipotoxicity (De Fronzo 2010).

In this study, evidence of cardiac ectopic fat accumulation was analyzed and it was found that in high-fat diet-fed rats, despite elevated plasma TG, TC, TG/HDL-C, and TC/HDL-C (Fig. 3), the cardiac status of these parameters remained normal or unaltered (Fig. 3). This shows that despite the evident insulin resistance, there was no ectopic lipid accumulation in the heart of high-fat diet-fed rats. These results on cardiac lipid after 6 weeks exposure to high-fat diet can be explained by the Randle effect (Randle et al. 1963). Randle et al. showed that elevation of fatty acid supply to isolated heart decreased glycolytic flux and increased fatty acid oxidation. The heart which is not a peripheral organ prefers fatty acid as metabolic fuel and allows the Randle effect when fatty acid delivery increases. A limitation of this study is that cardiac glycogen level was not analyzed which could inform cardiac insulin resistance or accumulation of glucose due to reduced glycolytic activity. Another possible consequence of the Randle effect in the heart is increased LDH activity in favor of lactate production which is in accord with the inhibition of glucose utility and supports a progressing oxidative stress and tissue damage. Cardiac LDH activity was elevated with high-fat diet compared with control and other experimental groups in this study (Fig. 5b). However, further studies that include analysis of lactate accumulation and mitochondrial function will possibly further support the evidences in this study.

In order to analyze the biochemical evidence of oxidative stress, MDA and GSH levels were measured in the plasma and heart of animals in this study. MDA is the product of lipid peroxidation especially at the cell membrane which liberates superoxides. GSH is an antioxidant dependent on glucose-6-phosphate dehydrogenase activity in the pentose phosphate pathway (Hecker et al. 2013). The elevated MDA in the plasma (Fig. 6a) and depressed plasma and cardiac GSH (Fig. 6c, d) in high-fat diet-fed rats here indicate oxidative stress with evidence of antioxidant depletion. The consequence of deregulated oxidant production is overt excess inflammatory response and tissue damage. This is corroborated in this study by the observation of an overt increased circulating corticosterone (Fig. 7), an anti-inflammatory hormone produced to compensate oxidative and/or inflammatory stress. In line with this, a previous study revealed that high-fat diet can increase inflammation (Jakobsdottir et al. 2013). Also, in obese and diet-induced conditions, it is already conceded that increased FFA through interaction with Toll-like receptor type 4 and through a variety of other mechanisms can result in inflammatory responses (De Fronzo 2010).

However, this study proposes the involvement of UA or UA-dependent mechanisms in the inflammatory responses and oxidative stress associated with high-fat diet. This study is the first to focus attention on UA production as a plausible mechanism and therapeutic target in combating cardiac derangement in high-fat diet-induced metabolic syndrome. Plasma and cardiac UA levels were elevated in high-fat diet-fed rats (Fig. 4a, b) in this study via

Fig. 8 Schematic diagram illustrating the likely pathway through which BUT interferes with the high-fat diet-induced uric acid-associated glucose deregulation, oxidative stress, and eventual cardiac tissue damage. *HFD* high-fat diet, *BUT* sodium butyrate, *UA* uric acid, *IR* insulin resistance



mechanisms of gene expression of chemokines, oxidative stress and NO inhibition (Corry et al. 2008; Sui et al. 2008; Chao et al. 2008; Sautin et al. 2007; Feig et al. 2008). UA can cause chronic inflammation and tissue damage. Further on the UA-engendered inflammatory response, UA can be a danger signal for the nucleotide-binding domain and leucine-rich repeat-containing family, pyrin domain containing 3 (NLRP3) inflammasome. The NLRP3 inflammasome is a cytosolic protein that induces inflammation in response to danger signals like damage-associated molecular patterns (urate crystals or cholesterol crystals). It is upregulated within the myocardium secondary to infarction especially in fibroblasts. Deficiency of NLRP3 strikingly improves myocardial function after ischaemia–reperfusion injury (Sandanger et al. 2013). The action of NLRP3 leads to maturation and release of interleukin 1 β which is an inflammatory cytokine. Therefore, modulation of NLRP3 inflammasome with NLRP3 inhibitors may represent plausible therapeutic step in the treatment of cardiac diseases with underlying inflammatory events. In congruence, histological analysis of cardiac tissue herein shows cellular infarction, infiltration, and cellular fibrosis (Fig. 2c). This indicates that probably, the UA-initiated mechanisms were potent enough to degenerate cardiac architecture. Yet, a more mechanistic study is required, to establish the link between high-fat diet and elevated cardiac UA accompanying cardiac tissue damage.

Not surprisingly, BUT treatment to high-fat diet-fed female rats ameliorated glucose deregulation and improved IR in this study. This outcome is in accord with findings from other studies: improved insulin sensitivity was realized after infusion of butyrate-producing intestinal microbiota from lean donors to male subjects with metabolic syndrome (Vrieze et al. 2012). Alteration of the gut microbiota composition leading to higher BUT production causes reduction in body weight gain and IR in high-fat diet-fed and obese mice (Yadav et al. 2013). BUT in this study also attenuated high-fat diet-induced plasma TC and TG (Fig. 3a, b) and oxidative stress marker, MDA (Fig. 6a, b) while improving cardiac GSH levels (Fig. 6c, d). For the first time, it is shown here that there is evidence BUT

recovers the heart of high-fat diet-fed female rats from oxidative stress. Prevention of oxidative stress may be the mechanism by which BUT protects against high-fat diet-induced inflammatory responses and tissue damage in the liver according to a previous study (MattaceRaso et al. 2013). In line with this BUT-led protection, this study shows that BUT also protected the heart of high-fat-fed rats against cellular infiltration, infarction, and overt fibrosis as indicated in attenuated LDH levels (Fig. 5a, b) and histological analysis (Fig. 2d). Nevertheless, these BUT effects were accompanied by attenuation of UA levels (Fig. 4a, b) and corticosterone (a glucocorticoid hormone which increases in response to stress) level (Fig. 7). These show how both the peripheral and cardiac UA-associated stress-related deleterious effects in high-fat-fed rats were abated by BUT. Therefore, this study is the first to show that BUT might protect against glucose deregulation and cardiac tissue damage through suppression of UA. Further work is therefore required to elucidate the molecular link between SCFAs and reduced UA production especially in the heart.

Conclusion

In summary, the present study demonstrates that UA is involved in high-fat diet-induced cardiometabolic syndrome. However, data here shows that the UA-associated events in high-fat diet will chronically engender cardiac tissue damage. Interestingly, with UA suppression and augmentation of GSH, BUT treatment showed plausible beneficial glucoregulatory, anti-inflammatory, and antioxidant properties which were potent enough to confer protection on the cardiac tissue preventing overt damage in high-fat diet-fed rats (Fig. 8). Therefore, BUT may be considered for the development of suitable therapeutic candidate in the treatment of metabolic syndrome and cardiac derangements associated with heightened UA.

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Authors' contributions C. Badejogbin is a postgraduate student under the joint supervision of O. Adeyanju and I. Adeosun; K. Olaniyi and O. Adeyanju conceived and designed the experiments. C. Badejogbin and O. Adeyanju conducted the experiments and K. Olaniyi contributed in statistical and data analyses. C. Badejogbin and D. Areola both wrote the manuscript and O. Adeyanju revised and edited the same. All authors read and approved the manuscript for publication.

Compliance with ethical standards

The investigation was conducted in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and was approved by the University ethical review committee, with protocol identification number NHREC17/12/2018, and every effort was made to minimize both the number of animals used and their sufferings.

Conflict of interest The authors declare that they have no conflicts of interest.

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