



Butyrate ameliorates lithium-induced cardiometabolic disorders in male Wistar rats

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ABSTRACT

Background: Cardiometabolic disease is becoming a main cause of death worldwide with over ten million fatalities annually. Lithium (Li) has been reported to be one of the major causes of cardiometabolic disorders due to its narrow therapeutic index. Sodium butyrate (NaB) which is a short chain fatty acid is implicated to possess an amazing therapeutic effect against cardiometabolic disorders. As a result, the current study aims to evaluate sodium butyrate impact on lithium-induced cardiometabolic disorders.

Methods: Twenty male Wistar rats weighing between 230 and 250 g were used for the experiment. They were grouped into control and treated groups respectively as (CTR; normal chow), Lithium only (Li; 5 mg/kg, po), Sodium butyrate only (NaB) (200 mg/kg, po) and NaB +Lithium (Li; 5 mg/kg +NaB; 200 mg/kg, po) for six weeks, after a week of acclimation; n=5. The animals were anesthetized using sodium pentobarbital at a dose of 50 mg/kg intraperitoneally, blood samples were collected by cardiac puncture and cardiac tissue homogenates were measured for plasma Fasting Blood Sugar (FBS), plasma Insulin, Phosphatidylinositol 3 Kinase (PI3K), Nitric oxide (NO), Glucose-6-phosphate dehydrogenase (G6PDH), Malonyldehyde (MDA), Catalase (CAT), Superoxide Dismutase (SOD), Nicotinamide adenine dinucleotide phosphate (NADPH), Glutathione Peroxidase (GPx), and Adenosine deaminase /Xanthine oxidase /uric acid (ADA/XO/UA) using respective ELISA kits.

Results: The results showed that lithium significantly increased fasting blood sugar (FBS), plasma insulin, GPx, CAT, SOD, and MDA while causing a statistical reduction in plasma and cardiac concentration of NADPH, G6PDH, PI3K, endothelial nitric oxide synthase (eNOS), and Nitric Oxide (NO) in comparison with the control. However, butyrate attenuated plasma GPx, CAT, SOD, MDA, FBS, plasma insulin and significantly elevated plasma and cardiac PI3K, eNOS, NO, plasma NADPH and G6PDH levels in relation to control. Also no change was observed in the plasma and cardiac ADA/XO/UA following sodium butyrate.

Conclusion: Therefore, butyrate has a remarkable therapeutic potential in ameliorating lithium induced cardiometabolic disorders through glucometabolic control.

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Abbreviations

Li	Litium
NaB	Sodium Butyrate
CTR	Control
FBG	Fasting Blood Glucose
PIK3	Phosphatidylinositol 3 Kinase
NO	Nitric Oxide
G6PDH	Glucose-6-Phosphate Dehydrogenase
NADPH	Nicotinamide adenine Dinucleotide Phosphate
CAT	Catalase
SOD	Super oxide Dismutase
ADA/XO/UA	Adenosine deaminase/ Xathine Oxidase/ Uric acid
eNOS	Endothelial Nitric Oxide Synthase
GPx	Glutathione Peroxidase
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
AD	Alzheimer's Disease
HD	Huntington's Disease
Li ₂ CO ₃	Lithium Bicarbonate
UK	United Kingdom
PD	Parkinson's Disease
ELISA	Enzyme-linked Immunosorbent Assay
Ltd	Limited
ANOVA	Analysis of Variance
SPSS	Statistical Package for the Social Sciences
Ca ²⁺	Calcium ion

Introduction

Lithium which is a monovalent cation was first found in 1817 by Arfvedson August Johan and produced commercially in 1923 by Metallgesellschaft AG [1]. Its clinical effects as a mood stabilizer are well-documented. It has been shown to be effective in the treatment of many neurodegenerative illnesses such as Parkinson's (PD), Alzheimer's (AD) and Huntington's (HD) [2–6]. Lithium is also used as a supplement for the cure of depression, aggression, schizoaffective disease, attention deficit disorder, impulse control problem, eating disorders, and certain types of alcoholism [7]. Many medical conditions have been treated with lithium, including cluster headaches and skin problems (genital herpes, eczematoid dermatitis, and seborrheic dermatitis) [7].

Lithium is soluble in water and easily absorbed following oral treatment, reaching a peak level in 2–4 h [8]. It binds weakly to plasma proteins of low and high molecular-weight, but firmly to molecules with extremely low-molecular-weight [9]. It also takes 6–8 days to attain steady-state and therapeutic blood levels after moving from the extracellular to intracellular compartment [9]. It is distributed nearly uniformly throughout the body and accumulates in many tissues including the brain, thyroid, muscles, liver, bone and kidney along a concentration gradient [8]. Approximately 95% of absorbed Lithium carbonate (Li₂CO₃) is lost through urine, 3–4% in perspiration, and approximately 1% in feces [8].

In spite of the profound uses of lithium, it has been proven to induce cardiotoxicity in humans and animals owing to its narrow therapeutic index. The cardiotoxic effects are critical during lithium poisoning, but they can take place at therapeutic lithium levels as well [10]. These may involve bradycardia, decreased arterial blood pressure, decreased cardiac output and cardiac arrhythmias [10]. Moreover, Lithium is also associated with endocrine, neurologic, dermatologic, renal and gastrointestinal adverse effects and possible teratogenicity [7]. Its decreased excretion and progressive build up can predispose to poor renal function, drug interactions, volume depletion, and concomitant diseases such as cirrhosis and congestive heart failure [11].

Lithium has been reported to affect glucose metabolism; its administration to healthy Wistar rats could result to impairment or increase in the response to a glucose tolerance test [12]. It influences a variety of cellular activities by decreasing the formation of inositol, signalling pathway of the protein kinase C and glycogen synthase kinase 3 [13]. Also, many studies have revealed that lithium toxicity is partly mediated *via* oxidative stress [14,15] and oxidative DNA damage [16].

Sodium butyrate (NaB) is a short chain fatty acid formed when the proton from the COOH group of butyric acid is replaced by sodium ion with formula Na(C₃H₇COO). It is a naturally occurring fermentation product in the gut that is important for sustaining host metabolism and gut microbiome diversity [17]. Uncoated sodium butyrate and enteric-coated sodium butyrate with fat or fatty acid salts are the forms available. NaB is easily changed into butyric acid in the gut where it enhances the intestinal health *via* several ways. It contributes to the formation of the wall of gut tissues and regulates the growth of intestinal microflora involved in symbiosis [18–20]. It is also known to possess anti-inflammatory, anti-oxidative and lipid lowering properties [21,22]. It is reported to increase insulin sensitivity [23]. The onset of metabolic syndrome and cardiovascular disease is associated with a decrease in butyrate content in the gut [24]. Butyrate is also reported to prevent uric acid-induced heart tissue destruction in the rats fed with high-fat diet in a recent study [25]. Owing to the several

biological activities of Sodium butyrate, it is deemed to mitigate the cardiometabolic disorders caused by toxic effects of lithium in animals. Therefore, the current research work is aimed at evaluating the possible benefits of sodium butyrate on lithium-induced cardiometabolic disorders.

Materials and methods

Animals

Adult male rats (Wistar) of weight 230–250 g were procured from the Animal House Unit of the College of Health Sciences (COHES), University of Ilorin, Ilorin, Nigeria. They were fed with standard rat chow and given access to clean water *ad libitum*. An effort was taken to reduce suffering of animals and the amount of animals used for this study. The use and care of laboratory animals for the investigation were conducted in concordance with the globally accepted best practices as contained in the European Commission guidelines (Directives of 2010/63/EU as amended by Regulation (EU) 2019/1010) as well as the Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guidelines. All the protocols were reviewed and approved by the Faculty of Basic Medical Sciences, University of Ilorin Ethical Review Committee. The animals were randomly assigned to four groups (n = 5/group) after one week of acclimation. Group 1 was fed with normal rat chow (CTR), Group 2 received lithium (Li; 5 mg/kg, po) [26], Group 3 was given sodium butyrate (200 mg/kg, po) [27] and Group 4 was administered sodium butyrate + lithium (Li; 5 mg/kg + NaB; 200 mg/kg, po) for six weeks. The rats were kept in an Animal House with a temperature range of 22–26 °C, a relative humidity of 50–60%, and a 12 h dark/light cycle.

Preparation of sample

The rats were anesthetized using pentobarbital sodium at a dose of 50 mg/kg intraperitoneally [26] at the end of the drug regimen. Blood was collected by cardiac puncture into tube that contains heparin and centrifuged at 3000 rpm for 5 min at room temperature. The plasma was kept frozen until it was time for the biochemical assay.

Preparation of homogenates from the cardiac tissue

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

Biochemical test

Ray Biotechnology, Inc.'s ELISA kit was used to measure plasma insulin (Georgia, USA). The homeostatic model assessment for insulin resistance (HOMA-IR) was used to assess insulin resistance (IR) ($\text{HOMA-IR} = (\text{fasting insulin} * \text{fasting glucose}) / 22.5$).

Plasma and cardiac nitric oxide were measured through assessment of nitrite with the use of Griess Reagent. Phosphotyrosine 3 Kinase (also known as PI3K), assay was done using the Sandwich-ELISA kit purchased from Elabscience® with Cat.NoE0438Ra

Adenosine deaminase activity, xanthine oxidase activity, adenosine and uric acid concentration: Adenosine deaminase (ADA) and xanthine oxidase (XO) activities, as well as adenosine and uric acid concentrations, were determined from plasma and renal tissue homogenate using standard enzymatic and non-enzymatic colorimetric methods respectively using Randox Laboratory Ltd. (Co. Antrim, UK) assay kits and following the manufacturers' guide.

Ethical approval

All animal procedures were approved by the Committee on the Care and Use of Laboratory Animals of College of Basic Medical Sciences, University of Ilorin (UERC/ASN/2018/357).

Statistical analysis

The data was presented as Means $\pm$ SEM for all of the variables. SPSS was used to carry out statistical analysis of the data. The mean values of variables were compared using a one-way analysis of variance (ANOVA). Bonferroni's test was used to determine the significance of pairwise comparisons of mean values among the groups. The p-value ($P < 0.05$) was used to determine significant differences.

Results

Effect of sodium butyrate on fasting blood sugar, insulin, HOMA-IR and PI3K in rats fed lithium

As shown in Fig. 1, lithium caused a rise in FBS, insulin and HOMA-IR levels while it significantly reduced PI3K when compared with control. Furthermore, NaB caused a significant decrease in FBS, insulin and HOMA-IR while it increased PI3K

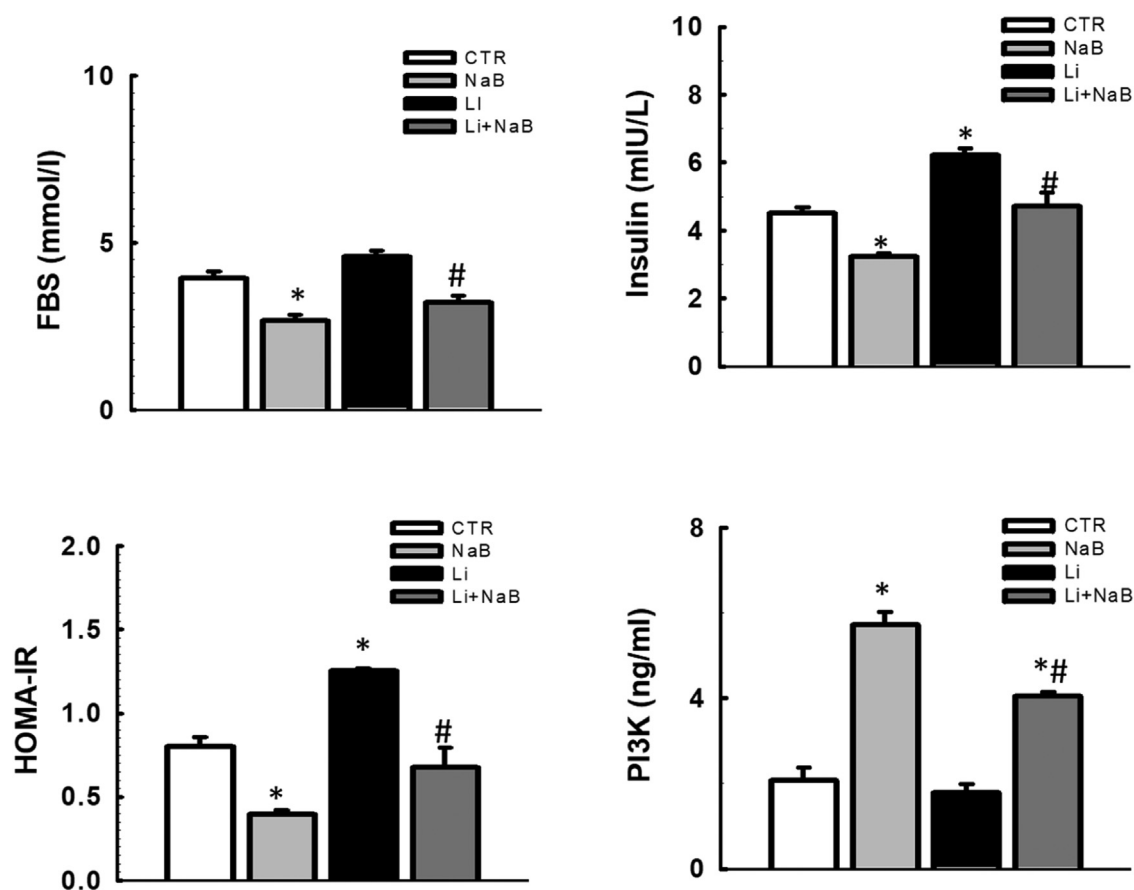


Fig. 1. Effect of sodium butyrate on Fasting blood glucose, insulin, HOMA-IR and PI3K in rats fed lithium. Values are expressed as Mean $\pm$ SEM; $n=5$ rats per group, * $p<0.05$ vs control; # $p<0.05$ vs Lithium. Data were analyzed by one-way ANOVA and Bonferroni's Post hoc analysis; CTR; Control, NaB; Sodium Butyrate, Li; Lithium, Li+NaB; Lithium and Sodium Butyrate simultaneous treated group.

when compared with control ($p<0.05$). However, NaB+Li increased PI3K significantly while causing a significant decrease in FBS, Insulin and HOMA-IR when compared with lithium ($p<0.05$).

Effect of NaB on plasma and cardiac NO and eNOS in rats fed lithium

Lithium caused a decline in plasma and cardiac eNOS and NO with no observable change in plasma NO when compared with control. NaB caused a statistical increase in plasma and cardiac nitric oxide in comparison with the control ($p<0.05$). Interestingly, administration of NaB+Li led to a statistical increase in plasma nitric oxide with no observable change in cardiac nitric oxide when compared with lithium. These observable changes are shown in Fig. 2.

Effect of NaB on Plasma and Cardiac GPx and G6PDH in rats fed lithium

There was a slight decrease in plasma and cardiac glutathione peroxidase (GPx) in Rats Fed Lithium and it was not significant when compared with control ($p>0.05$). Moreover, NaB led to an increase in plasma GPx only when compared with the control group (See Fig. 3). NaB+Li increased plasma GPx when related to control and lithium fed group ($p<0.05$). Lithium decreases cardiac G6PDH when compared with the control group ($p<0.05$). In addition, NaB led to an increase in plasma and cardiac G6PDH in comparison with the control ($p<0.05$). Similarly, NaB+Li caused a significant increase in plasma and cardiac G6PDH in relation to Lithium fed group. NaB+Li only caused a statistical increase ($p<0.05$) in Plasma G6PDH when compared to the control group (Fig. 3).

Effect of NaB on plasma and cardiac NADPH and SOD in rats fed lithium

Lithium increases plasma and cardiac NADPH and cardiac SOD significantly ($p<0.05$) while causing a decrease in plasma SOD when compared with control. Furthermore, NaB led to a decrease in plasma and cardiac NADPH while increas-

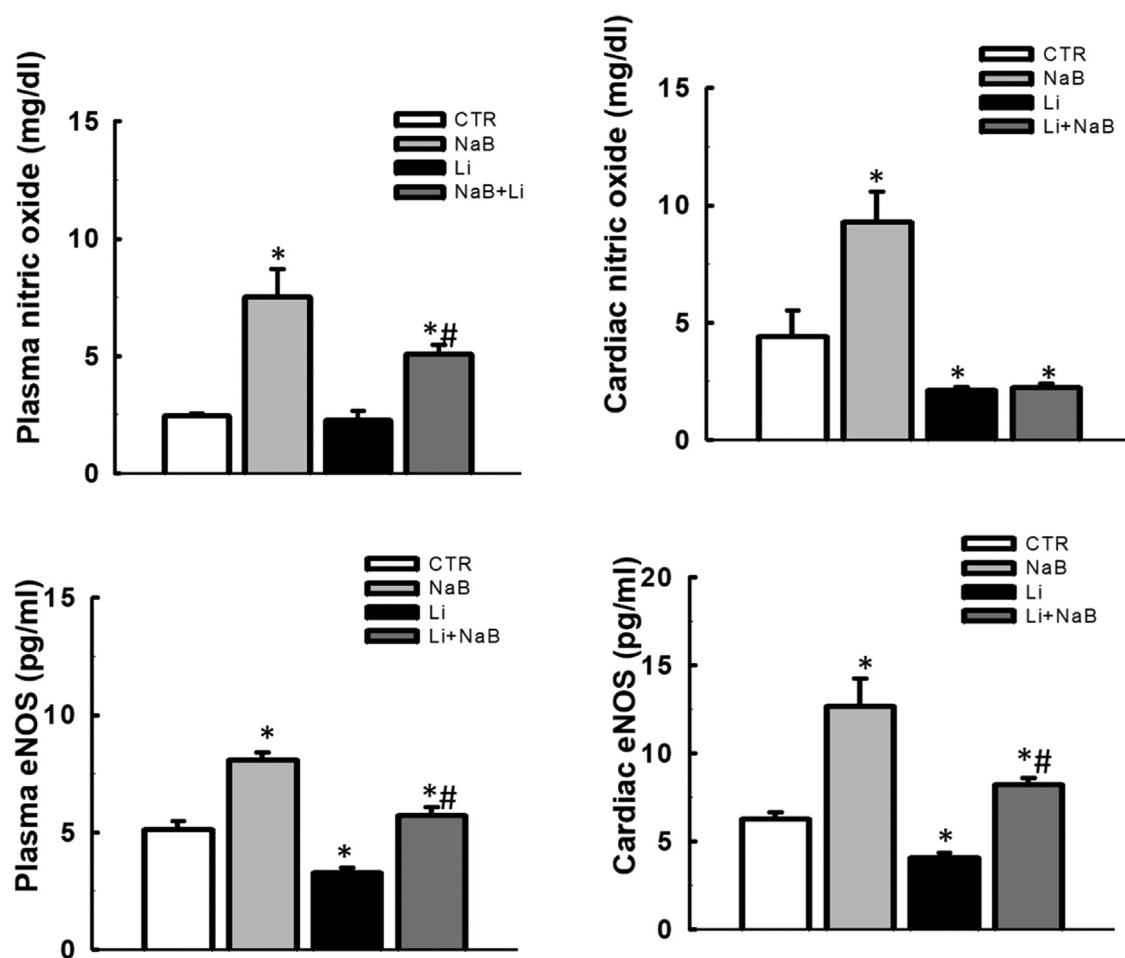


Fig. 2. Effect of Sodium butyrate on Plasma and cardiac nitric oxide & eNOS in rats fed lithium. Values are expressed as Mean $\pm$ SEM; n=5 rats per group, *p<0.05 vs control; #p<0.05 vs Lithium. Data were analyzed by one-way ANOVA and Bonferroni's Post hoc analysis; CTR; Control, NaB; Sodium Butyrate, Li; Lithium, Li+NaB; Lithium and Sodium Butyrate simultaneous treated group.

ing plasma and cardiac SOD ($p<0.05$). However, NaB+Li caused a decrease plasma and cardiac NADPH with a slight increase in plasma and cardiac SOD and no observable change in cardiac SOD when compared with lithium (as seen in Fig. 4).

Effect of NaB on plasma and cardiac ADP and XO in rats fed lithium

The result of NaB on plasma and cardiac ADP and XO in rat fed lithium is depicted in Fig. 5. Lithium caused a slight increase in plasma and cardiac XO which is not significant and no observable change in plasma and cardiac ADP when related to the control group. In contrast, administration of NaB resulted in a slight decrease in cardiac XO and ADP as well as plasma XO and ADP. Furthermore, NaB+Li led to no observable change in cardiac and plasma XO and ADP when compared to lithium fed rats ($p>0.05$).

Effect of NaB on plasma and cardiac MDA and catalase in rats fed lithium

Lithium caused an elevation in plasma and cardiac MDA while decreasing plasma and cardiac catalase when compared with control ($p<0.05$). Moreover, NaB led to a decrease in plasma and cardiac MDA while increasing plasma and cardiac catalase in comparison with control. However, NaB+Li decreased plasma and cardiac MDA while increasing plasma and

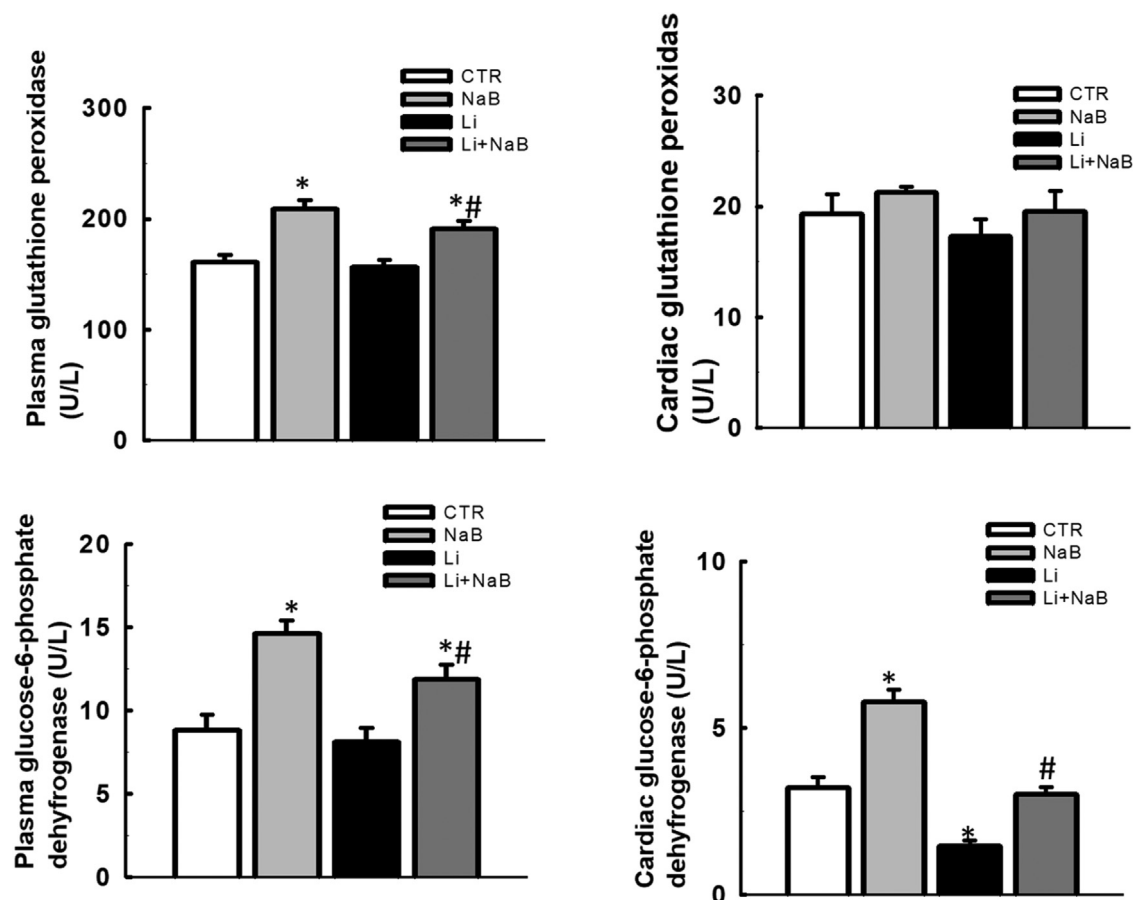


Fig. 3. Effect of Sodium butyrate on Plasma and cardiac G6PDH and GPx in rats fed lithium. Values are expressed as Mean $\pm$ SEM; $n=5$ rats per group, * $p<0.05$ vs control; # $p<0.05$ vs Lithium. Data were analyzed by one-way ANOVA and Bonferroni's Post hoc analysis; CTR; Control, NaB; Sodium Butyrate, Li; Lithium, Li+NaB; Lithium and Sodium Butyrate simultaneous treated group.

cardiac catalase when related to lithium fed group ($p<0.05$). The values for change in plasma and cardiac MDA and Catalase in rats fed lithium after giving NaB are shown in Fig. 6.

Discussion

The aim of this present research work was to evaluate the impact of NaB on lithium-induced cardiometabolic disorders. In this study, lithium administration increases FBS, plasma insulin concentration and HOMA-IR. The increase in FBS observed in the rat given lithium was in consonance with the result obtained by Ahmad and his co-workers [28] when rats were treated with lithium salt. The reason for the increase in FBS in the present study, may be due to interference of lithium with the carbohydrate metabolic clock of gluconeogenesis and glycogenolysis, which resulted to the elevation of blood sugar [28]. However, this result was in contrast to the report of Rodriguez-Gil and co-workers that observed a decline in glycemic level in normal and diabetic animals fed with lithium [29]. The discrepancies in their and our findings was due to different dosages used. They used low dosage of lithium (20 mM) while we used a high dosage (5 mg/kg body weight). Increased insulin secretion observed might be due to increase in FBS. Insulin secretion is known to be increased when there is increase in blood sugar to cause glucose uptake into its sink. In this study, increase in plasma glucose resulted in elevation of HOMA-IR activity which is used to produce an estimate of insulin sensitivity and beta cell function from fasting plasma insulin and glucose concentrations. The balance between hepatic glucose output and insulin glucose secretions, which is maintained by a feedback loop between the liver and beta cells, is reflected in the relationship between glucose and insulin in the baseline state. The elevated HOMA-IR in the present study indicated insulin resistance which is one the cardinal points of metabolic syndrome. Researchers have reported that insulin resistance/ glucose dysmetabolism is a key event in cardiometabolic syndrome [30] and this work also revealed the same findings with lithium-induced model of cardiometabolic disorder. When the animals given lithium were co-treated with NaB there were

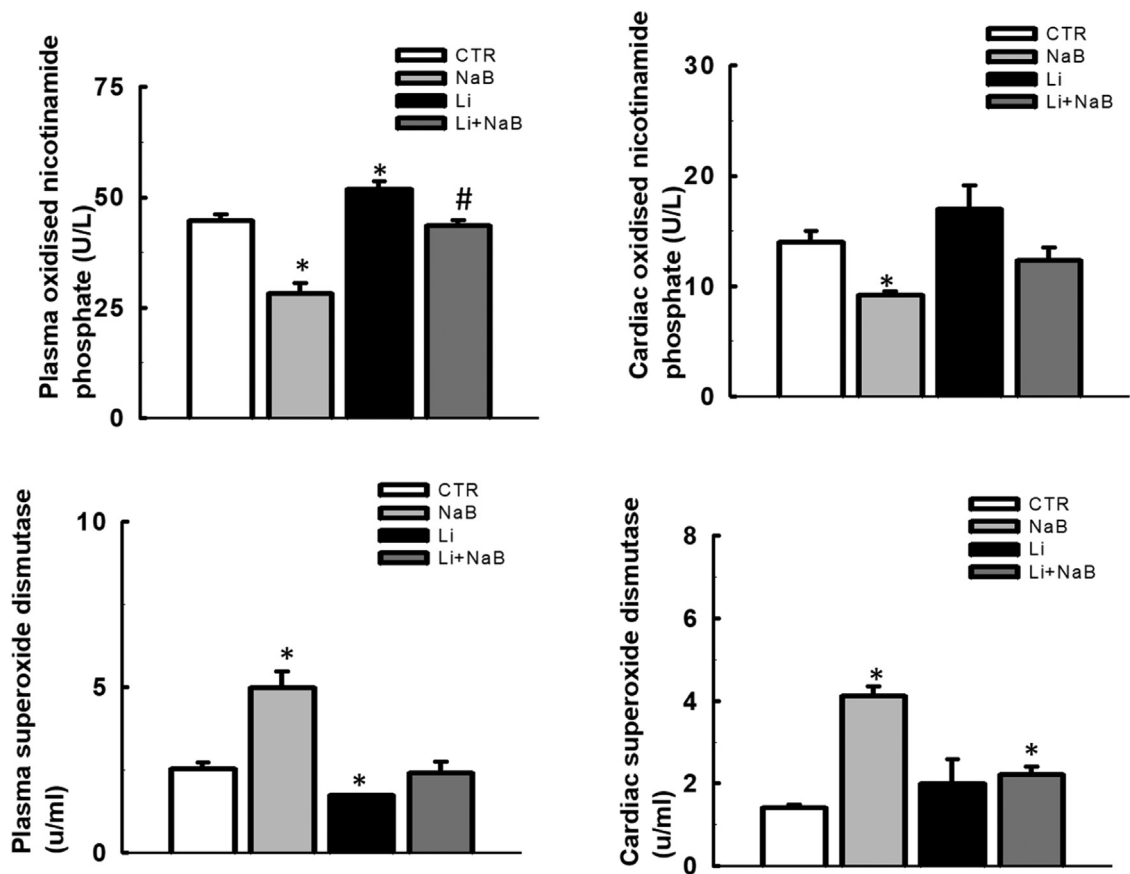


Fig. 4. Effect of Sodium butyrate on Plasma and cardiac NADPH⁺ and SOD in rats fed lithium. Values are expressed as Mean $\pm$ SEM; n=5 rats per group, *p<0.05 vs control; #p<0.05 vs Lithium. Data were analyzed by one-way ANOVA and Bonferroni's Post hoc analysis; CTR; Control, NaB; Sodium Butyrate, Li; Lithium, Li+NaB; Lithium and Sodium Butyrate simultaneous treated group.

significant reductions in FBG, Insulin level and HOMA-IR indicating that NaB attenuates the effects of lithium toxicity on glucose metabolism in rats. Also, there was a decrease PI3K in rats treated with the lithium. When the rats were administered Sodium butyrate, there was a substantial rise in plasma PI3K when compared to controls. The PI3K pathway might be involved in the mechanism through which NaB attenuates lithium induced-cardiometabolic disorders because when the concentration was low in animals treated with lithium, there was increase in FBS but when the concentration was high in animal treated with sodium butyrate, FBS was reduced. The PI3K (phosphoinositide 3-kinase) pathway is known to be linked to the production of the lipid second messenger PIP3/PtdIns(3,4,5)P3 (phosphatidylinositol (3,4,5)-triphosphate) and involved in metabolic regulation, hypertrophy activation, and survival pathways [31]. PI3Ks is also involved in the regulation of essential homeostatic processes in the cardiovascular system, which are linked to Ca²⁺ flow modulation directly or indirectly.

Furthermore, there was a significant reduction in plasma and cardiac eNOS in lithium treated Wistar rats in relation to the control group. Interestingly, NaB treatment elevates both plasma and cardiac eNOS compared with control rat group. In the experiment "The Vascular Consequences of Metabolic Syndrome: Rodent Models, Endothelial Dysfunction, and Current Therapies," Tran, et al. [32] further proves this point by showing that in obese Zucker rats, altered insulin signaling impairs insulin-mediated NO generation (through downregulation of eNOS expression) to decrease vasodilation in resistant arteries, and involvement of ROS and consequent degradation of BH₄ (a cofactor essential for NO synthesis from eNOS) production of insulin resistance which is believed to play a role in the impairment of NO dependent vasodilatation [33]. An infusion of BH₄ partially counteracted the diminished ACh-induced vasodilation in that study, suggesting that eNOS uncoupling and lower NO availability contribute to endothelial dysfunction in T2DM [34].

Toxicity of many metals, including lithium, is connected with the rise in production of reactive oxygen species (ROS) resulting to an oxidative stress in cells [35]. Malondialdehyde (MDA) is one of the metabolic products of lipid peroxides (LPO), which is produced by the reaction of lipid oxidation induced by oxygen-free radicals in tissues [36]. In

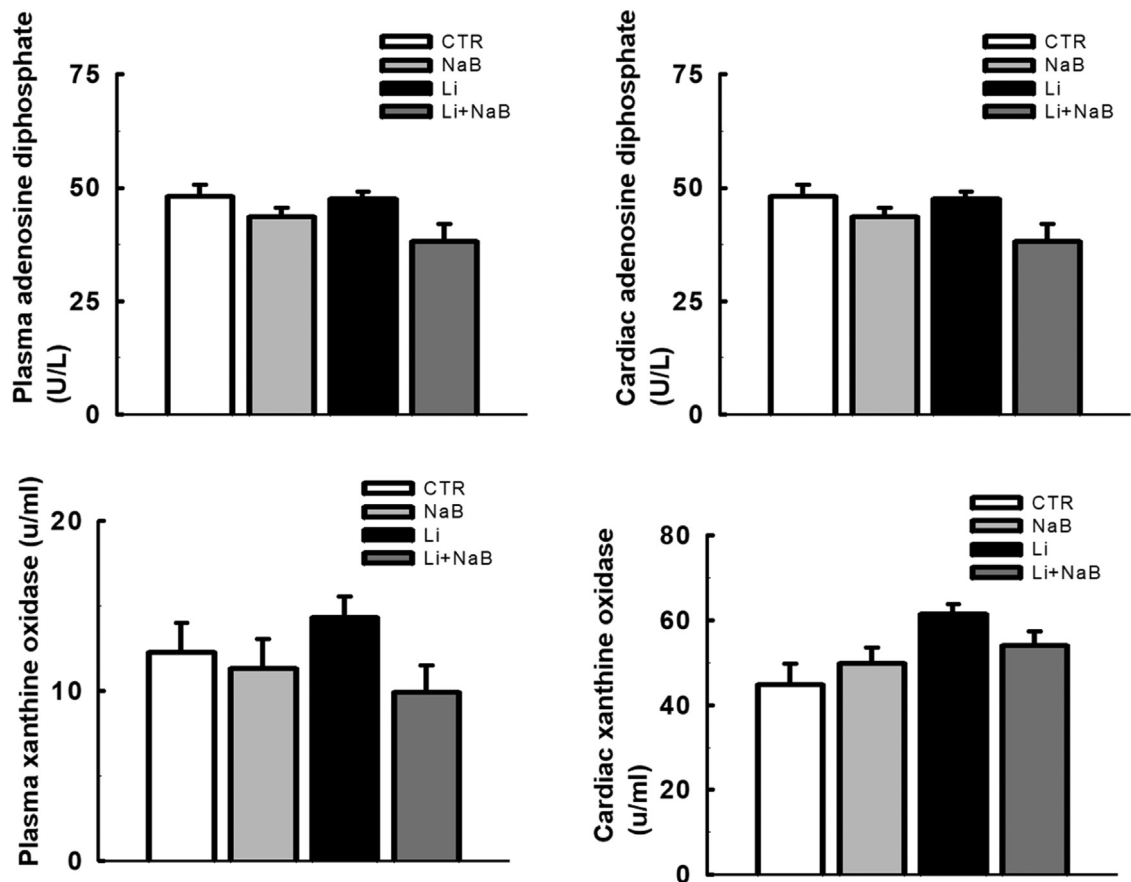


Fig. 5. Effect of Sodium butyrate on Plasma and cardiac NADP⁺ and XO in rats fed lithium. Values are expressed as Mean ± SEM; n=5 rats per group, *p<0.05 vs control; #p<0.05 vs Lithium. Data were analyzed by one-way ANOVA and Bonferroni's Post hoc analysis; CTR; Control, NaB; Sodium Butyrate, Li; Lithium, Li+NaB; Lithium and Sodium Butyrate simultaneous treated group.

this study, elevation in MDA level in the lithium-treated rats shows that there was severe oxidative stress. Many reports conceded that excessive lithium-treatment result to severe oxidative stress and a rise in lipid peroxidation [37]. It could be suggested that an increased lipid peroxidation may result from the decline in the activities of antioxidant enzymes. Our results revealed that treatment with NaB impaired lipid peroxidation in group 4 rats. Glutathione reductase is the enzyme that regenerates GSH and regulates the amount of oxidized glutathione in the body. The reduction in glutathione level in lithium-treated rats in this study was due to an increase in ROS generation. Enhancement in glutathione (Gpx) level by sodium butyrate in this study is in tandem with a study where healthy human subjects were administered (10,000 mg/kg) for 2 weeks and resulted in an increase in the antioxidant glutathione [38]. GP_x protects cells from cardiovascular diseases which increases in a healthy state and decreases in a diseased state. Our results showed a reduction in SOD and Catalase activities in lithium treated animals. This is similar to the results got previously [39] The decrease in SOD activity in lithium-treated animals may be due to the increase in production of superoxide radical anions [40]. Catalase scavenges hydrogen peroxide that has been produced by free radicals or by SOD in removal of superoxide anions. When rats given lithium were co-treated with the NaB, the reduction in SOD and CAT activities were inhibited. Hence the ameliorative effects of NaB was due to its antioxidant potentials. Also, there was no change observed in the plasma and cardiac ADA, XO and UA following sodium butyrate administration. Therefore, this suggests that amelioration of lithium-induced cardiometabolic disorder does not occur through adenosine deaminase pathway.

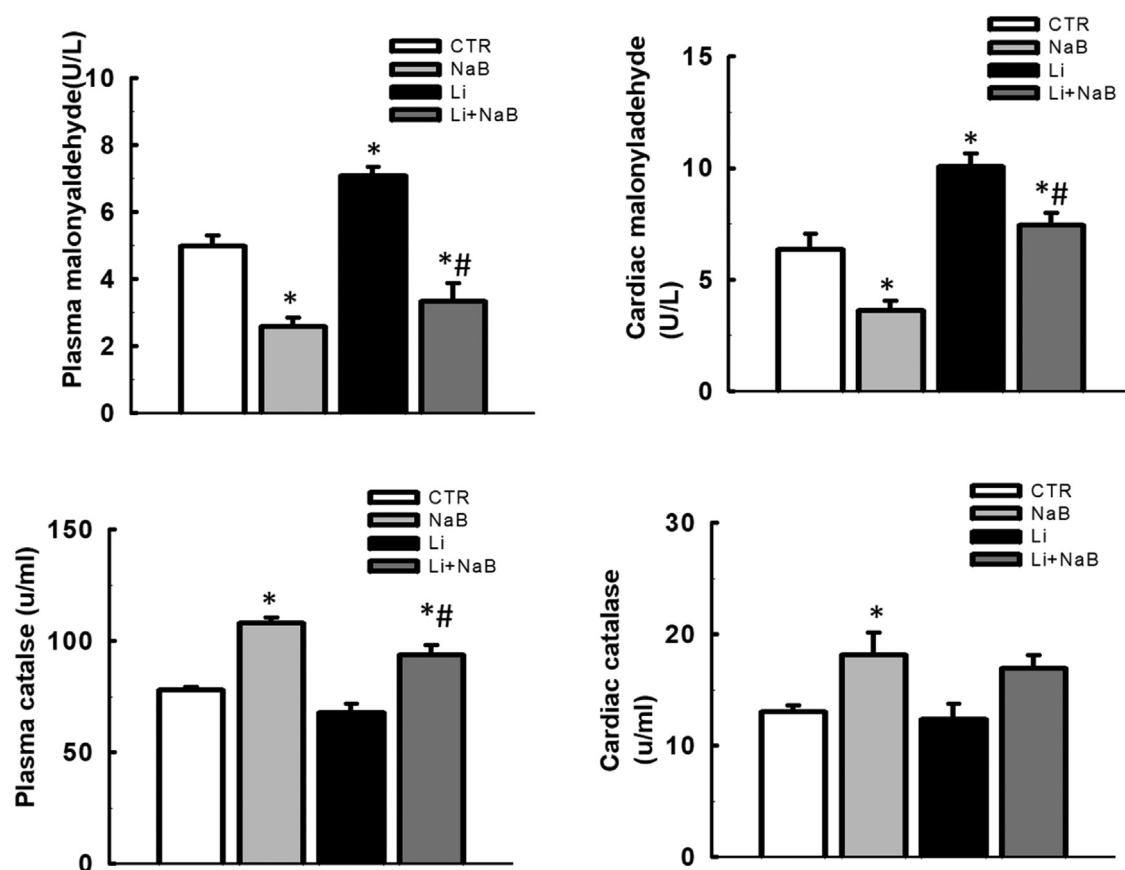


Fig. 6. Effect of Sodium butyrate on Plasma and cardiac MDA and catalase in rats fed lithium. Values are expressed as Mean $\pm$ SEM; n=5 rats per group, *p<0.05 vs control; #p<0.05 vs Lithium. Data were analyzed by one-way ANOVA and Bonferroni's Post hoc analysis; CTR; Control, NaB; Sodium Butyrate, Li; Lithium, Li+NaB; Lithium and Sodium Butyrate simultaneous treated group.

Conclusion

In summary, the present work showed that lithium induced cardiometabolic disorder at a concentration greater than the therapeutic value. However, administration of sodium butyrate in the animals treated with lithium showed beneficial glucoregulatory and antioxidant potentials which were potent enough to offer protection against cardiac damage. It is also evident in this study that sodium butyrate ameliorates lithium-induced cardiometabolic disorders through PI3K/eNOS pathway which is independent of adenosine deaminase in male Wistar rats.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Funding

No funding was obtained for this study.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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