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Effects of Caffeine Administration on Brain Sodium-Potassium ATPase Activity in Healthy and Streptozotocin-Induced Diabetic Female Wistar Rats

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Background: Diabetes mellitus affects the morphology and plasticity of the brain, leading to cognitive and electrophysiological impairment. We aim to determine effects of caffeine on brain Na^+/K^+-ATPase activity in streptozotocin-induced diabetic female rats.
Methods: Female Wistar rats weighing about 180–200 g were used for the study and were divided into three study groups. Study groups A 1, 2, 3 were healthy rats administered 15, 20, 25 mg/kg caffeine intraperitoneally (i.p), respectively, for 5 weeks; study groups B 1, 2, 3 administered 15, 20, 25 mg/kg caffeine (i.p), respectively, for 5 weeks and maintained on caffeine for 3 weeks after diabetes induction; study groups C 1, 2, 3, were diabetic rats administered 15, 20, 25 mg/kg caffeine (i.p), respectively, for 3 weeks; control and diabetic untreated were administered normal saline. After administration, brains were homogenized in sucrose solution and kept at 4°C. Enzyme assay was conducted.
Results: A significant ($p < 0.05$) decrease in Na^+/K^+-ATPase activity of diabetic untreated (250.9 ± 0.26) when compared with control (415.6 ± 0.26). Study groups A 1, 2, 3 showed an increase in Na^+/K^+-ATPase activities (1022.0 ± 0.51, 825.0 ± 0.22, 498.6 ± 0.04, respectively). Study groups B 1 and 3 showed a significant decrease in Na^+/K^+-ATPase activities (280.0 ± 0.40 and 232.4 ± 0.34, respectively) when compared with control and a significant increase in group 2 (374.0 ± 0.34) when compared with diabetic group. Diabetic rats in study C (groups 1, 2, 3) showed an increase in Na^+/K^+-ATPase activities (468.8 ± 0.51, 428.5 ± 0.50, and 259.9 ± 0.20, respectively) when compared with diabetic untreated.
Conclusion: This study shows that caffeine at low to moderate doses improves the brain Na^+/K^+-ATPase activities in diabetic rats.

Introduction

DIABETES MELLITUS (DM), commonly referred to as diabetes, is a group of metabolic diseases in which there is high blood sugar levels over a prolonged period. This is due to either the pancreas not producing enough insulin or because cells of the body do not respond properly to the insulin that is produced.[1] There are three main types of DM.[2] Type I DM is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency. This type can further be classified as immune mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, in which beta cell loss is a T-cell-mediated autoimmune attack.[3] Type 2 DM is the most common type characterized by insulin resistance, which may be combined with relatively reduced insulin secretion1. The ◀AU2 defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. This is due primarily to lifestyle factors and genetics.[4] Gestational diabetes mellitus (GDM) is defined by glucose intolerance of variable severity with onset of first recognition during pregnancy.[5] Hyperglycemia during pregnancy is found to be associated with various maternal and perinatal adverse outcomes.[6]

The cause of diabetes depends on the type. Type 2 diabetes is due primarily to lifestyle factors and genetics.[4] Type 1 diabetes is also partly inherited and then triggered by certain infections, with some evidence pointing at

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Coxsackie B4 virus. If the amount of insulin available is insufficient, the cells respond poorly to the effects of insulin (insulin insensitivity or resistance), or if the insulin itself is defective, then glucose will not have its usual effect, so it will not be absorbed properly by the body cells that require it, nor will it be stored appropriately in the liver and muscles. The net effect is persistent high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis.

The classical symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased hunger).[7] Symptoms may develop rapidly (weeks or months) in type 1 diabetes, while in type 2 diabetes they usually develop much more slowly and may be subtle or absent.

DM affects the morphology and plasticity of the brain, causing cognitive, memory, and electrophysiological impairment. Diabetes often leads to complications such as retinopathy, peripheral neuropathy, and stroke.[8] There is evidence signifying that type 1 and type 2 diabetes can cause complications within the central nervous system (CNS).[9,10] Manifestations of diabetes-induced CNS complications may include structural alterations or brain atrophy, as well as changes in electrophysiological features that ultimately result in deficits in cognitive activity.[11] Dysfunctional regulation of glucose elicits neuronal synaptic reorganization[12] and increased proliferation of astrocytes[13] in the hippocampus of streptozotocin (STZ)-induced diabetic rodents, an experimental model of type 1 diabetes.

When blood sugar levels start to climb in diabetes, a number of body systems are affected and that includes the brain, since studies have linked diabetes with a higher risk of stroke and dementia. A new study[14] reported that changes in blood vessel activity in the brains of diabetics may lead to drops in cognitive functions and their ability to perform daily activities

From studies performed in adults with type 1 diabetes, reductions in measures of motor speed and psychomotor efficiency can be seen in patients in midlife.[15] These neurocognitive changes have been associated with a reduction in white matter volume or alteration in white matter histology in some[16,17] but not all[18,19] investigations. Reduction in gray matter density in brain regions responsible for language processing and memory[19] and generalized atrophy[20] have also been identified in young adults with long-standing type 1 diabetes. Patients with chronic hyperglycemia,[21] early onset of disease,[22] or recurrent severe hypoglycemia[23] appear to be at particular risk for the development of changes in brain structure and function over time, although these associations have not been consistently observed in all groups of subjects with type 1 diabetes who have been investigated.[18,19]

Also, glucose and insulin are both instrumental regulators of cognitive function,[24–27] further supporting the hypothesis that improper regulation of these two factors may contribute to cognitive deficits in diabetes.[24–29]

Caffeine is the common name for 1,3,7-trimethylxanthine, which was derived from the German word *kaffee* and the French word *café*, each meaning coffee.[30] It is a naturally occurring alkaloid that is found in varying quantities in the beans, leaves, and fruits of more than 60 plants. Some common sources of caffeine are the kola nut (Cola acuminata), cacao bean (Theobroma cacao), yerba mate (Ilex paraguariensis), and guarana berries (Paullinia cupana); however, roasted coffee beans (Coffea Arabica and Coffea robusta) and tea leaves (Camellia sinensis) are the world's primary sources of dietary caffeine.[31]

Caffeine has been widely studied in a variety of areas regarding human health and performance.[32] Many studies confirm caffeine's ability to enhance mood and alertness,[33,34] exercise performance,[34] the speed at which information is processed, awareness, attention, and reaction time.[36] In addition, research has suggested that caffeine can aid in reducing symptoms associated with Parkinson's disease (PD) such as the deterioration of gross and small motor skills and tremors.[37,38] Since PD is a neurodegenerative disease that results in progressive loss of dopaminergic neurons of the substantia nigra, caffeine a nonselective adenosine antagonist is thought to aid in improving the performance of the dopaminergic system by blocking the AA_2 receptors, thus stimulating dopamine release.[38]

The relationship between caffeine and DM has been a controversial topic among scientists. However, caffeine has been reported to have both positive and negative effects on DM. Caffeine consumption has been associated with a lower risk of DM type 2. The majority of the studies on this topic were done on coffee. Test results indicate that consumers who drink at least three or more cups of either caffeinated or decaffeinated coffee every day show a decrease in the risk of type 2 diabetes. In Japan, a study was done to examine the relationship between consumption of green, black, and oolong teas and the risk of diabetes; and it was found that caffeine containing beverages were associated with a decreased risk of type II diabetes.[39]

Caffeine acts as an antagonist of adenosine A_1 and A_{2A} receptor at a nontoxic dose.[40] Caffeine consumption has been reported to alleviate cognitive impairment in both humans and animals.[41,42]

STZ-induced diabetes modifies the expression and density of adenosine receptors in the hippocampus[43] and also reduced the sodium-potassium ATPase (Na^+/K^+-ATPase) in the brain.[44]

Na^+/K^+-ATPase (sodium-potassium adenosine triphosphatase, also known as Na^+/K^+ pump, sodium-potassium pump, or sodium pump) is an antiporter-like enzyme (an electrogenic transmembrane ATPase) located in the plasma membrane of all animal cells.

Na^+/K^+-ATPase helps maintain resting potential, effect transport, and regulate cellular volume.[45] It also

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functions as a signal transducer/integrator to regulate MAPK pathway, ROS, as well as intracellular calcium. In most animal cells, Na^+/K^+-ATPase is responsible for about 1/5 of the cell's energy expenditure. For neurons, Na^+/K^+-ATPase can be responsible for up to 2/3 of the cell's energy expenditure.[46]

This enzyme, found in all mammalian cell membranes, is necessary for proper cellular function since it helps to preserve the ionic gradients across the cell membrane and thus the membrane potential and osmotic equilibrium of the cell.[47] This function is crucial for cell survival and body homeostasis, which is why it is a targeted focus of this study.

Na^+/K^+-ATPase malfunction and mutation have been implicated in renal dysfunction, hypertension, and Parkinsonism.[48]

Brain Na^+/K^+-ATPase enhances neuroprotection, memory consolidation, and diminishes cognitive deficits.[49]

Diabetes has a marked effect on the metabolism of a variety of tissues and because the Na^+/K^+-ATPase is critical for the membrane potential and many transports, a change in its activity in diabetes would have a profound consequence in these tissues.[50]

Among the diabetes-induced metabolic changes, disturbances of Na^+/K^+-ATPase activity have been widely reported.[51] Das and colleagues[52] first described a decrease of this enzyme activity in the sciatic nerve of diabetic rat, whereas an increase in enzyme activity was found in mucosa of the small intestine of diabetic rat.[53] These two examples illustrate the different effects of diabetes on Na^+/K^+-ATPase depending on the tissues. Thus, it has been observed that the brain Na^+/K^+-ATPase activity is reduced in the diabetic state in male animals.[44]

However, it has been reported[54] that female and male brains differ. The differences begin early during development due to the combination of genetic and hormonal events and continue throughout the life span of an individual. They further emphasized that female reproductive status has to be taken into account when studying sex differences in health and disease susceptibility, in the pharmacological effects of drugs, and in the study of brain and behavior.

Physiological sex differences account for marked differences in disease incidence, manifestation, prognosis, and treatment observed between the sexes. Differences in disease susceptibility, time of onset of symptoms, and drug response have become evident in diseases such as cancer, obesity, coronary heart disease, autoimmune and mental health disorders, among others.[55] This report highlights the need to conduct hypothesis-driven biomedical studies that take into account sex as a basic human variable. The report also validates the need for research on sex-based differences at the molecular, cellular, and whole organism levels and at different stages of the life span. Also, it further recommends the use of animal models that best mimic conditions being addressed.[55]

Since previous studies were carried out on male rodents treated after induction of diabetes with a specific dose of caffeine, we therefore aim to determine the effects of caffeine (an adenosine receptor antagonist) on brain Na^+/K^+-ATPase activity in STZ-induced diabetic female rats, considering exposure to caffeine treatment before induction of diabetes and maintained on treatment after induction of diabetes.

Materials and Methods

Experimental animals

Female Wistar rats, aged 12–13 weeks old and weighing about 180–200g, were used for the study. The animals were obtained from the Biochemistry Department University of Ilorin, Ilorin. The rats were maintained, with free access to food (rat pellet) and water, with a 12-hour light/12-hour dark cycle (lights on at 07:00 hour). Rats were used in accordance with the rules for the Care and Use of Laboratory Animals and the research was approved by the Ethics Committee of the University of Ilorin, Ilorin, Nigeria.

Study design

Eleven groups of seven female Wistar rats each were used for the study. Study groups A 1, 2, and 3 were healthy rats administered 15, 20, and 25 mg/kg caffeine intraperitoneally (i.p) per day, respectively, for 5 weeks; study groups B 1, 2, and 3 were healthy rats administered 15, 20, and 25 mg/kg caffeine (i.p) per day, respectively, for 5 weeks and were maintained on caffeine for 3 weeks after induction of diabetes; study groups C 1, 2, and 3 were diabetic rats placed on caffeine immediately after induction of DM at 15, 20, and 25 mg/kg (i.p) per day, respectively, for 3 weeks; the control and diabetic untreated group was administered normal saline.

Induction of diabetes

Type 1 diabetes was induced with freshly prepared 50 mg/kg STZ (in citrate buffer 0.1 M, pH 4.5), which induced sustained hyperglycemia after 3 days.[56] Dextrose saline was given after induction for rehydration. Food and water intake was closely monitored after induction. The animals were confirmed diabetic by the measurement of fasting blood glucose in the tail vein blood after 72 hours of injection with a portable glucometer (on-call plus). The animals with hyperglycemia (blood glucose >8.1 mM) and stable symptoms of DM such as polyuria and polydipsia were used for the study.

Glycemia assessment

Before glucose level estimation, the rats underwent 12 hours of overnight fasting as described previously.[57]

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After fasting, to determine baseline glucose levels, blood samples (0.1 μL) were collected from the distal end of the tail and analyzed immediately using an On-Call® Plus glucometer with the corresponding On-Call Plus test strips (Roche, Mannheim, Germany).

Caffeine dose and administration

Caffeine (Sigma-Aldrich, St. Louis, MO) was administered intraperitoneally. Doses of 15, 20, and 25 mg/Kg (BW)/day were given to specified groups.

Preparation of brain homogenate

At the end of the administration, animals were anesthetized, the brains were promptly removed, weighed, and homogenized in an ice-cold sucrose isotonic buffer solution. Crude homogenates were initially centrifuged at 1000 rpm for 10 minutes. The supernatant obtained was centrifuged again at 25,000 rpm for 3 minutes to obtain the mitochondrial pellet. The pellet was washed three times by resuspending it in the homogenizing buffer medium (pH 7.4). All the centrifugation steps were carried out at 4°C in an H1850R tabletop high-speed refrigerated centrifuge. Mitochondria-contained solutions were kept below 4°C for enzyme estimation. Protein determination and assay for the enzyme were carried out within 24 hours of sample collection. Na^+/K^+-ATPase activities were expressed as μmolPi/mg protein/hour $\times 10^{-3}$.

Na^+/K^+-ATPase assay

Na^+/K^+-ATPase assay was measured according to the method described by Akagawa and Tsukada.[58] The reaction mixture (1 mL) contains 200 mM NaCl, 40 mM KCl, 60 mM Tris (pH 7.4), 80 mM MgCl2.6H2O, 20 mM ethylene glycol-bis (2 aminoethylether) tetraacetic acid (EGTA), enzyme source, 8 mM ATP, after which it was incubated for 1 hour at 37°C. The reaction was stopped by adding 5% ice-cold sodium lauryl sulfate (SLS). After which the medium was centrifuged at 1000 g for 10 minutes. Inorganic phosphate produced in the supernatant was determined by the method of Fiske and Subbarow.[59] Protein determination was carried out according to the method of Lowry *et al.*[60] Na^+/K^+-ATPase activities were expressed as μmolPi/mg protein/hour $\times 10^{-3}$.

Statistical analyses

Statistical analyses were performed using the SPSS® statistical software, version 16.0 (SPSS, Inc., Chicago, IL) for Windows®. Data are presented as mean ± SE. Differences between continuous data were analyzed using the paired Student's *t*-test and analysis of variance using a Duncan *post hoc* comparison, as appropriate.

Results

Blood glucose level in healthy and diabetic rats

Healthy rats administered caffeine 15 mg/kg, 20 mg/kg, and 25 mg/kg showed no significant difference in the blood glucose level (4.60 ± 0.16, 4.17 ± 0.20, and 4.41 ± 0.07 respectively) when compared with control (4.14 ± 0.23), as shown in Figure 1. All diabetic groups showed a significant ($p < 0.05$) increase in blood glucose level when compared with control each week, but with varying glucose level changes when compared with the diabetic untreated group, as highlighted in Table 1. ◀F1 ◀T1

Brain Na^+/K^+-ATPase activities in healthy and diabetic rats

Table 2 shows a significant reduction in brain Na^+/K^+-ATPase activities in diabetic rats when compared with control. The brain Na^+/K^+-ATPase decreases from 4.16 ± 0.26 ($p < 0.05$) in control to 2.51 ± 0.26 ($p < 0.05$) in diabetic untreated group. ◀T2

Caffeine and its effect on brain Na^+/K^+-ATPase activities in normal rats

Caffeine increases the activities of brain Na^+/K^+-ATPase, as indicated in Figure 2. There is an increase in Na^+/K^+-ATPase activities in healthy rats administered caffeine, with 10.20 ± 0.51, 8.25 ± 0.22, and 4.99 ± 0.04 ($p < 0.05$) activity in study groups A 1, 2, and 3, respectively, when compared to 4.16 ± 0.26 ($p < 0.05$) in control. ◀F2

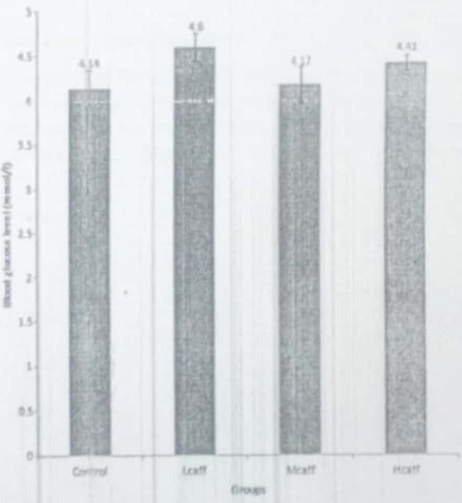


FIG. 1. Blood glucose level in healthy rats administered caffeine. Values are mean ± SEM, $n = 7$, paired *t*-test $p < 0.05$. Lcaff = caffeine administration 15 mg/kg; Mcaff = caffeine administration 20 mg/kg; Hcaff = caffeine administration 25 mg/kg.

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TABLE 1. EFFECT OF CAFFEINE ON THE BLOOD GLUCOSE LEVEL (MM) IN DIABETIC RATS

Groups Weeks	Control	Diabetic untreated	Caff 15 mg/kg Before/after diabetes	Caff 20 mg/kg Before/after diabetes	Caff 25 mg/kg Before/after diabetes	Caff 15 mg/kg After diabetes	Caff 20 mg/kg After diabetes	Caff 15 mg/kg After diabetes
Week 1	4.14 ± 0.21	21.82 ± 2.14[a]	15.80 ± 1.18[b]	22.17 ± 1.60[a]	20.92 ± 2.09[a]	22.36 ± 2.74[a]	20.76 ± 1.75[a]	22.36 ± 2.71[a]
Week 2	5.59 ± 0.20	18.77 ± 2.69[a]	11.80 ± 1.54[b]	24.42 ± 1.86[a]	19.18 ± 2.06[a]	19.67 ± 3.15[a]	29.31 ± 1.79[b]	16.74 ± 2.97[a]
Week 3	3.91 ± 0.32	19.67 ± 2.31[a]	19.62 ± 0.73[a]	32.22 ± 1.24[b]	30.66 ± 1.39[b]	21.57 ± 2.59[a]	26.13 ± 1.67[b]	22.33 ± 3.61[a]

Values are mean ± SEM, $n = 7$.
[a] $p < 0.05$ compared with control group.
[b] $p < 0.05$ compared with control and diabetic untreated group.
Caff, Caffeine treatment.

TABLE 2. EFFECT OF UNTREATED DIABETES ON BRAIN Na^+/K^+-ATPase ACTIVITY

Groups	Na^+/K^+-ATPase activity (μmolPi/mg protein/hour × 10^{-3})
Control	415.6 ± 0.26
Diabetic untreated	250.9 ± 0.26*

Values are mean ± SEM, $n = 7$.
*$p < 0.05$ compared with control group.

Caffeine and its effect on brain Na^+/K^+-ATPase activities in diabetic rats

Study groups B 1, 2, and 3 rats administered caffeine before inducing diabetes and also maintained on caffeine after inducing diabetes show reduced activities 2.80 ± 0.40, 3.74 ± 0.34, and 2.32.0.34 ($p < 0.05$), respectively, when compared to control 4.16 ± 0.26 ($p < 0.05$), with significant reduction in groups 1 and 3. Groups 1 and 2 show an increase in brain Na^+/K^+-ATPase activities (2.80 ± 0.40 and 3.74 ± 0.34 ($p < 0.05$), respectively) when compared to diabetic untreated group activity [2.51 ± 0.26 ($p < 0.05$)], and only group 2 [3.74 ± 0.34 ($p < 0.05$)] was significantly different from the diabetic group [2.51 ± 0.26 ($p < 0.05$)], as shown in Figure 3. ◀F3

Also, rats placed on caffeine treatment only after induction of diabetes (study groups C 1, 2, and 3), as shown in Figure 4, showed an increase in Na^+/K^+-ATPase activities ◀F4 [4.67 ± 0.51, 4.29 ± 0.50, and 2.60 ± 0.20 ($p < 0.05$)] when compared with the diabetic group [2.51 ± 0.26 ($p < 0.05$)], with a significant increase ($p < 0.05$) in groups 7 and 8.

Discussion and Conclusion

A series of studies[61–63] have been conducted on the effect of caffeine on blood glucose level with varying views, and this study shows that caffeine has no effect on blood glucose level in healthy rats but may lead to either an

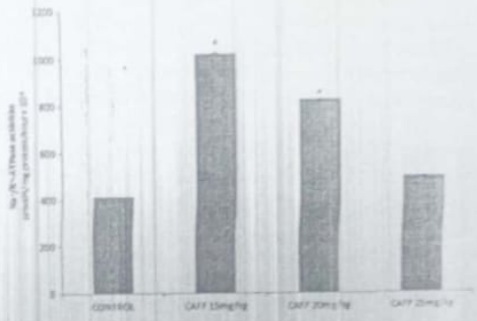


FIG. 2. Brain Na+/K+-ATPase activity in study groups A (healthy rats administered caffeine). Values are mean ± SEM, $n = 7$, paired t-test *$p < 0.05$ compared with control group. CAFF, caffeine administration.

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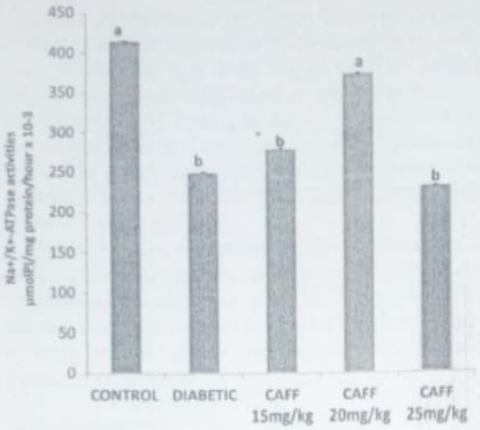


FIG. 3. Brain Na+/K+-ATPase activity in study groups B (rats administered caffeine before and maintained on caffeine after induction of diabetes). Values are mean ± SEM, $n=7$, ANOVA ($p<0.05$) and Dunn's *post hoc* test, bars with different letters are significantly different, $p<0.05$. CAFF = caffeine administration.

increase or decrease in blood glucose in the diabetic state depending on doses and periods of exposure.

Cognitive dysfunction and dementia have recently been proven to be common and underrecognized complications of DM.[64] This study shows that brain Na^+/K^+-ATPase activity is altered in the diabetic state as previously reported[44,65–67] and has also been able to confirm as such in female rats since most of the previous studies are based on the use of male rodents. The reduced activity is associated with the cognitive and memory impairment observed in diabetic state because the Na^+/K^+-ATPase is known to be a key enzyme involved in the maintenance of ionic gradient of Na^+ and K^+ and in the maintenance of action potential and resting membrane potential.[68] Therefore, alteration in the enzyme activity may be an important factor in the pathogenesis of metabolic complications observed in the CNS in diabetic state.[69] Also, the reduced activity can be directly linked to the observations by Chung *et al.*,[14] who reported diminished global and regional cerebral vasoreactivity and a decline in multiple cognitive tasks in diabetes due to inflammation.

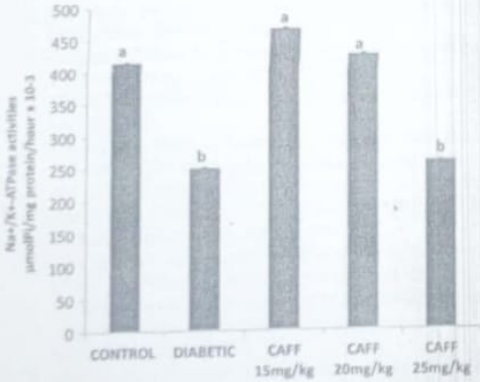


FIG. 4. Brain Na+/K+-ATPase activity in study groups C (diabetic rats administered caffeine). Values are mean ± SEM, $n=7$, ANOVA ($p<0.05$) and Dunn's *post hoc* test, bars with different letters are significantly different $p<0.05$. CAFF, caffeine administration.

This study also shows that caffeine increases the brain Na^+/K^+-ATPase activities in normal rats as indicated in Figure 2. This agrees with the work of Obochi *et al.*,[70] which revealed that kola nut and caffeine independently produced an increase in brain Na^+/K^+-ATPase activities.[35] However, there is paucity of information on the effect of caffeine on brain Na^+/K^+-ATPase activity in diabetic state, and this study shows that treatment with caffeine shows promising effect on increasing brain Na^+/K^+-ATPase activity in diabetics (Figs. 3 and 4). Naiara *et al.*[67] also reported a decrease in the cerebral cortex Na^+/K^+-ATPase in diabetic rats and reported that the observed reduction may result from both glycosylation in the b subunit of this enzyme and destabilization of plasmatic membrane by reactive species. They further reported an increase in Na^+/K^+-ATPase activity basically in the cerebral cortex of diabetic rats after treatment with caffeine. Although previous studies[67,69] made use of male rodents, this study considered female Wistar rats to rule out gender influence.

Caffeine is commonly consumed in different beverages and soft drinks in the society, since no report has been given to pretreatment of caffeine before diabetes onset, this study considered the effect/influence of caffeine intake before diabetic onset in study groups B (prediabetic treatment, Fig. 3), as opposed to postdiabetic treatment with caffeine, previously reported.[67] In this study, caffeine at a dose of 20 mg/kg restores Na^+/K^+-ATPase activity to normal, while in study groups C (postdiabetic treatment), caffeine at a dose of 15 and 20 mg/kg restores Na^+/K^+-ATPase activity to normal. This observation is due to caffeine tolerance in study groups B, and thus, it is this study group that majorly mimics the societal focus.

This study further evaluates different doses of caffeine treatment unlike the previous studies.[67,69] The highest dose of caffeine used in this study (25 mg/kg BW) shows very little or no effect on brain Na^+/K^+-ATPase activity both in healthy groups and pre/postexposure to caffeine in the diabetic groups and, as such, may be due to poor adaptation to the high dose of caffeine.

However, the observed improvement of brain Na^+/K^+-ATPase activity in diabetic states may be a linking factor with the findings of Duarte *et al.*,[56] who reported that caffeine prevents diabetes-induced memory impairment and synaptotoxicity in the hippocampus of diabetic mice.

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Hence, the current study shows that brain Na^+/K^+-ATPase activity is reduced in STZ-induced diabetic female Wistar rats. The brain Na^+/K^+-ATPase activity dysfunction has been implicated in electrophysiological abnormalities thus leading to poor excitation, cerebral vasoreactivity, poor nutrient delivery, and declined cognition. The result has also demonstrated the potential of caffeine to reverse brain Na^+/K^+-ATPase activity deficit in the diabetic state.

Therefore, more researches should be carried out to further unravel the mechanism of action of caffeine and its consequential effects on brain Na^+/K^+-ATPase. This can be a promising focus of coadjuvant treatment in ameliorating some of the CNS disorders resulting from complications of diabetes.

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Author Disclosure Statement

No competing financial interests exist.

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