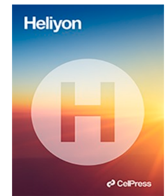
Heliyon 9 (2023) e22008

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Glucoregulatory effect of butyrate is associated with elevated circulating VEGF and reduced cardiac lactate in high fructose fed rats

Adewumi Oluwafemi Oyabambi [a,b], Olubayode Bamidele [b,*], Aindero Blessing Boluwatife [a], Lawrence Dayo Adedayo [b]

[a] Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, University of Ilorin, Ilorin, Nigeria
[b] Physiology Programme, College of Health Sciences, Bowen University, Iwo, Osun State, Nigeria

ARTICLE INFO

Keywords:
Sodium butyrate
HiSodium butyrate
High fructose drink
Glucoregulation
Vascular endothelial growth factor
Cardiometabolic disorders
Gh fructose drink

ABSTRACT

Background: High fructose diet has been linked with impaired body metabolism and cardiovascular diseases. Sodium butyrate (NaB) was documented to improve glucoregulation and cardiometabolic problems associated with high fructose diet (HFrD) but the mechanisms behind it are unclear. As a result, the purpose of this study was to look into the effects of NaB on VEGF and cardiac lactate in HFrD-induced dysmetabolism.

Methods: Twenty male Wistar rats of weight 130–140 g were assigned randomly after a week of acclimation into four groups: Control diet (CTR), High fructose drink (HFrD); 10 % (w/v), NaB (200 mg/kg bw), and HFrD + NaB (200 mg/kg bw). The animals were induced to be unconscious with 50 mg/kg of pentobarbital sodium intraperitoneally, blood samples were taken via cardiac puncture and cardiac tissue homogenates were obtained for Fasting Blood Sugar (FBS) and plasma insulin, cardiac glycogen, plasma and cardiac glycogen synthase, plasma and cardiac nitric oxide as well as vascular endothelial growth factor (VEGF).

Result: HFrD resulted in statistical elevation body and cardiac weight, plasma glucose, plasma insulin, cardiac lactate, glycogen and decreased nitric oxide level (NO) when compared with the control group. Administration of NaB reduced cardiac weight, blood glucose, plasma insulin, cardiac lactate while nitric oxide and glycogen increased ($P < 0.05$). NaB increased plasma glycogen synthase in normal rats, plasma and cardiac circulating VEGF in HFrD administered rats ($P < 0.05$) while no change was produced in plasma and cardiac glycogen synthase level of HFrD treated rats.

Conclusion: Sodium butyrate improves glucoregulation by reducing cardiac lactate and increasing circulating VEGF in HFrD-treated rats.

1. Introduction

Fructose is a simple carbohydrate found naturally in fruits, sugar, and honey [1]. As a result of its sweetness, palatability, and taste enhancement, it is now found in processed foods and beverages. It is largely consumed in Western diets [2]. Fructose consumption has

* Corresponding author. Physiology Programme, College of Health Sciences, P.M.B. 284, Bowen University, Iwo, Osun State, Nigeria.
E-mail addresses: adewumi.oyabambi@bowen.edu.ng (A.O. Oyabambi), olubayode.bamidele@bowen.edu.ng (O. Bamidele), ainderoblessing@gmail.com (A.B. Boluwatife), lawrence.adedayo@bowen.edu.ng (L.D. Adedayo).

https://doi.org/10.1016/j.heliyon.2023.e22008
Received 23 June 2023; Received in revised form 1 November 2023; Accepted 1 November 2023
Available online 7 November 2023
2405-8440/© 2023 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

risen since the 1970s. Between the 1970s and the early 2000s, the average fructose consumption *per* individual increased by about 32 %. During that time, there was a 41 % increase in total carbohydrate intake, which also indicated an upsurge in glucose intake [3]. Consuming foods high in fructose is thought to be one of the main contributors to the development of the metabolic syndrome by causing oxidative stress, which then results in hyperglycemia, insulin resistance, and obesity [4].

Dietary intake of fructose has been associated with certain human diseases [5–7]. A high-fructose diet is associated with an increase in the risk of diabetes, cancer, insulin resistance, non-alcoholic fatty liver disease, hypertension, dyslipidemia and obesity [1]. Lactate derived from fructose may also have an impact on total body energy balance. Excess intake of fructose results in endogenous glucose production and lipid synthesis in the liver [1,8]. Fructose has been shown to have a significant effect on gene expression, reduce cellular angiogenic potential, and disrupt endothelial vascular function [9].

The synthesis and maintenance of blood vessel structures is known as angiogenesis. It is essential for the physiological processes of the tissue as well as the development of illnesses like cancer and inflammation. It has been shown that the vascular endothelial growth factor (VEGF) plays crucial roles in both physiological and most pathological angiogenesis, including cancer [10]. Vascular endothelial growth factors (VEGFs) and vascular endothelial growth factor receptors (VEGFRs) control both angiogenesis and vascular endotheliogenesis, the early formation of blood vessels from cell precursors and pre-existing vessels, respectively [11]. In order to maintain different tissues at physiological levels and to treat ischemic diseases, VEGFs have the potential to promote angiogenesis [12]. Within the cardiovascular system, VEGF is crucial. Recent research has shown that cardiac myofibroblasts, non-endothelial cells with fibroblastic morphology, express VEGF [13].

A short-chain fatty acid called butyrate is formed in the colon by anaerobic bacteria fermenting dietary fibers [14]. Butyrate functions as a signal to regulate various cellular processes in addition to being a nutrient [15]. Dietary supplementation with butyrate has been shown to prevent high-fat diet-induced obesity and insulin resistance in mice [16–18] or non-alcoholic fatty liver disease in rats [19] through a mechanism involving the promotion of energy expenditure and induction of mitochondrial function. Butyrate is also thought to help delay the onset of metabolic syndrome due to its anti-inflammatory, anti-oxidative, improved insulin sensitivity, lipid-lowering, and anti-inflammatory effects [20]. The effect of NaB on vascular endothelial growth factor in humans and animals has produced conflicting results. It has been shown that administration increases the formation of anti-angiogenic vascular endothelial growth factor variants in human lung microvascular endothelial cells [21]. Katakami and colleagues demonstrated that sodium butyrate promotes angiogenesis by increasing the expression of vascular endothelial growth factor and its receptors in vascular endothelial cells [22]. Also, sodium butyrate was observed to improve insulin sensitivity and energy expenditure by increasing the level of VEGF in the adipose tissue of treated mice [23]. Owing to the conflicting results of sodium butyrate on VEGF expression in laboratory animals and the fact that lactate produced from fructose affect total body energy balance, the current study was therefore conducted to assess the effect of butyrate on circulating VEGF and cardiac lactate yield in high fructose diet-exposed rats.

2. Materials and methods

2.1. Experimental animal and study design

Twenty male Wistar rats in Ogbomosho, Oyo state. The rats, five (5) in each group were kept in hyg of age 6–7 weeks, weighing between 130 g and 140 g after a week of acclimatization, were used in the study. The rats were kept under standard environmental conditions, 40 % relative humidity, room temperature of about 25 °C and 12 h light/dark cycle. These rats were procurred from Funke Animal Breederienic cages with ample ventilation at the Animal House of the University of Ilorin in Ilorin, Kwara State. The acclimatization period lasted seven (7) days, during which time they were given access to drinking water and fed grower feed in pellet form (Vital poultry feed) made at Ogo-Oluwa feed mill, Sango', Ilorin. The administration was done for a period of six weeks and the study was conducted following the guideline of care and use of laboratory animals of the Ethical Committee of the Department of Anatomy, University of Ilorin.

2.2. Experimental procedure

Twenty male Wistar rats of 5 rats each (n = 5) were divided into four groups consisting of Control (CTR; normal chow), HFr drink; 10 % fructose (w/v), NaB (200 mg/kg) only [24] and NaB + HFr; 10 % fructose (w/v) given *per ostium* for six weeks. The rats were given no food overnight (12 h) on the final day of the experiment, and blood glucose levels were measured using a glucometer before sacrifice. The animals were sedated with 50 mg/kg intraperitoneal pentobarbital sodium [25], and blood samples were collected via cardiac puncture.

2.3. Biochemical assay

Fasting blood sugar levels were measured with a one-touch extra glucometer, and plasma insulin levels were determined using rat insulin ELISA kit (cat number:IS130D) from Ray Biotechnology, Inc. (Georgia, USA). The homeostatic model assessment for insulin resistance (HOMA-IR; (fasting insulin × fasting glucose)/22.5) was used to assess insulin resistance (IR). Nitrite quantification using Griess Reagent was used to measure plasma and cardiac nitric oxide. Cardiac glycogen was determined using a standard spectrophotometric method, whereas plasma and cardiac glycogen synthase were determined using standardized enzymatic colorimetric methods and reagents obtained from Randox Laboratory Ltd. (Antrim, UK). The Sandwich-ELISA kit from Elabscience® (cat number: Rat VEGF-A: E-EL-R2603) was used for the vascular endothelial growth factor (VEGF) assay.

2.4. Preparation of cardiac tissue homogenates

The heart was removed after dissection, eliminated of adhering connective tissues, blotted, and weighed. After carefully removing 100 mg of tissue, it was homogenized in phosphate-buffered solution (PBS) with a glass homogenizer and centrifuged at 10,000 rpm for 10 min at 4 °C.

2.5. Body weight, heart weight and food intake measurement

Body and heart weights were measured weekly by using sensitive weighing balance. Daily food intake by individual rat in each group was determined. There were five rats in a group and each group was put in cage partitioned into five compartments. The daily food intake was calculated by weighing the feed given to the individual rat in each group and the left over feed the following morning before they were fed again using weighing balance. The weight of the left over feed was subtracted from the weight of the feed given to each rat.

Mathematically, Daily food intake = Feed given – Left over feed.

2.6. Water intake measurement

Daily water intake was measured and given to individual rat in each group in a cage partitioned into five compartments, each containing a single rat. This was measured using a measuring cylinder. The daily water intake was calculated by measuring the remaining water and subtracting the volume from the initial one given to the rats.

Mathematically, Daily water intake = Water given – Left over water.

2.7. Statistical analysis

All data were presented as Mean ± SEM. The data was analyzed using graph pad prism version 9.5.1 for Windows statistical software. The mean values of variables were compared using one-way analysis of variance (ANOVA). A p-value of less than 0.05 was considered statistically significant.

2.8. Ethical approval

Following a recommendation from the Faculty of Basic Medical Sciences Ethical Review Committee at the University of Ilorin in Ilorin, Nigeria, the ethical approval was granted by the University of Ilorin Research Ethical Committee with the ethical approval number (UERC/ASN/2018/357).

3. Results

3.1. Effects of NaB on mean body weight, heart weight, food and water intake in high fructose fed rats

The result in Table 1 shows that there was a small rise in body weight and statistical increase in Cardiac weight of the animals in HfrD group compared to the control group. The body weight of the rats treated with NaB was decreased when compared with the rats in HfrD group while the cardiac weight was unaffected. Co-administration of HfrD and NaB increased body weight of the rats in the group in comparison with the control group but cardiac weight did not change. The food intake was reduced in the HfrD, NaB and HfrD + NaB groups relative to the control group ($p < 0.05$). Co-administration of HfrD and NaB increases the food intake when compare with the HfrD group ($p < 0.05$). Sodium butyrate and its co-administration with HfrD significantly increase water intake ($p < 0.05$) in relation to the control group.

Table 1
Effect of Fructose and Sodium Butyrate on mean Body weight, Food Intake and Water.

	CONTROL	NaB	FRU	FRU + NaB
Body weight (g)				
Final	165.40 ± 4.69	154.60 ± 7.45	181.50 ± 10.01	173.00 ± 8.45
Initial	108.57 ± 4.69	105.60 ± 1.85	110.57 ± 3.61	112.71 ± 4.78
Weight gain	56.83 ± 0.72	48.57 ± 5.6*	70.93 ± 6.4*	60.29 ± 3.67#
Food intake (g/kg/day)	80.83 ± 2.84	114.86 ± 6.15*	138.93 ± 4.29#	74.71 ± 1.89
Water Intake (ml/kg/day)	62.80 ± 0.3	100.1 ± 8.6	65.7 ± 4.4	93.6 ± 5.9
Heart weight (g/kg/bw	0.62 ± 0.05	0.65 ± 0.04	0.86 ± 0.18	0.64 ± 0.05

*$p < 0.05$ vs CTR, #$p < 0.05$ vs FRU.

3.2. Effects of sodium butyrate on fasting blood sugar (FBS)¸ plasma insulin, homeostatic model of insulin resistance (HOMAR-IR) in high fructose fed rats

Fructose increased FBS, insulin, pericardial fat and HOMAR-IR when compared to the control group, as shown in Fig. 1(A-D). However, it was discovered that sodium butyrate (NaB) reduced FBS, insulin, and HOMAR-IR in comparison to control and fructose-fed rats. Additionally, when compared to rats given fructose, NaB + Fru decreased FBS, HOMAR-IR, and insulin.

3.3. Effects of sodium butyrate on plasma and cardiac nitric oxide, cardiac lactate and cardiac glycogen in high fructose fed rats

The result in Fig. 2(A-D) showed that fructose reduced plasma and cardiac nitric oxide and also cause an increase cardiac lactate as well as cardiac glycogen when compared with control. Administration of NaB significantly increased plasma and cardiac nitric oxide but reduced cardiac lactate and cardiac glycogen in comparison to control and high fructose fed rats ($p < 0.05$). Furthermore, NaB + Fru increase plasma nitric oxide but did not affect cardiac nitric oxide. It reduced cardiac lactate and cardiac glycogen in relation to control and high fructose fed rats (Fig. 2[C and D]).

3.4. Effects of sodium butyrate on plasma and cardiac glycogen synthase and vascular endothelial growth factor (VEGF) in high fructose fed rats

Sodium butyrate increased plasma glycogen synthase, cardiac glycogen synthase and plasma VEGF in comparison to control and fructose fed rats. There was no difference in plasma and cardiac glycogen synthase level in high fructose administered rats compared to the control group. Rats fed a high fructose diet had slightly lower plasma levels of VEGF than the control group. (see Fig. 3 [A-C]). In addition, co-administration of sodium butyrate and high fructose diet increase cardiac glycogen synthase and plasma VEGF when compared with high fructose fed rats (Fig. 3[B and C]).

3.5. Discussion

This research work demonstrated that High fructose diet resulted in an elevation of the body and cardiac weight, plasma glucose, plasma insulin and cardiac lactate but a decrease in nitric oxide level (NO) when compared to the control. The increase in body weight was in consonance with the work done by Lozano and coworker [26]. They found that Wistar rats fed a high-fructose diet gained more weight than rats fed with normal rat chow. They therefore suggested that the increase may be as a result of higher caloric content of fructose in comparison to other sugars, coupled with the fact that fructose is more readily changed to fat in the liver [26]. Obesity and cardiovascular mortality are caused by sugar. Clinical studies have demonstrated that consuming more added sugars raises weight gain, visceral obesity, hypertension, type 2 diabetes, dyslipidemia, and cardiovascular disease risk factors. People who consume a lot of fructose may expend fewer calories than those who consume an equivalent number of calories from a diet high in glucose and starch, leading to weight gain [27].

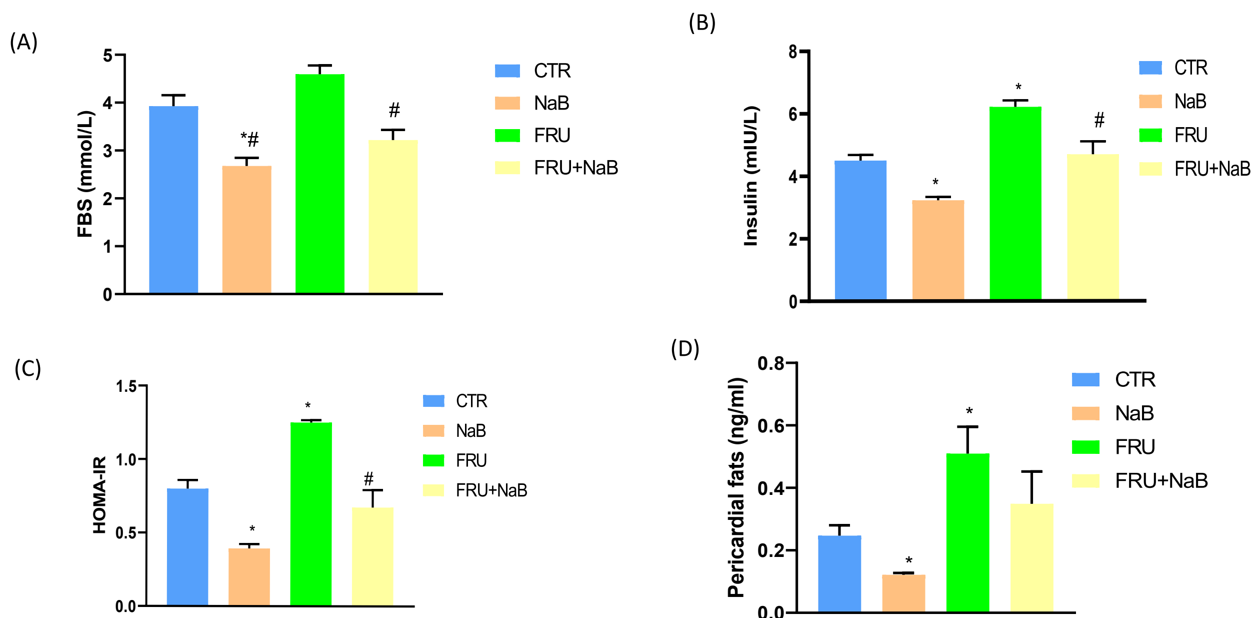


Fig. 1. Effect of Sodium Butyrate on **(A)** fasting blood sugar (FBS), **(B)** insulin, **(C)** Homeostatic model of insulin resistance (HOMA-IR) and **(D)** pericardial fats × $p < 0.05$ *vs* CTR, #$p < 0.05$ *vs* FRU.

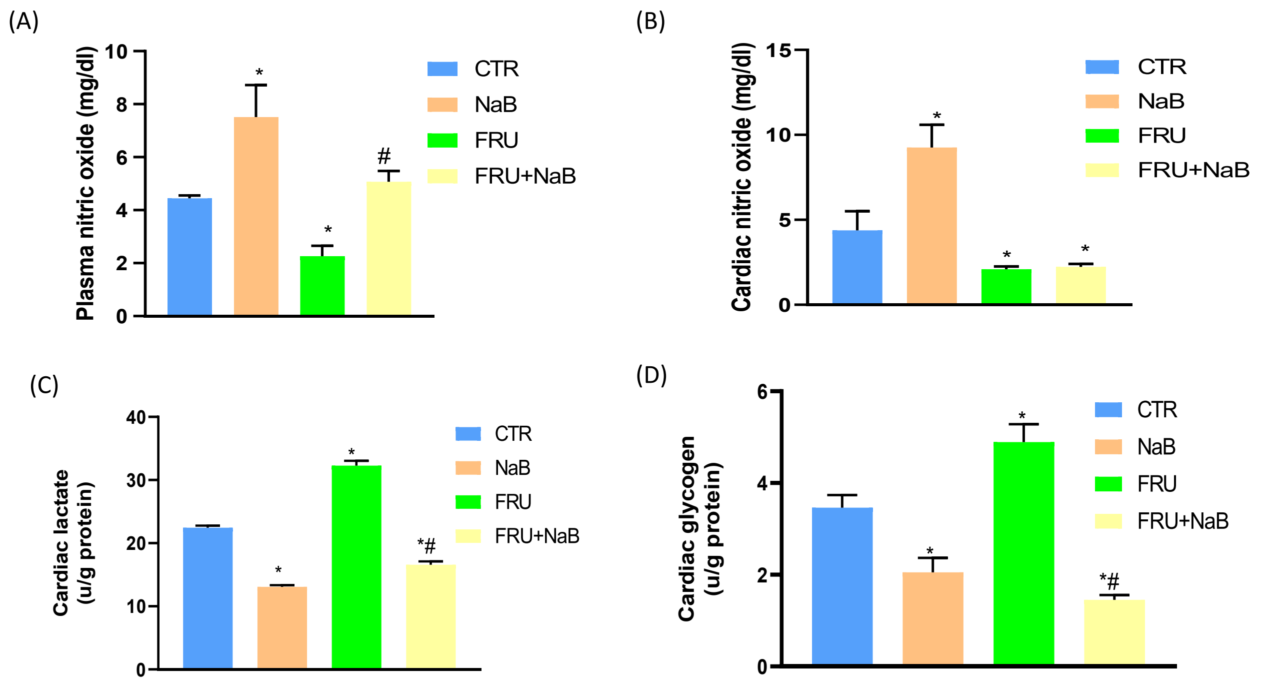


Fig. 2. Effect of Sodium Butyrate on **(A)** plasma nitric oxide, **(B)** cardiac nitric oxide, **(C)** cardiac lactate and **(D)** cardiac glycogen × $p < 0.05$ *vs* CTR, #$p < 0.05$ *vs* FRU.

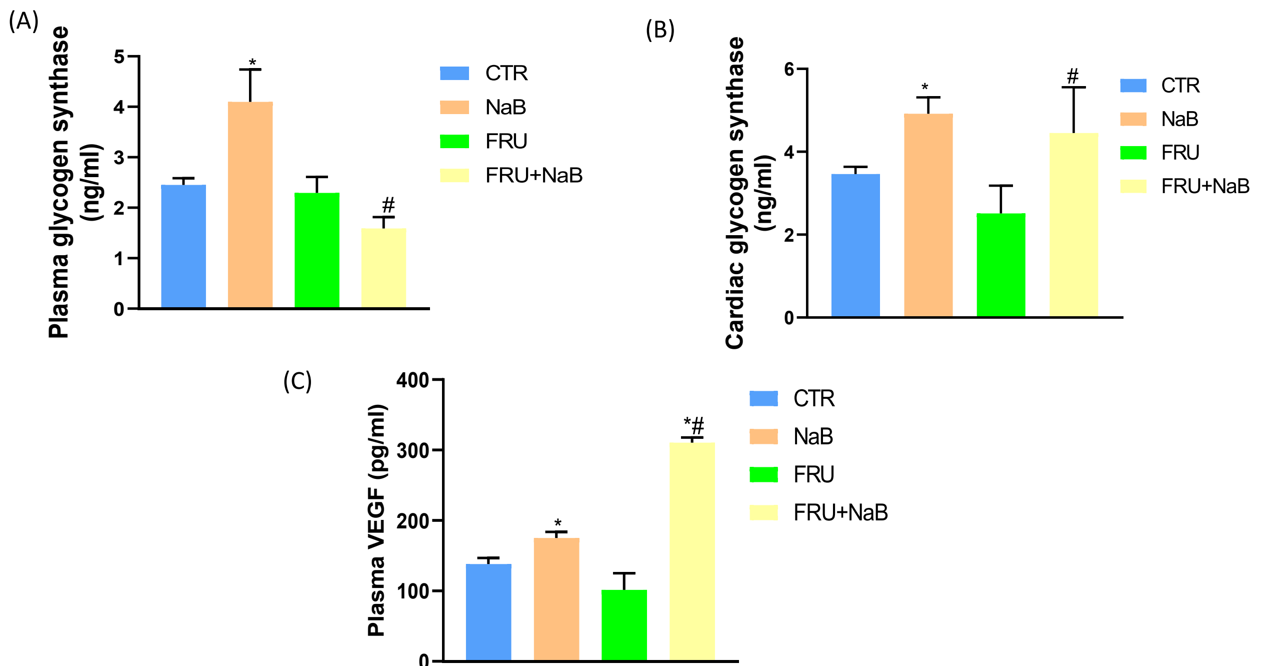


Fig. 3. Effect of Sodium Butyrate on **(A)** plasma glycogen synthase, **(B)** cardiac glycogen synthase, and **(C)** plasma Vascular Endothelial Growth Factor (VEGF) *$p < 0.05$ *vs* CTR, #$p < 0.05$ *vs* FRU.

It is noteworthy to show that high fructose diet increases blood sugar, insulin secretion and HOMA-IR in this work. The increase in insulin secretion following an increase in blood glucose occurs to regulate blood glucose [28]. Also, chronic high-fructose diet administration has been reported to be linked to increased hyperglycemia and insulin resistance [29]. This is consistent with the findings of this study. An upsurge of HOMA-IR in the current study is a reflection of insulin resistance which is one of the key

components of metabolic syndrome [28]. Hyperglycemia increases ROS production in the mitochondria, lowering the glutathione/glutathione disulphide ratio. The production of ROS triggers a pro-inflammatory cascade that leads to increased adipogenesis, the release of inflammatory cytokines, and a decrease in adiponectin, all of which lead to insulin resistance. In mice, a high fructose diet causes nocturnal hypertension and autonomic imbalance, which may be related to sympathetic and RAS system activation. According to research, changes in autonomic modulation may be an inhibitory mechanism underlying the clustered symptoms connected to cardiometabolic disease [30]. The increase in Cardiac lactate observed in this current study after administration of High fructose was linked to an excessive production of pyruvate by fructolysis which undergoes glycolysis in the liver, distributing lactate to the peripheral tissues and organs [31].

Moreover, our results showed that sodium butyrate reduces cardiac weight, blood glucose, plasma insulin, and cardiac lactate of HFrD-fed rats. NaB also increase plasma glycogen synthase in normal rats, plasma and cardiac circulating VEGF in HfrD + NaB administered rats while producing no change in plasma and cardiac glycogen synthase level of HFrD treated rats. Sodium butyrate improves glucoregulation via increased circulating VEGF in HFrD-exposed rats. An elevation in the circulating VEGF was due to promotion of angiogenesis in the endothelial vascular cells [22]. Proangiogenic molecules like VEGF promote glycolysis through improving glucose uptake and driving the expression of glycolysis activators like phospho-fructokinase-2/fructose-2,6-bisphosphatase 3 (PFKFB3) [32] According to Sanja et al. (2017), over consumption of fructose up-regulates pro-inflammatory makers and decreases anti-oxidative power in young female rats' visceral adipose tissue (VAT), leading to the development of adiposity [33]. It increases glycemia and insulinemia and affects blood antioxidant capacity negatively in hypertensive rats.

Administration of NaB increases glycogen synthase activity which in turns elevate glycogen store and bring about reduction in blood glucose in the animal. The cardiac muscle stores more glycogen during fasting which inhibits glycolysis more than it does glucose uptake and directs glucose toward glycogen synthesis. As a result of insulin's stimulation of glucose transport and glycogen synthase activity, glycogen stores increase [34].

Butyrate stimulates the release of GLP-1 from the intestinal cells which reduces apoptosis and insulin synthesis and secretion. Mediates increase in postprandial GLP-1 level and decreases homeostatic model assessment of insulin resistance (HOMAR-IR) [35]. From the data obtain in this study, HOMAR-IR and insulin were reduced in animals administered sodium butyrate and was statistically increased in rats administered fructose in comparison to the control. Showing that sodium butyrate plays a significant role in regulating insulin levels elevated by fructose consumption. In oxygen-deficient environments, tissue restriction of fructose metabolism can be overridden. Consuming fructose is associated with the emergence of insulin resistance. Increased rates of coronary artery disease, heart failure, stroke, and renal insufficiency and failure are closely correlated with rising prevalences of diabetes and hypertension [27].

4. Limitation of the study

The main limitation of this study is the small animal sample size, which is sufficient for statistical testing (ANOVA). The small number (5 in each group) resulted from the scarcity of male rats chosen for this study.

5. Conclusion

In conclusion, result from the experiment indicates that sodium butyrate improved glucoregulation by increasing cardiac circulating VEGF and glycogen synthase activity, reducing HOMAR-IR, serum insulin levels and also by causing a decline in lactate concentration in high fructose fed rats.

Data availabity

The data are yet to be deposited in any repository because the research is still ongoing and this is the first phase of the work. Therefore, the data supporting the results presented in this work will be made available together with others when the work is completed upon reasonable request.

CRediT authorship contribution statement

Adewumi Oluwafemi Oyabambi: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Olubayode Bamidele:** Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Aindero Blessing Boluwatife:** Writing – original draft, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lawrence Dayo Adedayo:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] L. He, G.S. Babar, J.M. Redel, S.L. Young, C.E. Chagas, W.V. Moore, Y. Yan Fructose intake, Metabolism and role in diseases, in: L.J. Martins (Ed.), Sugar Intake - Risks and Benefits and the Global Diabetes Epidemic, Intechopen, London, 2021, pp. 1–25, https://doi.org/10.5772/intechopen.95754.
[2] A. Miller, K. Adeli, Dietary fructose and the metabolic syndrome, Curr. Opin. Gastroenterol. 24 (2) (2008) 204–209, https://doi.org/10.1097/MOG.0b013e3282f3f4c4.
[3] B.P. Marriott, N. Cole, E. Lee, National estimates of dietary fructose intake increased from 1977 to 2004 in the United States, J. Nutr. 139 (2009), https://doi.org/10.3945/jn.108.098277, 1228S–35S.
[4] A. El Mehi, M. Faried, Effect of high fructose diet-induced metabolic syndrome on the pituitary gonadal axis from adolescence through adulthood in male albino rats and the possible protective role of ginger extract. A biological, histological and immunohistochemical study, Folia Morphol. 19 (4) (2020) 690–708.
[5] J.M. Rippe, T.J. Angelopoulos, Fructose-containing sugars and cardiovascular disease, Adv. Nutr. 6 (2015) 430–439, https://doi.org/10.3945/an.114.008177.
[6] P. Jegatheesan, J.P. De Bandt, Fructose and NAFLD: the multifaceted aspects of fructose metabolism, Nutrients (2017) 9, https://doi.org/10.3390/nu9030230.
[7] L. Tappy, Caloric sweeteners as a cause of obesity and metabolic disorders, J. Exp. Biol. (2018) 221, https://doi.org/10.1242/jeb.164202.
[8] S.W. Rizkalla, Health implications of fructose consumption: a review of recent data, Nutr. Metab. 7 (82) (2010) 1–17, https://doi.org/10.1186/1743-7075-7-82.
[9] C. Schiano, V. Grimaldi, M. Scognamiglio, D. Costa, A. Soricelli, G.F. Nicoletti, C. Napol, Soft drinks and sweeteners intake: possible contribution to the development of metabolic syndrome and cardiovascular diseases. Beneficial or detrimental action of alternative sweeteners? Food Res. Int. 143 (2021), 110220.
[10] F. Gillian, S. Ines, D. Katrien, The Warburg effect in Endothelial cells and its potential as anti-angiogenic target in cancer, 2018, Front. Cell Dev. Biol. 11 (2018).
[11] N. Ferrara, R.S. Kerbel, Angiogenesis as a therapeutic target, Nature 438 (2005) 967–974.
[12] S. Masahumi, VascularEndothelial growth factor (VEGF)and its receptor (VEGFR) signaling in angiogenesis, Gene Cancer 2 (12) (2011) 1097–1105.
[13] V. Chintalgattu, D.M. Nair, L.C. Katwa, Cardiac myofibroblasts: a novel source of vascular endothelial growth factor (VEGF) and its receptors Flt-1 and KDR, J. Mol. Cell. Cardiol. 35 (2003) 277–286.
[14] S.E. Pryde, S.H. Duncan, G.L. Hold, C.S. Stewart, H.J. Flint, The microbiology of butyrate formation in the human colon, FEMS Microbiol. Lett. 217 (2002) 133–139.
[15] C.R. Berni, M.C. Di, L. Leone, The epigenetic effects of butyrate: potential therapeutic implications for clinical practice, Clin. Epigenet. 4 (2012) 4.
[16] T.M. Henagan, B. Stefanska, Z. Fang, A.M. Navard, J. Ye, N.R. Lenard, P.P. Devarshi, Sodium butyrate epigenetically modulates high-fat diet-induced skeletal muscle mitochondrial adaptation, obesity and insulin resistance through nucleosome positioning, Br. J. Pharmacol. 172 (2015) 2782–2798.
[17] M.A. Vinolo, H.G. Rodrigues, W.T. Festuccia, A.R. Crisma, V.S. Alves, A.R. Martins, C.L. Amaral, J. Fiamoncini, S.M. Hirabara, F.T. Sato, R.A. Fock, G. Malheiros, M.F. dos Santos, R. Curi, Tributyrin attenuates obesity-associated inflammation and insulin resistance in high fat-fed mice, Am. J. Physiol. Endocrinol. Metabol. 303 (2012) E272–E282.
[18] Z. Gao, J. Yin, J. Zhang, R.E. Ward, R.J. Martin, M. Lefevre, W.T. Cefalu, J. Ye, Butyrate improves insulin sensitivity and increases energy expenditure in mice, Diabetes 58 (2009) 1509–1517.
[19] R.G. Mattace, R. Simeoli, R. Russo, A. Iacono, A. Santoro, O. Paciello, M.C. Ferrante, R.B. Canani, A. Calignano, R. Meli, Effects of sodium butyrate and its synthetic amide derivative on liver inflammation and glucose tolerance in an animal model of steatosis induced by high fat diet, PLoS One 8 (2013), e68626.
[20] C. Badejobin, D. Areola, K. Olaniyi, O. Adeyanju, I. Adeosun, Sodium butyrate recovers high-fat diet-fed female wistar rats from glucose dysmetabolism and uric acid associated cardiac tissue damage, Naunyn Schmeidebergs Arch Pharmacol 392 (11) (2019) 1411–1419.
[21] J. Ciura, P. Jagodziński, Butyrate increases the formation of anti-angiogenic vascular endothelial growth factor variants in human lung microvascular endothelial cells, Mol. Biol. Rep. 37 (2010) 3729–3734, https://doi.org/10.1007/s11033-010-0026-1.
[22] N. Katakami, H. Kaneto, et al., Sodium butyrate stimulates expression of vascular endothelial growth factor and its receptors in vascular endothelial cells and promotes angiogenesis, Biochem. Biophys. Res. Commun. 293 (1) (2002) 5–10, https://doi.org/10.1016/S0006-291X(02)00199-4.
[23] L. Gao, F.Q. Liang, et al., Sodium butyrate improves insulin sensitivity and increases energy expenditure in mice, J. Med. Food 12 (1) (2009) 104–111, https://doi.org/10.1089/jmf.2007.0666.
[24] I.Y. Torshin, O.A. Gromova, K.S. Ostrenko, M.V. Filimonova, I.V. Gogoleva, V.I. Demidov, A.G. Kalacheva, Lithium ascorbate as a promising neuroprotector: fundamental and experimental studies of an organic lithium salt, Molecules 27 (2022) 2253.
[25] A.O. Adeyanju, O.C. Badejogbin, D.E. Areola, K.S. Olaniyi, C. Dibia, O.A. Soetan, A.A. Oniyide, O.S. Michael, L.A. Olatunji, A.O. Soladoye, Sodium butyrate arrests pancreato-hepatic synchronous uric acid and lipid dysmetabolism in high fat diet fed Wistar rats, Biomed. Pharmacother. 133 (2021), 110994.
[26] I. Lozano, R.V. Werf, C. Peronet, M. Pinget, N. Jeandidier, E. Maillard, Marchioni, S. Sigrist, S. Dal. High fructose and high fat diet-induced disorders in rats: impact on diabetes risk, hepatic and complications. Nutr. Metab. 13:15..
[27] M. Peter, J. Cholsoon, A. Zoltan, K. Wilhelm, Fructose metabolism, cardiometabolic risk, and the epidemic of coronary artery disease, Eur. Heart J. 39 (2018) 2497–2505, https://doi.org/10.1093/eurheartj/ehx518K.
[28] A.O. Oyabambi, O. Bamidele, A.B. Boluwatife, Butyrate ameliorate lithium-induced cardiometabolic disorder in male Wistar rats, Sci. Afr. 20 (2023), e01697.
[29] D.M. Zhang, R.Q. Jiao, L.D. Kong, High dietary fructose: director indirect dangerous factors distributing Tissue and Organ, Nutrients 9 (4) (2017) 335.
[30] Z. Khitan, D.H. Kim Fructose, A key factor in the development of metabolic syndrome and hypertension, J. Nutr. Metabol. (2013), 682673, https://doi.org/10.1155/2013/68267331.
[31] S.Y. Yoo, H. Ahn, Y.K. Park, High dietary fructoseintake on cardiovascular disease related parameter in growing rats, Nutrients 9 (1) (2017) 11–28.
[32] K. De Bock, M. Georgiadou, S. Schoors, A. Kuchnio, B.W. Wong, et al., Role of PFKFB3-driven glycolysis in vessel sprouting. Cell 154 (2013) 651–663.
[33] k. Sanja, N. Jelena, M. Gordana, E. Ivana, Fructose-enriched diet induces inflammation and reduces antioxidative defense in visceral adipose tissue of young female rats, Eur. J. Nutr. 56 (1) (2017) 151–663.
[34] D. Christophe, J. Jean-Louis, T. Henrich, Glucose for the heart, Circulation 99 (1999) 578–588, https://doi.org/10.1161/01.CIR.99.4.578.
[35] S. Coppola, C. Avagliano, A. Calignano, R. Berni Canani, The protective role of butyrate against obesity and obesity-related diseases, Molecules 26 (3) (2021) 682, https://doi.org/10.3390/molecules26030682.