RESEARCH

Diet-induced insulin resistance altered cardiac GLUT4 and FATP/CD36 expression in rats

Oladele Ayobami Afolabi[1], Babatunde Adebola Alabi[2*] and Olufemi Oluranti[3]

Abstract

Background: Altered substrate transport protein expression is central to the effect of insulin resistance on cardiac metabolism. The present study was thus designed to investigate the comparative effects of high fat, high sucrose and salt-induced IR on cardiac expression of fatty acid transporter (FATP) and glucose transporter (GLUT4) in rats.

Results: Rats fed with high fat, high sucrose and salt diets developed impaired glucose tolerance ($p > 0.05$) and hyperinsulinemia ($p < 0.05$) compared with control group. Myocardial glucose transporter expression was significantly increased ($p < 0.001$ for salt-induced IR; $p < 0.01$ for sucrose-induced IR; $p < 0.01$ for fat-induced IR) across all IR groups compared with control. Fatty acid transporter expression was also increased ($p < 0.001$) in high salt diet-induced IR rats, and high fat diet-induced IR rats ($p < 0.05$).

Conclusions: Our results demonstrate that salt and not caloric excess has a potential role in IR alteration of myocardial substrate transport protein expression in the rat.

Keywords: Energy substrate, Cardiac metabolism, Transport protein, Substrate utilization, Hyperinsulinemia

1 Background

Insulin resistance (IR) is a state in which the cells of the body do not respond properly to the hormone insulin. It is a characteristic feature of metabolic syndrome in a number of disorders such as diabetes mellitus, hypertension, obesity and dyslipidemia [1]. While the exact cause of IR is still not fully understood, factors that could lead to IR include genetic factors, high caloric intake, high carbohydrate intake, chronic stress and a sedentary life style [2]. Since insulin is the most potent anabolic hormone which promotes the metabolism of glucose, fatty acids and amino acids in most tissues of the body [3], it affects the ability of body tissues to take up major substrates such as glucose and fatty acids for energy production. Cardiac dysfunction is known to be the leading cause of death in type 2 diabetic patients [4]. Central to the effect of IR on cardiac tissue metabolism

is altered substrate transport protein expression in cardiac myocytes [5, 6]. The two keys substrate transport protein in the heart include FAT/CD36 and GLUT4 [7]. These two transport proteins are the primary steps in the utilization of their respective substrate for metabolism in the heart. FAT/CD36 is responsible for the uptake of long chain fatty acids into the myocardium, this accounts for about 70% of the energy generated in the healthy heart, while GLUT4 is responsible for the uptake of glucose into the myocardium and accounts for about 20% of the energy generated in the healthy heart [8]. Indeed, the heart is known to be a metabolic omnivore as it can use fatty acids, glucose, lactate and ketone bodies as substrate for energy generation [9]. The heart is flexible in its choice of energy substrate [10, 11] and factors that determine its choice include substrate availability, translocation of substrate transport proteins and metabolic effectors. In postprandial states insulin increases the uptake of glucose in the myocardium from 20% to about 60% [12, 13]. In insulin resistance, there is a reported alteration in the expression of substrate transport protein in the sarcolemma

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of cardiac myocytes [6]. From the study of Jameel and Zhang [14], decreased myocardial tissue expression of GLUT4 correlate with insulin resistance that is different from the hyperglycemic whole body insulin resistance and thus suggests that myocardial hypertrophy is associated with its peculiar insulin resistance independent of diabetes. Mechanical stress-induced insulin resistance associated with myocardial hypertrophy along with a significant decrease in GLUT4 expression in rats was also reported by Afolabi et al. [15]. However, it is not clear whether dietary factors leading to insulin resistance (IR) have any influence on the substrate transport protein expression in cardiac tissue. The present study was thus designed to investigate the comparative effects of high fat, high sucrose and salt-induced IR, respectively, on cardiac expression of FATP and GLUT4 in rats.

The outcome of this study can help to explain the role of diet-induced insulin resistance in myocardial substrate transporter proteins. This study can also clarify the role of myocardial GLUT4 during high fat, high sucrose and salt-induced IR. Through this study, differential role of myocardial glucose transporter during cardiac hypertrophy-induced IR and hyperglycemic state-induced IR was established.

2 Methods

2.1 Animals

Forty male adult rats of Wistar strain (*Rattus norvegicus*), weighing between 150 and 200 g were obtained from the Experimental Animal Unit of the Faculty of Veterinary Medicine, University of Ibadan. They were housed in plastic cages placed in a well-ventilated animal house and were given ad libitum access to rat chow (Ladokun Feeds Ltd., Ibadan, Nigeria) and subjected to natural photoperiod of 12 h light–12 h dark cycle. All the animals received humane care according to the criteria outlined in the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Science (2011). Ethical regulations were followed in accordance with national and institutional guidelines for the protection of animal welfare during experiments (PHS 1996). The ethical approval number assigned for animal use in this study by Bowen University animal care and use for research committee was BUTH/REC-175.

The rats were divided randomly into 4 groups of 10 rats as follows:

Group A (control rats); rats in this group were given normal diet and clean tap water only for 6 weeks,

Group B (High fat-induced IR); rats were given 55% fat feed and clean tap water for 6 weeks, **Group C** (High sucrose-induced IR); rats were allowed to feed on normal rat diet and 35% sucrose in drinking water for 6 weeks,

Group D (High salt-induced IR); rats were fed with normal feed which contain 8% salt and clean tap water for 6 weeks.

3 Oral glucose tolerance test

A standardized oral glucose challenge (OGTT) was used to assess the severity of glucose intolerance by administering a 2 g/kg dose of D-glucose (0.5 g/mL) after a 12-h fasting period and measuring glucose levels 0, 30, 60, 90 and 120 min after administration using the One-touch glucometer (Abbott Diabetes Care, Alameda, CA).

3.1 Measurement of insulin in serum

Blood insulin level was measured using ELISA kit, following the manufacturing protocol of Boehringer-Mannheim Kit, Mannheim, Germany.

3.2 Blood pressure measurements

At completion of feeding the rats with high fat, sucrose and salt diets, blood pressure parameters, including systolic, diastolic, and mean arterial blood pressures, were measured, using noninvasive blood pressure monitoring machine (CODA, Kent Scientific, USA).

3.3 Electrocardiography

Standard lead II electrocardiogram was recorded in rats immobilized with xylazine–ketamine combination using a 6/7-lead ECG machine (EDAN VE-1010, Shanghai, China). The machine was calibrated at 20 mm/mV paper speed and 50 mm/s paper speed. From the electrocardiogram, parameters such as heart rate, PR interval, QRS wave duration, R-wave amplitude and QT/QTc values were determined.

3.4 Immunohistochemistry of GLUT4 and FATP/CD36

Immunohistochemistry of paraffin-embedded heart and kidney tissues was performed after the tissues were fixed with 10% formalin based on the methods described by Todorich et al. [16], with slight modifications as described by Alabi et al. [17]. Briefly, paraffin sections were melted at 60 °C in the oven. Dewaxing of the samples in xylene was followed by passage through ethanol of decreasing concentrations (100–80%). Peroxidase quenching with 1% H_2O_2/methanol was followed by antigen retrieval performed by microwave heating in 0.01 mol/L citrate buffer (pH 6.0) to boil. All the sections were blocked in normal goat serum (10%, HistoMark, KPL, Gaithersburg, Maryland, USA) and probed with anti-GLUT4 and anti-FATP/CD36 antibodies, as appropriate (Bioss, San Diego, California, USA), 1:200 overnight at room temperature. Detection of bound antibody

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was carried out using biotinylated (goat anti-rabbit, 2.0 g/mL) secondary antibody and subsequently, streptavidin peroxidase (horseradish peroxidase–streptavidin) according to manufacturer's protocol (HistoMark, KPL, Gaithersburg, Maryland, USA). The reaction product was enhanced with diaminobenzidine (DAB, Amresco, USA) for 2–3 min and counterstained with high definition hematoxylin (Enzo, New York, USA), with subsequent dehydration in ethanol. The slides were covered with coverslips and sealed with resinous solution. The immune-reactive positive expression of GLUT4 and FATP/CD36-intensive regions were viewed starting from low magnification on each slide then with 400× magnifications using a photo microscope (Olympus) and a digital camera (Toupcam; Touptek Photonics, Zhejiang, China). The measurement of immune-reactive positive expression of GLUT4 and FATP/CD36 were assessed digitally with the aid of a quantification software (ImageJ 1.48 v; National Institutes of Health, Bethesda, MD, USA). Five photomicrographs were analyzed per group for each parameter.
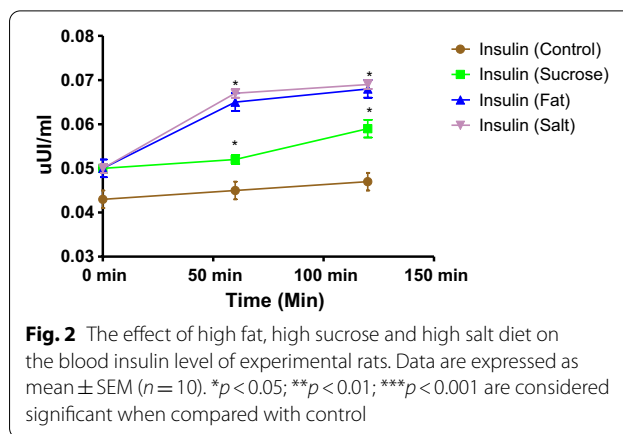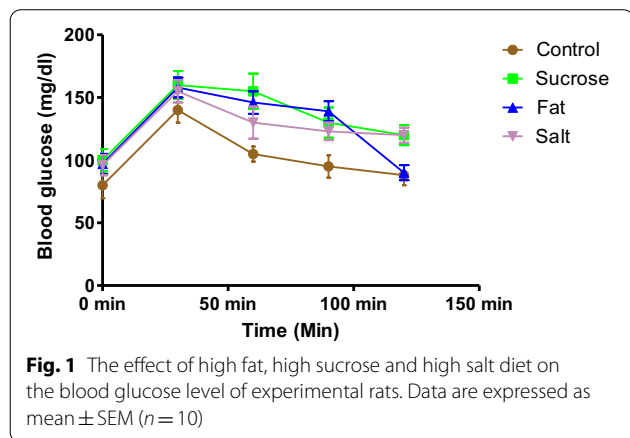
3.5 Statistical analysis
Statistical analysis was carried out using one-way analysis of variance (ANOVA) to compare the experimental groups, along with least significant difference (LSD) post hoc analysis, using GraphPad Prism software (version 5.0). $p < 0.05$ was considered statistically significant.

4 Results
4.1 Effect of high fat, high sucrose and salt diet on OGTT and insulin
Rats fed with high fat, sucrose and salt diets, respectively, for 6 weeks consistently developed impaired glucose tolerance (IGT) as determined by OGTT (Fig. 1). There was a significant increase in the insulin level rats fed with high fat and salt diet compared with control group

Fig. 1 The effect of high fat, high sucrose and high salt diet on the blood glucose level of experimental rats. Data are expressed as mean ± SEM ($n = 10$)

Fig. 2 The effect of high fat, high sucrose and high salt diet on the blood insulin level of experimental rats. Data are expressed as mean ± SEM ($n = 10$). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ are considered significant when compared with control

(Fig. 2). Insulin level of rats fed with high sucrose was also increased but not significant.

4.2 Effects of high fat, sucrose and salt diets on cardiovascular parameters
High fat, sucrose and salt diets had no significant effect on systolic blood pressures in rats when compared with control. However, high salt diet caused a significant increase in diastolic pressure in rats. High sucrose diet caused a significant increase in heart rate in rats compared with control, salt diet caused a significant decrease in heart rate and high fat diet had no significant effect on heart rate. High fat feed rats for six weeks had significant elongated QTc when compared with control (Table 1).

4.3 Effect of high fat, sucrose and salt diet on FATP/CD36 expression
Table 2 represents the effects of six weeks administration of high fat, high sucrose and salt diet on FATP/CD36 expression in the rat heart. Photomicrographs **A**–**D** (Fig. 3) are group representative photographs of FATP/CD36 cardiac tissue expression in rats examined by immunohistochemical staining (× 400 magnification). **A** represents immunohistochemical staining in control. **B** represents immunohistochemical staining in the salt-induced insulin-resistant group of rats. **C** represents immunohistochemical staining in the sucrose-induced insulin-resistant group of rats. **D** represents immuno-histochemical staining in the high fat-induced insulin-resistant group of rats. While salt diet caused a highly significant increase in cardiac FATP/CD36 activity, high sucrose diet caused a significant decrease in cardiac FATP/CD36 activity and high fat diet had no significant effect on cardiac FATP/CD36 activity when compared with control.

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Table 1 The effect of high fat, high sucrose and high salt diet on the systolic pressure, diastolic pressure and ECG of experimental rats. Data are expressed as mean $\pm$ SEM ($n = 10$)

Parameters	Control	Fat-induced IR	Salt-induced IR	Sucrose-induced IR
SBP (mmHg)	150 ± 10.53	142 ± 8.02	158 ± 7.91	130 ± 6.0
DBP (mmHg)	114 ± 13.92	118 ± 7.60	129 ± 8.67*	107 ± 6.3
Heart Rate (BPM)	234 ± 19.22	237.67 ± 11.35	223.33 ± 28.39*	252 ± 20*
P duration (ms)	21.00 ± 8.54	24.67 ± 7.09	20.6 ± 4.16	25.00 ± 8.72
PR Interval (ms)	55.33 ± 5.86	53.67 ± 3.79	48.00 ± 7.55	41.00 ± 17.78*
QRS (ms)	11.33 ± 2.08	11.00 ± 3.46	18.00 ± 2.65*	26.33 ± 16.17*
QT Interval (ms)	76.00 ± 14.18	82.00 ± 5.20	76.33 ± 10.41	87.33 ± 15.37
QTc (ms)	148.67 ± 18.58	167.67 ± 15.14***	145.67 ± 11.37	173.00 ± 25.16***
R amplitude (mV)	0.43 ± 0.11	0.36 ± 0.11	0.64 ± 0.22	0.33 ± 0.10

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ are considered significant when compared with control

Table 2 FATP/CD36 percentage for individual animals/group

Rat (n)	Control (% expression)	Fat-induced IR (% expression)	Salt-induced IR (% expression)	Sucrose-induced IR (% expression)
Rat 1	22.37	29.40	64.76	4.72
Rat 2	19.40	30.31	58.13	5.87
Mean $\pm$ SEM	20.89 ± 1.49	29.86 ± 0.46*	61.45 ± 3.39***	5.30 ± 0.58

*$p < 0.05$; **$p < 0.01$ and ***$p < 0.001$ are considered significant compared with control

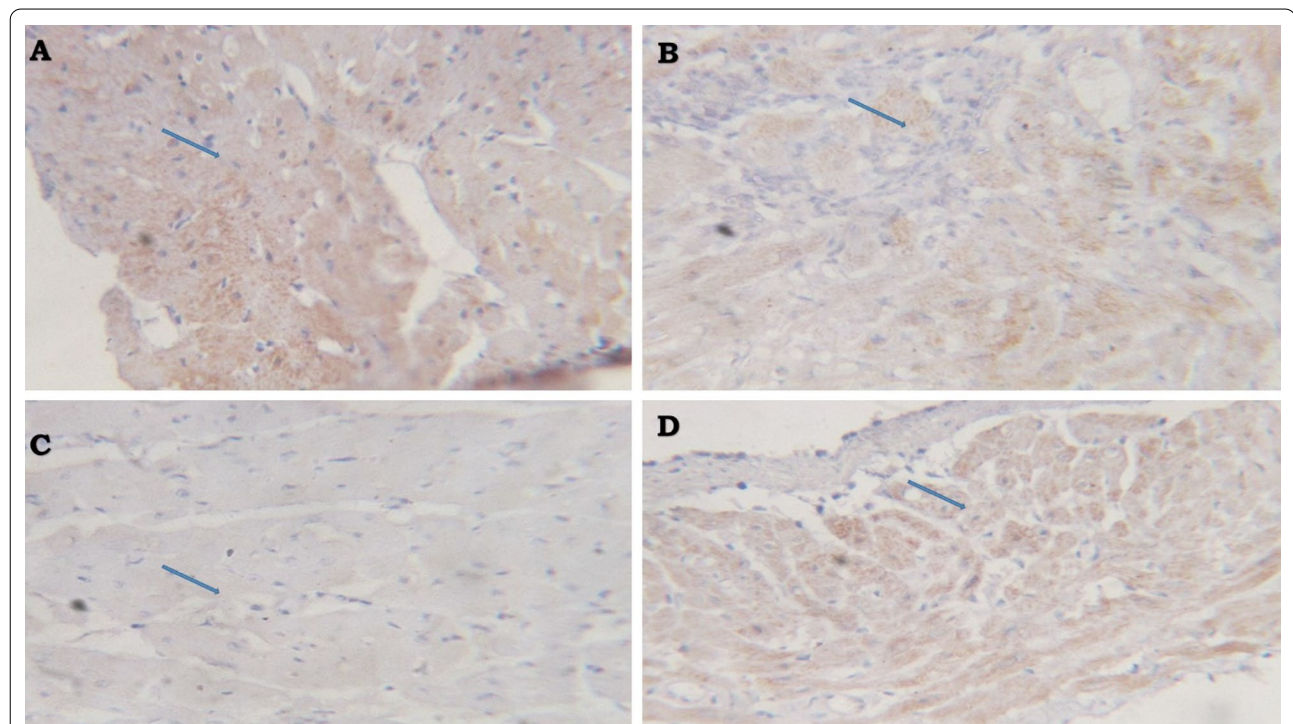**Fig. 3** Photomicrons **A–D** are group representative photographs of FATP/CD36 cardiac tissue expression in rats (×400). **A** Represents immunohistochemical staining in control. **B** Represents immunohistochemical staining in salt-induced insulin-resistant group of rats. **C** Represents immunohistochemical staining in sucrose-induced insulin-resistant group of rats. **D** Represents immunohistochemical staining in high fat-induced insulin-resistant group of rats

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Table 3 GLUT4 percentage for individual animals/group

Rat (*n*)	Control (% expression)	Fat-induced IR (% expression)	Salt-induced IR (% expression)	Sucrose-induced IR (% expression)
Rat 1	3.72	14.43	27.13	10.56
Rat 2	4.88	12.05	25.80	12.79
Mean ± SEM	4.30 ± 0.58	13.24 ± 1.19**	26.67 ± 0.67***	11.68 ± 1.12**

*$p < 0.05$; **$p < 0.01$ and ***$p < 0.001$ are considered significant compared with control

4.4 Effect of high fat, high sucrose and salt diet on GLUT4 expression

Table 3 represents the effects of six weeks administration of high fat, high carbohydrate and salt diet on GLUT4 expression in the rat heart. Photomicrographs **A–D** (Fig. 4) are group representative photographs of GLUT4 cardiac tissue expression in rats examined by immunohistochemical staining (×400 magnification). **A** represents immunohistochemical staining in control. **B** represents immunohistochemical staining in salt-induced insulin-resistant group of rats. **C** represents immunohistochemical staining in sucrose-induced insulin-resistant group of rats. **D** represents immunohistochemical staining in high fat-induced insulin-resistant group of rats. Six weeks administration of different diet types, respectively, increased cardiac GLUT4 expression in rats significantly ($p < 0.05$) when compared with control, the most significant increase being in rats treated with salt diet.

5 Discussion

The present study demonstrates the effect of different diet-induced systemic insulin resistances on myocardial substrate transport protein expression in rats. The most common indicator of systemic insulin resistance in mammals is reduced glucose utilization which manifests as reduced glucose tolerance, as measured by OGTT [18]. OGTT is referred to as standard test for diagnosing early insulin-resistant type of diabetes [19]. In this study, rats fed with high fat, high sucrose or salt diet developed reduced glucose tolerance as evidenced by an elevated 1-h post-load blood glucose level during OGTT. The
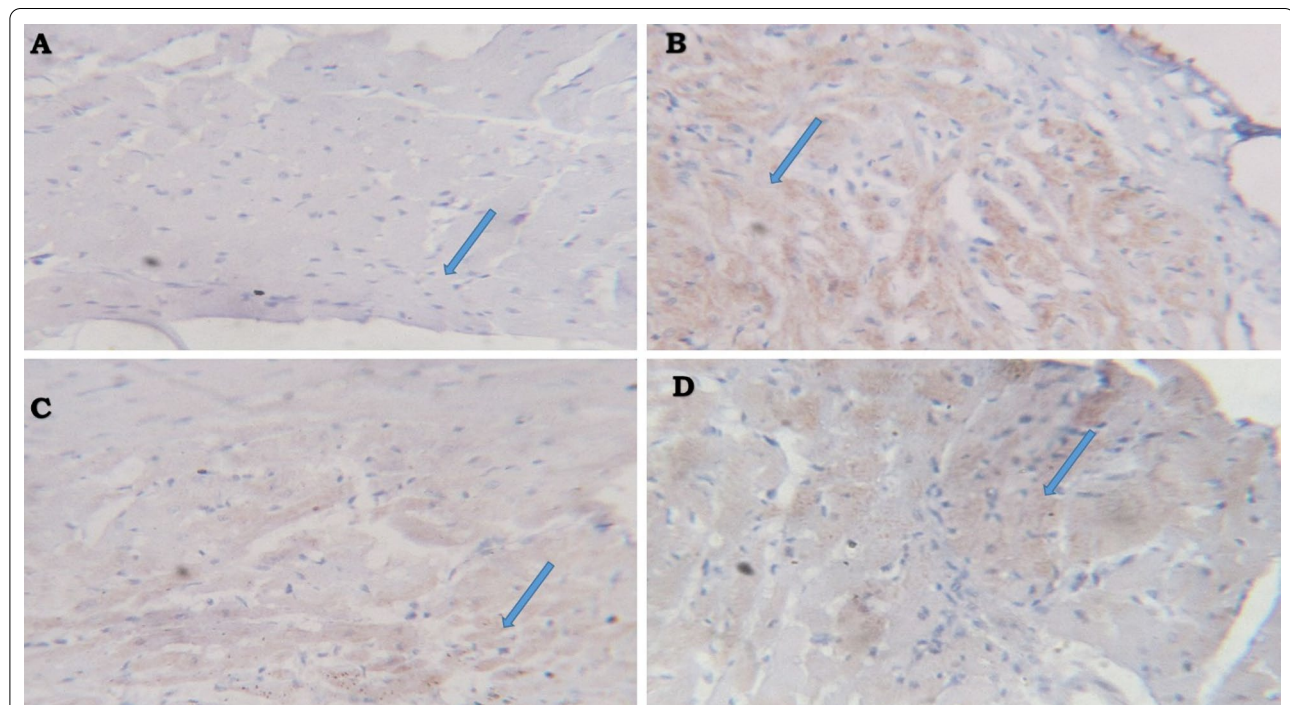

Fig. 4 Photomicrons **A–D** are group representative photographs of GLUT4 cardiac tissue expression in rats (×400). **A** represents immunohistochemical staining in control. **B** represents immunohistochemical staining in salt-induced insulin-resistant group of rats. **C** represents immunohistochemical staining in sucrose-induced insulin-resistant group of rats. **D** represents immunohistochemical staining in high fat-induced insulin-resistant group of rats

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significant increase in the level of blood insulin across all these groups further confirms the role of diets on systemic insulin resistance.

The most striking result obtained from the OGTT was the sustained higher glucose level in the salt-induced insulin-resistant rats at 120 min compared with high fat and high sucrose hyperglycemic rats. This result corroborates the study of Ogihara et al. [20] and Mainasara et al. [21], which showed that excessive consumption of salt-induced high blood pressure coexisted with insulin resistance in rats. The slight elevation of systolic pressure and diastolic pressure further agrees with these results although neither the systolic nor the diastolic blood pressure of the other diets showed any significant elevation compared with the control rats. This could probably be due to the relatively short duration of feeding the rats with the diets since other investigators have fed high sucrose diets for up to eight weeks [22]. High salt-induced insulin resistance could be due to gradual increase in cardiac output and peripheral resistance, causing the blood pressure to increase. Since pressure overload that results from hypertension is directly related to increase in afterload of aorta and peripheral resistance [23], hemodynamic stress during myocardial overload could be responsible for reduced insulin sensitivity through desensitization of IRS-protein kinase Akt pathway [24, 25].

Although the impaired glucose tolerance in various diet groups in the present study was similar, their effects on the expressions of cardiac GLUT4 and FATP/CD36 activities were significantly different, suggesting that the underlying dietary factors that lead to insulin resistance may be important in determining the activity of cardiac substrate transport proteins. Under normal resting conditions, the heart expresses fatty acid transporters (FATP/CD36) and depends to a large extent on the mitochondrial oxidation of fatty acids (60–70%) for the generation of energy in the form of ATP, while glucose and lactate contribute to the remaining 30–40% [26, 27] through myocardial glucose transporter (GLUT4) uptake. However, during the postprandial state, glucose contributes to 60–70% ATP required for myocardial activity through enhanced activity of insulin [28]. Cardiac dysfunction is known to alter myocyte energy substrate preference from predominantly fatty acid to glucose [29]. This change in energy substrate is thought to be associated with increased activity of glucose transporter (GLUT4 and GLUT1), although GLUT4 is more predominant in the adult myocardium [30–32]. Indeed, the heart is known to be a metabolic omnivore and flexible in its choice of substrate for energy metabolism [9]. Factors such as substrate availability influence the cardiac substrate of choice [12, 13] which also further buttresses

the premise that the factor causing insulin resistance may also affect the expression and activity of cardiac substrate transport protein.

The significant increase in GLUT4 expression in various diet-induced insulin-resistant rats in the present study demonstrates that systemic insulin resistance increased the expression of GLUT4 in the cardiac tissue. This contradicts the results obtained from previous studies that showed a significant decrease in myocardial GLUT4 expression in rats with cardiac insulin resistance during heart dysfunction-related disease. A study conducted by Hamirani et al. [31] revealed that reduced glucose uptake correlates with decreased expression of GLUT4 transporter in myocardial tissue and suggests that a lowered GLUT4 expression and glucose uptake may be the molecular basis of myocardial insulin resistance in cardiac hypertrophy. A study by Afolabi et al. [15] further revealed that rats with cardiac hypertrophy are GLUT4 deficient. However, the observation in this study is similar to the report of Zorzano et al. [33] and Becker et al. [34]. These studies revealed that cardiac GLUT4 expression was scanty until factors like hemodynamic stress and insulin activate its expression and translocation to the plasma membrane during pressure overload and volume overload. This study suggests that the effect of systemic insulin resistance on myocardial expression of GLUT4 is different from that of myocardial dysfunction-induced insulin resistance.

In addition, the outcome of this study also differentiates the effect of sucrose-induced insulin resistance on FATP from salt and fatty acid-induced insulin resistance. High fat and salt seems to increase FATP expression in myocardial tissue, while sucrose-induced IR decreased the expression. Based on this result, sucrose-induced IR appears to cause a shift in myocardial metabolic preference from fatty acid to utilization of glucose, a canonical IR metabolic pathway that is widely accepted [29]. High fat and salt-induced IR seems to activate the expression of both GLUT4 and FATP/CD36 in the heart, and this result further suggests that salt and fatty diet-induced IR may be strong activator of AMPK, PPAR-α and mTOR01. These protein kinase and transcription factors were reported to enhance the expression and translocation of FATP and GLUT4 [35].

6 Conclusions
This study demonstrate that salt and not caloric excess has a more significant role in insulin resistance alteration of myocardial substrate transport protein expression in the rat.

These findings have important implications for the design of models of insulin resistance and diabetes for the study of their effects on the heart. This study also

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established the difference in myocardial transport protein expression between salt, fat and sucrose-induced IR.

Abbreviations
FATP/CD36: Fatty acid transporterCD36; GLUT4: Glucose transporter4; IR: Insulin resistance; OGTT: Oral glucose tolerance test; PPAR-α: Peroxisome proliferation activator receptor alpha; AMPK: Adenosine monophosphate-activated protein kinase; mTOR01: Mammalian transcription factor of rapamycin 01.

Availability of data and materials
All data and material for this study will be provided upon request.

Declarations

Ethics approval and consent to participate
All of the experiments were conducted according to the approved guidelines set by Bowen University Animal Care and Use Research Ethics Committee, which is in agreement with the 'Guide for the Care and Use of Laboratory Animals' prepared by the National Academy of Science and published by the National Institutes of Health. The ethical approval number assigned for animal use in this study was BUTH/REC-125.

Consent to participate
Not applicable.

Competing interests
Authors declare no conflict of interest.

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