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Comparative Effects of Sucrose and Saccharin on Glucose metabolism and Metabolic Health

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ABSTRACT

Background: Over the years, sweetening agents have been utilized to heighten the flavor and aesthetics of food items. However, the influence of sweeteners on blood glucose homeostasis is still a source of discussion and worry. While some research imply that sweeteners have little or no effect on blood sugar levels, others suggest that they can affect glucose metabolism. This study was aimed to assess the precise impact of sweeteners on blood glucose regulation, investigating whether different types of sweeteners affect glucose metabolism differently.

Methodology: Thirty male Wistar rats, weighing between 140-160 g, were randomly grouped into three: Group one served as the control, Group Two received sucrose (100 mg/kg body weight), and Group Three was administered saccharin (5 mg/kg body weight). After the administration was complete, the animals were anaesthetized and sacrificed, Blood samples were obtained for insulin assays. The pancreas was dissected and used for both histological examination and determination of relative expression of Peroxisome Proliferator-Activated Receptor Gamma (PPARγ).

Results: The results show that both sucrose and saccharin caused significant increased body weight, blood glucose level, insulin level and relative expression of PPARγ gene. Saccharin seems to exert more profound effects on glucose metabolism via marked increase in body weight and insulin level compared to sucrose.

Conclusion: These findings suggest that saccharin exerts more profound effects on glucose metabolism via marked increase in body weight, predisposing one to obesity and obesity-related diseases, while sucrose has increased tendency to cause glucose intolerance.

Keywords: Sweeteners; PPARγ gene; glucose metabolism; insulin

INTRODUCTION

Glucose metabolism has been a topic of immense physiological and biochemical interest, considering its impact on general health and well-being, and the consequences of its maladjustment or dysregulation (1). It involves a series of vital stages, including the digestion, assimilation, transportation, and utilization of glycans, along with intracellular mechanisms like glycolysis, glycogen synthesis, glycogenolysis, and the pentose phosphate pathway (2). For optimal systemic functionality, the body relies on precise regulation of blood sugar levels orchestrated by hormones and neuropeptides secreted by various organs, maintaining blood glucose level within a narrow range, despite the fluctuations in blood sugar levels following meals and physical activity (3).

Over the years, sweetening agents have been utilized to heighten the flavor and aesthetics of food items (4). These sweeteners can either be naturally-derived or artificially synthesized (5). Sweeteners are commonly used to manage weight and blood glucose levels, but there is concern that their consumption may lead to glucose intolerance (6). This is due to their impact on responses that regulate glucose and energy homeostasis, as well as changes in gut micro-flora. Sweeteners interact with sweet taste receptors throughout the digestive system, which play a role in glucose absorption and insulin secretion (7).

Sweeteners, both natural and artificial, are increasingly popular in modern diets (10). However, the influence of sweeteners on blood glucose homeostasis is still a source of discussion and worry. While some research imply that sweeteners have little or no effect on blood sugar levels (8, 9), others suggest that they can affect glucose metabolism (10, 11). Given the increased prevalence of diabetes and metabolic disorders globally, knowing factors that control blood glucose homeostasis is vital for public health. Investigating how different sweeteners affect glycemic control can assist enhance dietary options for diabetes care, thereby reducing medication reliance and increasing overall health outcomes. Investigating the processes underlying sweeteners' influence on blood glucose homeostasis can help us better understand metabolic pathways and hormone control (11). Thus, this study seeks to understand the precise impact of sweeteners on blood glucose regulation, investigating whether different types of sweeteners affect blood glucose levels, insulin sensitivity, and other characteristics that contribute to overall metabolic health.

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MATERIALS AND METHOD

Ethical Considerations

This study was approved by institutional ethical review committee, Life Sciences, University of Benin, Benin city, Edo state (LS22035) on March 1, 2021. All the animals used were handled and maintained according to the guidelines of the committee.

Animals

Thirty male Wistar rats (140-160g) were be obtained from Animal house of Igbinedion University Okada for this study. The animals were acclimatized in well-ventilated cages for two weeks with free access to feed and water in a well-ventilated room.

Experimental Procedures

Pure sucrose and saccharin sweeteners (CDH-China) were purchased from Pyrex-IG scientific company, Edo state, Nigeria. All other chemicals used in this experiment were of analytical grade.

The animals were weighed at the start of the experiment, and randomly divided into three (3) groups (n=10) and treated as follows using oral gavage tube:

- Group 1: Control
- Group 2: Sucrose treated group (100 mg/kg body weight for 8 weeks)
- Group 3: Saccharin treated group (5 mg/kg body weight for 8 weeks) (12)

Analysis

Body Weight: After 8 weeks, the body weight was measured using an animal weighing scale (GMETLLAR-China) which was cleaned and calibrated to the manufacturer's standards. A compact, capacious container was employed on the scale as a sturdy platform. The rat was placed on the scale and gently handled to ensure accuracy. Weight was recorded in grams.

Blood Glucose Level: Accu-chek glucometer was used to determine the fasting blood sugar of the rats. They were fasted overnight for 12 hours before the procedure, and the tip of the rat tail was snipped using scissors (sterilized with spirit) in order to let out blood from the tail vein. Blood from the rat tail was dropped on the strip in the glucometer and the blood sugar reading was noted and recorded in mg/dL. Afterwards, all animals were sacrificed using light anesthesia with Ketamine (80mg/kg) and Xylazine (8mg/kg) given as a single intraperitoneal injection.

Pancreatic Weight: After dissection, pancreas was removed and weighed using a digital weighing (GMETLLAR-China) scale. The weights were recorded in grams.

Insulin Level: Blood was collected from each rat into ethylenediaminetetraacetic acid (EDTA) bottles. Plasma samples were obtained by centrifugation at 3500rpm for 10 min and the clear plasma obtained for insulin assay. Insulin level was assayed using Abcam's Insulin Rat ELISA A (Enzyme-Linked Immunosorbent Assay) Kit following instructions on the manufacturer's manual.

Histology of the Pancreas: Pancreas were obtained from rats, and immediately fixed in 10% formalin, and then treated with absolute grade of alcohol and xylol, embedded in paraffin and sectioned at 5–6 µm thickness. The sections were stained with routine Hematoxylin and Eosin (H&E) stain for studying the histopathological changes. Histological sections of pancreas were studied under light microscope (Olympus, Tokyo, Japan) 100x magnification with attached Omax 10.0MP digital camera and pancreas micrographs were obtained.

Gene expression: The relative expression of Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) gene in the pancreas was studied as described by Olumegbon *et al.* (13). The GAPDH gene was used to normalize the relative level of expression of each gene, and quantification of band intensity was done using "image J" software (13).

The primer sequence for PPARγ gene is given below:

Forward CGAGCTGGGAGTAGCCTGA

Reverse GATCACCAGCAGAGGTCCAG

Data Analysis

GraphPad Prism version 8.0.1 was used for the data analysis. One-way Analysis of Variance (ANOVA) was used to determine the differences between means among the groups, and followed by Tukey's post-hoc-test. The results were expressed as mean ± SEM. Differences between means were considered statistically significant at $p<0.05$.

RESULTS

Table 1 shows the results obtained for body weight, pancreatic weight, insulin level and blood glucose level. Body weight was significantly higher ($p <0.0001$) in Sucrose group (283.48±5.25) when compared with Control group (240.66±5.38), and in Saccharin group (310.30±2.36) when compared with Sucrose ($p=0.0262$) and Control groups ($p<0.0001$). Pancreatic weight was significantly higher ($p=0.0171$, $p=0.0070$ respectively) in Sucrose group (0.32±0.01) and in Saccharin group (0.33±0.01) when compared with Control group (0.24±0.03), but there was no significant difference in pancreatic weight between the Sucrose and the Saccharin groups ($p=0.9278$). Blood glucose level was significantly higher ($p <0.0001$) in Sucrose group (122.60±1.21) when compared with Control group (96.8±1.39), and it was also significantly higher ($p <0.0001$) in Saccharin group (115.60±1.36) when compared with Control

group. Also, blood glucose level was significantly higher (p=0.0074) in Sucrose group compared with Saccharin group. Insulin level was significantly higher (p <0.0001) in Sucrose group (2.38±0.06) when compared with Control group (1.05±0.06), and it was also higher (p <0.0001) in Saccharin group (2.64±0.05) when compared with control group. Also, insulin level was significantly higher (p=0.0182) in Saccharin group when compared with Sucrose group.

Figure 1 shows significantly higher (p<0.0001) relative expression of PPARγ gene in Sucrose group (182.00±1.46) and Saccharin group (205.60±1.96), compared to the Control group (110.80±0.87). Also, there was significantly higher (p>0.0001) expression in Saccharin group compared with the Sucrose group.

Figure 2.0 shows the histology (H&E stained) of the pancreas. Scale bar = 50µm. 3Pi shows Control group with normal exocrine acini (EA), islets of Langerhans (IL) and interlobar blood vessels (BV), 3Pii shows Sucrose group (100 mg/kg body weight) with normal interlobar artery (IA), exocrine acini (EA) and islets of Langerhans (IL), 3Piii shows Saccharine group (5 mg/kg body weight) with normal islets of Langerhans (IL), exocrine acini (EA), pancreatic duct (PD) and interlobar artery (IA).

Table 1: Results obtained in the different groups, presented as MEAN±S.E.M

	Control	Sucrose	Saccharin
Body weight (g)	240.66±5.38	283.48±5.25*	310.30±2.36*#
Pancreatic weight (g)	0.24±0.03	0.32±0.01*	0.33±0.01*
Blood glucose (mg/dl)	96.8±1.39	122.60±1.21*	115.60±1.36*#
Insulin level (µu/ml)	1.05±0.06	2.38±0.06*	2.64±0.06*#

*denotes significant difference (p<0.05) when compared with Control group.
#denotes significant difference (p<0.05) when compared with Sucrose group.

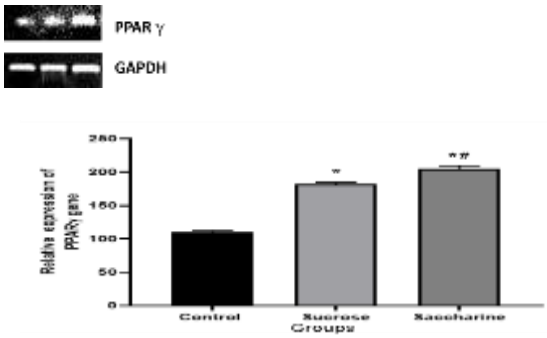

Figure 1: Showing the effect of Sucrose and Saccharine on relative gene expression of PPARγ gene in male wistar rat.
*denotes significant difference (p<0.05) when compared with Control group.
#denotes significant difference (p<0.05) when compared with Sucrose group.

DISCUSSION

Glucose serves as the primary metabolic substrate for the production of energy in tissues (14). It is essentially regulated by the body within a close range by a mechanism termed glucose homeostasis (15).

The result of this study shows that both the artificial sweetener (saccharin) and the natural sweetener (sucrose) increases blood glucose level, and this result is in concordance with existing literature (16, 17). Markedly elevated plasma glucose concentration as seen in the Sucrose group, may be due to the fact that sucrose is a disaccharide containing one unit of glucose and fructose (18) while saccharin has no carbohydrate content as it is known as a zero calorie/carb sweetener (19). However, the ability of saccharin to even cause a rise in blood glucose level at all may be due to its tendency to lead to glucose intolerance as a result of the alterations it causes in the composition and function of the intestinal microbiota after a long consumption period (6).

Insulin, a peptide hormone released by pancreatic beta cells, plays immense role in the regulation of glucose levels in the body. It helps in maintaining glucose homeostasis by promoting cellular glucose uptake and influencing the metabolism of carbohydrates, proteins, and lipids (20). The findings from this research indicates that both classes of sweeteners lead to increased insulin secretion, in line with previous research (21). Saccharin's ability to greatly stimulate the beta cells of the pancreatic islet during the cephalic stage of its digestion (22), might account for its greater effect on insulin secretion as observed in this study. Also, the significantly increased insulin level in the Saccharin group (compared with the Sucrose group) can be tied to the decreased blood glucose level and markedly increased body weight observed, following the established anabolic role of insulin.

Peroxisome proliferator-activator receptor gamma (PPARγ) controls lipid and glucose metabolism by indirectly promoting glucose uptake by the fat cells, liver cells and cells of the skeletal muscles (23). An upregulation in the relative expression of PPARγ gene was observed in in the test groups, in tandem with previous research (24, 25). This increase in PPARγ gene expression might account for the increase in glycemic rate in the test groups, thereby increasing glucose uptake by fat cells, liver cell and cells of the skeletal muscles as a regulatory mechanism (26), and can be linked to the increased body weights observed in the test groups, confirming the regulatory role of PPARγ gene in absolute fat mass storage and obesity development (27), accounting for the marked increase in body weight in the Saccharin group. The study also observed a positive correlation between and insulin level in the Saccharin group, further confirming the role of gene in glucose metabolism.

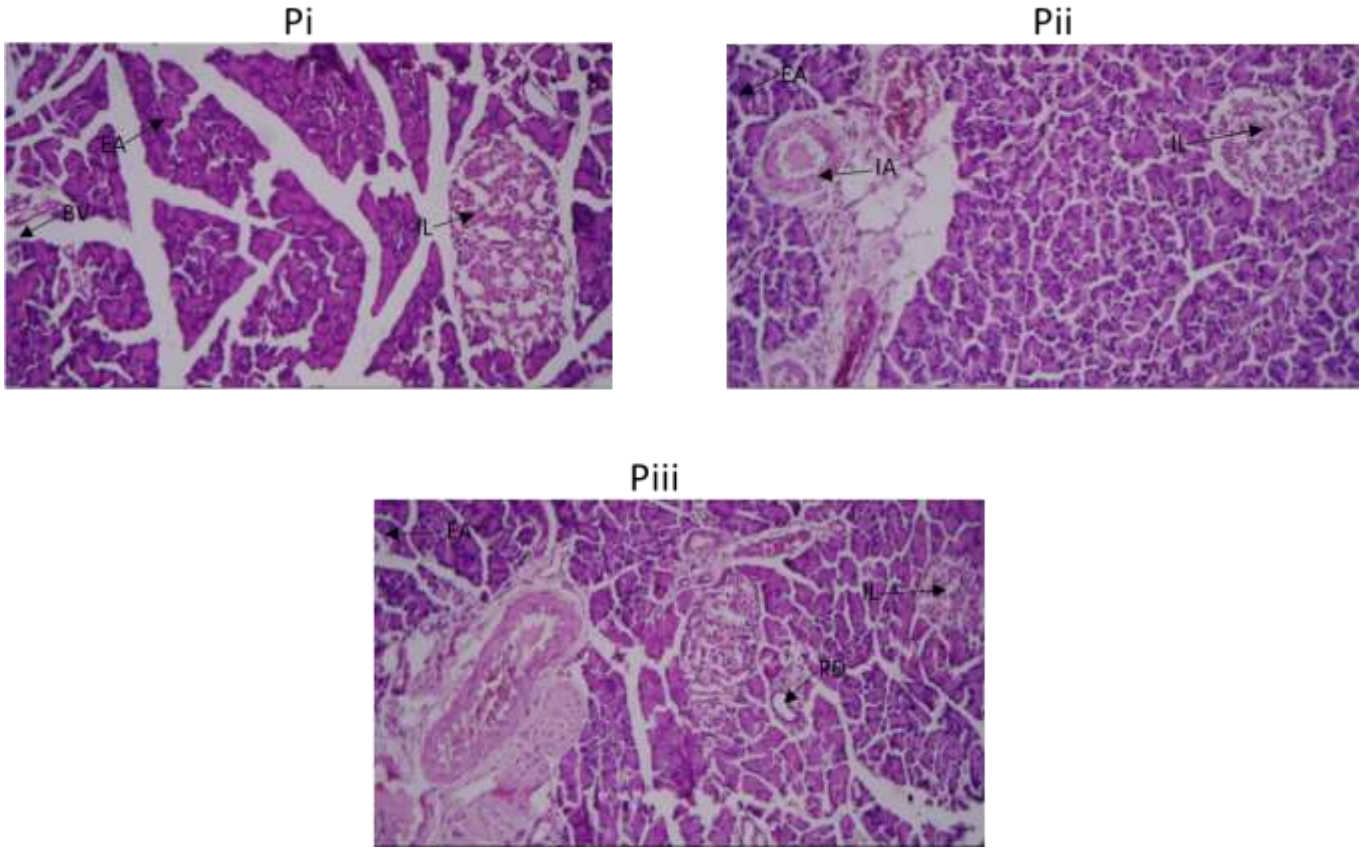

Figure 2.0: Photomicrograph of Pancreas (Pi, Pii and Piii) of control group, sucrose fed group and saccharin fed group of male Wistar rats (H&E; 100x). 3Pi shows Control group with normal exocrine acini (EA), islets of Langerhans (IL) and interlobar blood vessels (BV), 3Pii shows Sucrose group (100 mg/kg body weight) with normal interlobar artery (IA), exocrine acini (EA) and islets of Langerhans (IL), 3Piii shows Saccharine group (5 mg/kg body weight) with normal islets of Langerhans (IL), exocrine acini (EA), pancreatic duct (PD) and interlobar artery (IA).

The pancreas is a dual functional organ which carries out both exocrine and endocrine activities, the endocrine part of the pancreas comprises of the cells of the pancreatic islet of Langerhans which includes; the alpha, beta, delta, epsilon and upsilon cells (28). The result of this research shows that both sucrose and saccharin lead to increased pancreatic weight, as reported by previous work (29, 30). The increase in pancreatic weight brought about by these sweeteners may be due to their tendency to cause pancreatic inflammation, as well as fatty infiltration in the pancreas (29, 30).

Conclusion: Intake of sucrose and saccharin both significantly elevates blood glucose level, insulin secretion and PPARγ gene expression. Saccharin seems to exert more profound effects on glucose metabolism via marked increase in body weight, predisposing one to obesity and obesity-related diseases, while sucrose has increased tendency to cause glucose intolerance.

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