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Dietary Management of Diabetes with Unripe Plantain (*Musa paradisiaca*): Its Effects on Glucose Transporters (Glut1 and Glut4) and Amp-Activated Protein Kinase Activities in Streptozotocin-Induced Diabetic Rats

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ABSTRACT

This study was aimed at investigating the biochemical basis of dietary management of diabetes mellitus using unripe plantain in streptozotocin (STZ) induced diabetic rats. The effects of unripe plantain incorporated feeds on the regulation of glucose transport protein 1 (GLUT 1), glucose transport protein 4 (GLUT 4) and AMP-activated protein kinase (AMPK) activities was studied using acceptable chemical and biochemical methods. Twenty-five (25) male albino Wistar rats were divided into five (5) groups of five (5) rats each. Group 1 (non-diabetic/normal control), group 2 (diabetic, not treated) and group 3 (diabetic, treated with glibenclamide 5mg/kg body weight) all received standard rat feed. Group 4 (diabetic, fed unripe plantain incorporated feed 600mg/kg body weight) and group 5 (diabetic, fed unripe plantain incorporated feed 800mg/kg body weight). The experiment lasted for 28days. The biochemical parameters were measured at the end of the experiment. Groups 3, 4 and 5 rats showed a significant ($P<0.05$) increase in GLUT 4 activity when compared with group 1/normal control rats, whereas group 2 rats showed a significant ($P<0.05$) decrease in activity. Rats in group 4 and group 5 showed a non- significant ($P>0.05$) difference whereas rats in group 2 and group 3 showed a significant decrease in GLUT 1 levels when compared to the control group. There was no significant ($P>0.05$) difference in AMPK levels of all the groups. The results obtained show that unripe plantain possesses anti-diabetic properties and may be effective as a dietary management option for diabetics.

Keywords: Diabetes, Streptozotocin, Glucose transporters, GLUT1, GLUT4

INTRODUCTION

Diabetes Mellitus is a global metabolic disease characterized by hyperglycaemia and affects essential biochemical pathways in the body resulting to complications such as; renal disorders, neuropathy, retinopathy, ketoacidosis, and cardiovascular diseases [1]. It is caused by impaired regulation of the metabolism of carbohydrate and lipids where although there is sufficient supply of glucose, the body still behaves as if it is starved; hence glucose produced by the liver is not utilized by other tissues [2]. The global prevalence of diabetes continues to be on the increase with Type 2 being the most common form. Type 2 diabetes mellitus is typified by gradual development of resistance to insulin and beta-cell dysfunction, in addition to decreased insulin secretion in some cases [3].

Glucose movement across the cell membrane is the rate limiting step of glucose utilization and is regulated by a family of membrane proteins known as Glucose Transporters (GLUTs) [4]. Notwithstanding whether there is translation or transcription, insulin and physical activity causes acute stimulation and recruitment of GLUT4 to the surfaces of the cells of skeletal muscle and fat tissue [5]. Insulin also stimulates GLUT1 which is expressed in the blood. Insulin appears to be the main hormone affected in diabetes since the pancreas is involved in insulin production [6]. GLUT4 translocation, in response to insulin, in the skeletal

muscle of people suffering from type 2 diabetes is usually decreased by approximately 90% [7] The main cellular mechanism for clearance of glucose taken from foods is insulin-mediated glucose transport into the cells of skeletal muscle [8].

The GLUT4 glucose transporter is an important facilitator of glucose clearance out of the blood and is therefore a core controller of glucose homeostasis [7]. Studies have proven that although glucose transporters move from their intracellular membrane compartment to the surface of the cells in response to insulin, the affinity of the transporters for glucose binding is not affected by insulin [9,10]. There is a reduced GLUT4 protein content in intracellular and plasma membranes of skeletal muscles of STZ-induced diabetic rats. In STZ-treated rats, insulin caused the mobilization of GLUT4 out of the vesicles, but the fusion of GLUT4 with the plasma membrane was diminished. Conversely, the GLUT1 transporter protein increased in the cell membrane of the diabetic rats [11]. After the coming of insulin and other drugs there exist quite a number of limitations in their use even though they have been useful for managing the disease. These limitations include their side effects and high cost as well as lack of accessibility to low income countries. Another important limitation is the need to combine two or more of these drugs for better effects. These reasons have made it preferable to embrace and adopt alternatives which include dietary management. Increasing consumption of soluble fiber is one effective dietary treatment. Its benefits in terms of serum cholesterol concentrations and colonic function are well established [12]. Some diets contribute to the management of diabetes via ensuring low glycaemic index. Diets that incorporate low glycaemic index foods reduce hyperglycemia in type 2 diabetes [3].

Adenosine monophosphate-activated protein kinase (AMPK) performs a vital function in maintaining equilibrium of whole-body energy, insulin signaling and the catabolism/anabolism of glucose and fats [13]. It is a probable controller of the sequence of reactions concerned with stress-induced translocation of GLUT4. Previous studies show that myocardial ischemia and skeletal muscle contraction stimulate AMPK and that AMPK activation causes a surge in glucose uptake. Some studies confirm that AMPK activation causes the translocation of myocardial GLUT4 thereby raising glucose uptake [14,15]. Stimulation of AMPK by a number of different mechanisms was shown to result in a rise in glucose uptake by the skeletal and cardiac muscle, and also in cell culture [1] There is indication that stimulation of AMPK is adequate for activation of uptake of glucose into the muscle cells and that long term expression of the constitutively active AMPK mutant raised the expression of GLUT1 and of GLUT4 protein [15].

Following the alarming rate at which the incidence of diabetes is snowballing and in the light of the potentials that unripe plantain has in its management, there is need for studies that could help in our understanding of the biochemical basis for such dietary management of the disease. No doubt many studies have corroborated that unripe plantain is effective in diabetes management, this study however seeks to delve into the effect that unripe plantain has on regulation of GLUT4 and GLUT1 glucose transport proteins in the skeletal muscle and blood respectively in a bid to tackle hyperglycaemia.

METHODOLOGY

Sample collection and preparation

The unripe plantain (*Musa paradisiaca*) variety was obtained from the Ahia ohuru market in Aba, Nigeria. It was identified and authenticated by Mr. Ibe of the Forestry Department, Michael Okpara University of Agriculture, Umudike, Nigeria. The plantain was properly peeled and soaked in water for 10minutes, and washed. It was then air dried to constant weight, and processed to flour. The processed flour was used to formulate the test feed.

Formulation of test feed

The plantain feed was formulated in two concentrations tagged 60% and 80% unripe plantain feeds respectively. The 60% unripe plantain feed contained 600g of unripe plantain per kg of the formulated feed, whereas the 80% unripe plantain feed contained 800g of unripe plantain per kg of the formulated feed. The source of protein, casein 300g/kg and 100g/kg weight of formulated feed was incorporated into the 60% and 80% unripe plantain respectively. Vitamins, salt and oil (vegetable oil) were also incorporated into the feeds at 50g/kg, 20g/kg and 30g/kg respectively. The mixture was processed into pellets and fed to the rats in that form.

Animal Experiments

Selection of animals

Twenty-five (25) male albino Wistar rats with an average body weight 95.48g were obtained from the animal house of the Department of Veterinary Medicine, University of Nigeria, Nsukka, Enugu State, were used for the study. The animals were kept in metabolic cages in the animal house of the Department of Biochemistry, Michael Okpara University of Agriculture, Umudike. The rats were allowed to acclimatize for a period of one week under a constant 12- hour light and dark cycle at room temperature prior to the commencement and throughout the duration of the experiment. They were provided animal feed (pelletized commercial growers feed produced by UAC Nig Ltd.) and water *ad libitum*.

Animal grouping

The rats were divided into five (5) different groups of 5 rats each and given the following treatment.

Group 1: Normal control (animal feed and water).

Group 2: Positive control (animal feed and water).

Group 3: Standard control (treated with glibenclamide [5mg/kgbwt], animal feed and water).

Group 4: Test group 1 fed with formulated diet 600g/kgwt unripe plantain and water.

Group 5: Test group 2 fed with formulated diet 800g/kgwt unripe plantain and water.

NOTE: Rats in groups 2-5 were confirmed diabetic by inducing them with 65mg/kgbwt of STZ intraperitoneally.

Induction of diabetes mellitus

Freshly prepared solution of streptozotocin (0.1g dissolved in 5ml of freshly prepared sodium citrate buffer 0.1M, pH 4.5) was injected intraperitoneally to the rats in groups 2-5 at a dose of 65mg/kg body weight while rats in group 1 serve as normal control. After a period of 72 hours, blood was collected from the tail vein of the rats, and their blood glucose levels were measured using a blood glucose kit (One touch glucometer). Rats with moderate diabetes (blood glucose ≥200mg/dl) were selected for the experiment in groups 2-5.

Experimental procedure

The STZ treated rats with stable diabetic condition were used for the experiment. They were grouped as stated earlier. Their diets and water were given from day 1 of the experiment to day 28. The anti-diabetic standard drug, glibenclamide was dissolved in water and administered to the group 3 rats orally via the use of a gavage at a dose of 5mg/kgbwt. Proper sanitation was observed within and around the animal house. The cages were cleaned daily. The rats were weighed daily and their blood glucose level taken on a weekly basis.

Preparation of tissue homogenate for GLUT1, GLUT4 and AMP-kinase analysis

For GLUT 1 and GLUT 4: Crude membrane fractions of whole blood and crude membrane fraction of thigh muscle were washed once with TES buffer (20 mM Tris, 1 mM EDTA, 250 mM sucrose and 0.1 mM phenyl methyl sulfryl flouride (PMSF), pH 7.4), and then homogenized with a potter (Clearance, 0.2 mm) in a total volume of 4.7 ml. The samples were then spun down for 30 min at 50,000g at 4ºC and the pellet of the centrifugation re-suspended in 350 µL of TES buffer. The resulting crude membrane fractions were used for analysis.

For AMP-kinase: The excised liver was washed with normal saline, blotted dry and weighed, and then minced into small pieces using very clean scalpel. The minced tissue was transferred into a Potter-Elvehjem homogenizer on ice, and cold homogenization buffer (250 mM sucrose, 1 mM EDTA, 10 mM Tris HCl buffer, pH7.2 plus protease inhibitors) was added to the homogenizer and the tissue was properly homogenized by using up to 20 strokes. The sample was then transferred to microfuge tube and sonicated for two 10 seconds pulses with the help of probe sonicator. Thereafter, the sample was kept in ice bath and probes were kept away from the sample-air interface to minimize foaming. The homogenate was used for analysis.

Determination of glucose transporter 4 (GLUT4) concentration

The reagents used were prepared as directed by the instructions found on the kit. All standards and samples were duplicated as recommended to the Microelisa Strip plate. 50 µL of the standard was added to the standard wells while 10 µL of each testing samples and 40 µL of diluent sample were added to the testing sample wells. 100 µL of HRP-conjugate reagent was added to each well and covered with an adhesive strip, thereafter the samples were incubated for 60 minutes at 37ºC. Each well was then aspirated and washed. The process was repeated four times for a total of five washes. Each well was washed by filling with wash solution (400 µL) using a squirt bottle. The liquid at each step was completely removed for good performance. After the last wash, all the remaining wash solution was removed by aspirating or decanting, and the plate was inverted and blotted against clean paper towels. Thereafter, 50 µL chromogen solution A and 50 µL chromogen solution B was added to each well. The mixture was gently mixed and incubated for 15 minutes at 37ºC. It was protected from light. 50 µL of stop solution was then added to each well and the colour in the wells changed from blue to yellow. The optical density was then read at 450 nm using microtiter plate reader within 15 min against a blank. The GLUT4 concentration was measured in ng/mL.

Determination of glucose transporter 1 (GLUT1) concentration

The reagents used were prepared as directed by the instructions found on the kit. All standards and samples were duplicated as recommended to the Microelisa Strip plate. 50 µL of the standard was added to the standard wells while 10 µL of each testing samples and 40 µL of diluent sample were added to the testing sample wells. 100 µL of HRP-conjugate reagent was added to each well and covered with an adhesive strip, thereafter the samples were incubated for 60 minutes at 37ºC. Each well was then aspirated and washed. The process was repeated four times for a total of five washes. Each well was washed by filling with wash solution (400 µL) using a squirt bottle. The liquid at each step was completely removed for good performance. After the last wash, all the remaining wash solution was removed by aspirating or decanting, and the plate was inverted

and blotted against clean paper towels. Thereafter, 50 µL chromogen solution A and 50 µL chromogen solution B was added to each well. The mixture was gently mixed and incubated for 15 minutes at 37ºC. It was protected from light. 50 µL of stop solution was then added to each well and the colour in the wells changed from blue to yellow. The optical density was then read at 450 nm using microtiter plate reader within 15 min against a blank. The GLUT1 concentration was measured in ng/mL.

Determination of AMP-kinase concentration

The reagents used were prepared as directed by the instructions found on the kit. All standards and samples were duplicated as recommended to the Microelisa Strip plate. 50 µL of the standard was added to the standard wells while 10 µL of each testing samples and 40 µL of diluent sample were added to the testing sample wells. 100 µL of HRP-conjugate reagent was added to each well and covered with an adhesive strip, thereafter the samples were incubated for 60 minutes at 37ºC. Each well was then aspirated and washed. The process was repeated four times for a total of five washes. Each well was washed by filling with wash solution (400 µL) using a squirt bottle. The liquid at each step was completely removed for good performance. After the last wash, all the remaining wash solution was removed by aspirating or decanting, and the plate was inverted and blotted against clean paper towels. Thereafter, 50 µL chromogen solution A and 50 µL chromogen solution B was added to each well. The mixture was gently mixed and incubated for 15 minutes at 37ºC. It was protected from light. 50 µL of stop solution was then added to each well and the colour in the wells changed from blue to yellow. The optical density was then read at 450 nm using microtiter plate reader within 15 min against a blank. The AMP-Kinase concentration was measured in nmol/L.

Statistical analysis

The data obtained in the study was analyzed with statistical products and service solutions (SPSS) version 20.0 using one-way analysis of variance (ANOVA). The statistically analyzed data were reported as mean ± standard deviation. Significant difference was accepted at 95% confidence level of probability ($p<0.05$).

RESULTS

GLUT 4 concentration of treated rats

The results as shown in table 1 shows that there was a significant ($p<0.05$) decrease in GLUT 4 concentration of group 2 rats when compared with group 1 rats. Groups 3, 4 and 5 showed a significant ($p<0.05$) increase when compared to group one rats.

Table 1: GLUT 4 concentration of treated rats

Groups	GLUT 4 concentration (ng/ml)
Group 1	15.34±0.40^{b}
Group 2	13.38±0.51^{a}
Group 3	15.92±0.41^{bc}
Group 4	18.32±0.64^{d}
Group 5	17.11±2.16^{c}

Values are means±SD

$^{a-d}$Means with different superscripts along the column are significantly different ($p<0.05$).

GLUT 1 concentration of treated rats

The results show that there was a significant ($p< 0.05$) decrease in GLUT 1 concentration of group 2 rats when compared to group 1 rats. Similarly, group 3 rats show a significant ($p< 0.05$) decrease when compared to group 1 rats. Conversely, group 4 rats showed a non-significant ($p>0.05$) increase when compared with group 1 rats.

Table 2: GLUT 1 concentration of treated rats

Groups	GLUT1 concentration (ng/ml)
Group 1	120.02±7.05^{bc}
Group 2	92.45±15.35^{a}
Group 3	98.14±21.79^{a}
Group 4	124.04±12.71^{bc}
Group 5	115.89±15.11^{ab}

Values are means±SD

$^{a-c}$Means with different superscripts along the column are significantly different ($p<0.05$).

AMP-kinase levels of treated rats

The results as shown in table 3 shows that there was a non-significant ($p<0.05$) decrease in AMP-kinase levels of group 2 and group 3 rats when compared with group 1 rats. On the other hand, group 4 and 5

rats showed a non-significant ($p>0.05$) increase when compared with group 1 rats.

Table 3: AMP-kinase levels of treated rats

Groups	AMP-kinase (nmol/L)
Group 1	199.20±7.05[a]
Group 2	198.80±50.18[a]
Group 3	189.00±10.93[a]
Group 4	214.60±14.05[a]
Group 5	211.60±18.80[a]

Values are means±SD

Values with same superscripts are not significant ($p>0.05$)

DISCUSSION

The significant increase in GLUT4 concentration of diabetic rats fed unripe plantain incorporated feed and that given glibenclamide when compared to the diabetic control rats may be a result of increased insulin sensitivity and thus increased movement of GLUT4 into the plasma membrane of the cells since it has been determined that insulin signaled the release/translocation of glucose transporters from intracellular membrane compartment to cell surface [16,17]. Diabetic animals with defective glucose uptake in skeletal muscle appear to be the result of low level of GLUT4 expression [18, 19, 20]. Therefore, the improvement of GLUT4 contents and/or translocation to the plasma membrane has long been regarded as a potential target in the treatment of diabetes mellitus [21, 22, 23, 24]. In this study, the increase in the muscular GLUT4 concentration indicated that the unripe plantain diet improved glucose utilization in skeletal muscle by restoring translocation of GLUT4 to the plasma membrane. Diabetic control rats showed a significant decrease in GLUT4 concentration when compared with non-diabetic rats [23, 25, 26]. This suggests reduced insulin sensitivity and reduced uptake of glucose by cells and by extension posits that unripe plantain may possess antihyperglycemic effects. It is pertinent to note that studies on the effect of unripe plantain on glucose transporters have not been reported as no literature could be found in that regards.

The decreased GLUT1 concentration in diabetic control rats when compared with non-diabetic rats is a result of its hyperglycemic state. This is in agreement with the work of Wang *et al*., which reported that GLUT1 concentration was reduced in erythrocyte membrane of people with diabetes [18].

The significant increase in GLUT1 concentration of diabetic rats fed with the formulated diet when compared with the diabetic control rats suggests that unripe plantain also has the potentials to improve glucose transport even in non-insulin dependent glucose transporters. Although, there was a non-significant difference in GLUT1 concentration of diabetic rats fed with the formulated diet when compared with the non-diabetic rats, the results suggests that the difference was sufficient enough to have an ameliorative effect on the diabetic state.

The non-significant increase in the AMP-kinase levels of diabetic rats fed the formulated diet when compared with the non-diabetic rats, as well as the diabetic control rats is an indication that its activation is adequate for the uptake of glucose into the muscle cells via an increase in cell surface expression of GLUT1 and GLUT4. The decreased GLUT1 concentration in diabetic control rats when compared with non-diabetic rats is a result of its hyperglycemic state. This is in agreement with the work of Wang et al., which reported that GLUT1 concentration was reduced in erythrocyte membrane of people with diabetes [18]. The significant increase in GLUT1 concentration of diabetic rats fed with the formulated diet when compared with the diabetic control rats suggests that unripe plantain also has the potentials to improve glucose transport even in non-insulin dependent glucose transporters. Although, there was a non-significant difference in GLUT1 concentration of diabetic rats fed with the formulated diet when compared with the non-diabetic rats, the results suggests that the difference was sufficient enough to have an ameliorative effect on the diabetic state.

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