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High Caffeine- Containing Energy Drink- Induced Metabolic Stress in RatsKweki, G.R.^{1,2}, Ichipi-Ifukor, P.C.^{2*}, Asagba, S.O.²

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Abstract

This study was carried out to comparatively assess the potentiating effects of majorly consumed brands of energy drinks (red bull, power horse and bullet) on several metabolic stress indicators. The study comprised four groups. Group I which served as control had normal feed and water only, group II-IV was given normal feed and 0.8ml/Kg body weight of Red Bull, Bullet and Power Horse energy drinks respectively for 42 days. Animals were sacrificed on the 43rd day following an overnight fast and samples collected for tissue and plasma assay of biochemical markers. There was significant rise ($p < 0.05$) in plasma and tissue ALT, AST, plasma ALP activities in rats administered all three brands of energy drinks, while plasma creatinine and urea only increased in rats that consumed Power Horse compared to controls. Changes in tissue (brain, kidney, heart and liver) lipid peroxidation indicates significant ($p < 0.05$) increase relative to controls. Tissue oxidative enzymes (AO and SO) were significantly increased and depleted respectively compared to controls. The uncontrolled consumption of energy drinks is overtly unsafe as it has the capability of inducing metabolic stress via the induction and depletion of several tissue and plasma metabolic stress markers.

Keywords: Energy Drink, Caffeine and Metabolic Stress

Introduction

The popularity of energy drinks has over the years attracted a significant patronage to its consumption by most young populations

especially as it relates to boosting energy capacities during studying, sports, driving, clubbing and decreasing mental fatigue during long periods of cognitive activities (Akanke and Bamjoo, 2011; Kaminer, 2010; Malinauskas *et al.*, 2007; Alford *et al.*, 2001). Its' main ingredients have been identified to include caffeine, sugar, taurine and glucuronolactone (Ayuob *et al.*, 2016; Reseig *et al.*, 2009; Van den Eynde *et al.*, 2008). They also contain vitamin B-complex, plant-based stimulants (guarana, ephedrine yerbamate), and herbs (various forms of ginseng, ginko bibloba) and maltodextrin (Higgins *et al.*, 2012; Ishak *et al.*, 2012; Alford *et al.*, 2001).

Caffeine (1,3,7-trimetilxantine) which has been identified as the leading psychoactive component in most energy drinks has been reported to be present in very high concentrations thus resulting in certain symptomatic intoxications when taken in excess (Usman *et al.*, 2012; Seifert *et al.*, 2011). The attraction of energy drinks to mostly young adolescent populations is due to its marketing which often times claims that it “gives you wings” thus suggesting that upon consumption, they will be provided with more energy and enhanced performance, both mentally and physically (Ayuob *et al.*, 2016; Hossain *et al.*, 2014; Frances *et al.*, 2010). Their acceptances of these claims have been identified due to the absence of appropriate knowledge of its potential risks (Wolk *et al.*, 2012; Atilair and Calkie, 2011; Malinauskas *et al.*, 2007).

Presently, there exists evidence-based literatures

that have linked the consumptions of energy drinks in the induction of several levels of toxicity in humans and animals (Gunja and Brown 2012; Starling 2008). Their consumption has particularly been associated with a decrease in heart rate and an increase in the systolic blood pressure and pain tolerance (Frances *et al.*, 2010; Bronstein *et al.*, 2008). Also, the administration of energy drinks via oral route was reported to affect blood chemistry and liver enzymes activities (Ebuechi *et al.*, 2011; Oteri *et al.*, 2007), while Akande and Banjoko (2011) revealed their potency in the alteration of hepatic, renal function and ultrastructure of rats. Despite these reports on the beneficial and possible toxicological profile of these drinks, there still exists scarcity of reports on the comparative potentiating effects of majorly consumed brands of energy drinks (red bull, power horse and bullet) on several metabolic stress indicators (lipid peroxidation, oxidative enzymes, alkaline phosphatase and the transferases) in several tissues (Liver, Kidney, Heart and Brain) as well as serum stress indicators of clinical significance in rats.

Materials and Methods

Experimental Animals

Twenty (20) female Albino rats of the Wistar strain weighing between 180g-200g were purchased from the animal house of the Department of Anatomy, College of Medicine Delta State University Abraka Nigeria and transported to the Department of Biochemistry, Faculty of Science Delta State University using a rectangular plastic bowl covered with wired mesh to allow for ventilation. On arrival they were randomly distributed into four groups of five rats respectively and housed in a wooden cage within the confinement of the Departmental animal house and allowed to acclimatize for 10 days. The environment had a temperature ranging between 25-30°C, 12hrs dark and light cycles respectively. The animals were fed with standard laboratory feed and water during this period. After the acclimatization period, the rats were treated according to the groups outlined below for six weeks (42 days).

Group I: Control Normal Feed

Group II: Normal Feed+ 0.8mlKg⁻¹ Red bull

Group III: Normal Feed+ 0.8mlKg⁻¹ Bullet

Group IV: Normal Feed+ 0.8mlKg⁻¹ Power Horse

Treatment was done daily for a period of six weeks

Sample Collection and Preparation

At the end of the treatment period (42 days), the rats were euthanized following cervical dislocation after an overnight fast. Blood samples were collected through cardiac puncture using a sterile syringe and needle and immediately transferred into a lithium heparinized test tube. Tissues (liver, kidney, heart and brains) were harvested and transferred into pre-chilled labeled containers.

Sample Preparation

The Blood samples collected were centrifuged at 3200g for 15 minutes and the plasma collected for various biochemical assays. Wet tissues measuring 0.5g was homogenized in 9.0ml of normal saline using pre-chilled mortar and pestle and the supernatant obtained was stored in the refrigerator and used for biochemical analysis following standard procedures within 48 hours.

Biochemical Analysis

Determination of serum creatinine was done using Teco diagnostic kit (Teco Diagnostic, U.S.A) while urea and serum ALP was done using Randox diagnostic kit (Randox Laboratories, UK) according to the manufacturers' manual. All other reagents used for biochemical assays were of analytical grades and employed the use of the following standard methods. Estimation of alanine amino transferase (ALT) and aspartate amino transferase (AST) activities in the serum and tissue homogenates was carried out using the method of Reitman and Frankel (1957). Assay for level of lipid peroxidation (MDA) (Gutteridge and Wilkins, 1982) and oxidative enzymes as follows; aldehyde oxidase (AO) (Omarov *et al.*, 1998), sulphite oxidase (Macleod *et al.*, 1961)

Statistical Analysis

Analysis of data was carried out using the single Factor analysis of Variance (ANOVA) with the aid of the Statistical Package for the Social Sciences version 17 (SPSS 17). Post hoc analysis

(comparisons across groups) was done using Bonferroni at $p \leq 0.05$ level of significance.

Results and Discussions

Metabolic stress status occasioned by changes in plasma enzyme activities and alterations in lipid peroxidation, oxidative enzymes and certain plasma biochemical markers were examined in rats after six (6) weeks of treatment with different brands of energy drinks. The significant rise in plasma ALT and AST of rats administered various brands (Red Bull, Bullet and Power Horse) compared to control (Table 1 and 2). Plasma and tissue rise in activities of AST and ALT are known significant markers of metabolic

stress in rats and humans as well as possible alteration in tissue ultra-structure. It is important to note that rise in plasma and tissue ALT and AST has been previously reported as early markers of metabolic stress syndromes in animals and humans (Esteghamati *et al.*, 2010; Asagba, 2008; Asagba and Obi, 2005). The observed rise in ALT and AST activities (Table 1 & 2) may be likened to increased accumulation in levels of pro-oxides occasioned by the deleterious effects of energy drink metabolism and may have also been influence by the observed drop in tissue (Heart, liver, kidney and brain) activities of these enzymes.

Table 1: Effect of Different Energy Drinks on Plasma and Tissue ALT

	Group I	Group II	Group III	Group IV
Plasma	48.12±1.08 ^a	59.18±2.05 ^b (+22.98)	53.12±3.65 ^b (+39.49)	55.38±4.16 ^b (+14.28)
Brain	56.02±4.59 ^a	45.22±3.55 ^b (-19.28)	29.05±1.12 ^c (-48.14)	48.09±2.51 ^d (14.15)
Heart	213.05±09.21 ^a	333.13±3.14 ^b (56.36)	371±64.05 ^c (74.13)	248.3±11.05 ^d (16.54)
Kidney	267.00±10.6 ^a	111.13±8.45 ^b (-58.37)	65±2.33 ^c (-75.7)	286±12.05 ^a (7.11)
Liver	462.13±12.25 ^a	426.54±10.05 ^{ab} (-7.70)	398.22±14.10 ^c (-10.39)	405.64±08.45 ^{bc} (-12.22)

All values are expressed as Mean ± SD. Values followed by different alphabet superscripts in the same row indicate a significant difference while values in brackets indicate percentage change relative to control.

Table 2: Effect of Different Energy Drinks on Plasma and Tissue AST

	Group I	Group II	Group III	Group IV
Plasma	52.7±5.68a	72.98±6.95b (+38.48%)	73.5±5.45b (+39.49%)	60.2±5.66c (+14.28%)
Brain	88.25±8.759a	50±3.55b (-43.34%)	39.5±0.5c (-55.24%)	366±18.75d (318.13%)
Heart	253.75±28.19a	533.3±103.1a (110.16%)	371±64.05a (46.20%)	663.3±91.35b (161.39%)
Kidney	307±16.6a	47.3±8.25b (-84.59)	85±1.0c (-72.31%)	366±18.75a (19.21%)
Liver	682.5±6.05a	656.25±80.05b (-3.84%)	637±41.1b (-6.66%)	446±60.45c (-34.65%)

All values are expressed as Mean ± SD. Values followed by different alphabet superscripts in the same row indicate a significant difference while values in brackets indicate percentage change relative to control.

Table 3: Effect of Energy Drinks on Tissue Lipid Peroxidation

	Group 1 (Control)	Group 2 (Red bull)	Groups 3(Bullet)	Group 4 (Power Horse)
Brain	20.84±2.45 ^a	25.22±3.16 ^b (21.02)	25.08±1.87 ^b (20.34)	30.27±5.85 ^c (45.25)
Heart	37.65±9.44 ^a	43.75±3.93 ^b (16.20)	48.05±1.80 ^{bc} (27.62)	49.15±3.41 ^c (30.5)
Kidney	39.95±3.22 ^a	48.65±2.26 ^b (21.77)	52.25±3.57 ^{bc} (30.78)	56.93±3.9 ^c (42.5)
Liver	45.92±1.21 ^a	48.90±1.04 ^b (6.51)	52.41±2.62 ^c (14.1)	58.35±1.05 ^c (27.07)

All values are expressed as Mean ± SD. Values followed by different alphabet superscripts in the same row indicate a significant difference while values in brackets indicate percentage change relative to control.

The justification for these claims is linked to the observed rise in tissue lipid peroxidation levels (Table 3) in the brain, kidney, heart and liver of rats that consumed various brands of energy drinks in this study and the possible alteration in tissue structural integrity which has also been reported in earlier studies (Meier and Barry, 2013; Leung *et al.*, 1993) and may have influenced the increased leakage of the ALT and AST into the blood hence increased activities in the plasma. It is important to note also, that caffeine has been reported to be one of the major constituents of energy drinks of which its metabolism has been previously reported to cause possible damage to tissues like liver and kidney when taken in excessive amounts (Ugwuja, 2014; Ebuehi *et al.*, 2011; Alford *et al.*, 2001).

Evidence from literature succinctly reveals that tissue levels of lipid peroxidation are evidence-based markers of the presence of reactive oxygen and nitrogen species (ROS/RNS) occasioned by increased reduction in tissue antioxidant capacities that contribute to the scavenging buffering of hydroxyl radicals, peroxides and pro-oxides (Ramalingam, 2012; Hurrell, 2003;

Sies, 1997; Jacob, 1995). Simply put Oxidative stress is a product of increased imbalance in formation of reactive oxygen/Nitrogen species (ROS/RNS) compared to antioxidants whether enzymatic or non-enzymatic (Marrocco *et al.*, 2017). Bearing this in mind, a careful analysis of the results presented in table 4 revealed rising plasma alkaline phosphatase activities in rats that consumed the three brands of energy drinks and increased plasma creatinine and urea levels in rats that consumed Power Horse. Rise in serum levels of these biochemical markers have been previously reported to occur in cases of oxidative metabolic stress in rats (Selmi *et al.*, 2015). ALP has also been identified to play a very critical role in the detoxification of xenobiotics as well as synthesis of essential energetic macromolecules for various functions of which interference in its activities may lead to several biochemical impairment or tissue lesion (Rezg *et al.*, 2008). Also, rising plasma activities of ALP as observed in Table 4, may have been a result of increased permeability of the plasma membrane or cellular necrosis arising from energy drink consumption (Rahman *et al.*, 2000).

Table 4: Effect of Energy Drinks on Plasma ALP, Urea and Creatine Nitrogen

	Group I	Group II	Groups III	Group IV
ALP (U/L)	40.43±7.8 ^a	103.95±6.67 ^b (+57.11)	86.63±5.76 ^{bc} (+114.2)	80.85±5.57 ^c (+99.97)
Urea (mg/dl)	15.59±0.56 ^a	14.2±0.58 ^a (-8.91%)	17.64±0.95 ^a (+13.14%)	7.59±0.69 ^b (-51.31)
Creatinine (mg/dl)	11.97±0.80 ^{ab}	15.93±3.19 ^{ac} (+33.08)	7.69±1.5 ^b (-35.75)	18.94±0.17 ^c (+58.22)

All values are expressed as Mean ± SD. Values followed by different alphabet superscripts in the same row indicate a significant difference while values in brackets indicate percentage change relative to control.

On the other hand, increase in plasma and serum creatinine and urea has been established indicator of poor glomerular filtration and often used as a clinical marker for kidney malfunction (Achuba, 2018; Ogbeke *et al.*, 2016; Azeez *et al.* 2009; Yaqoob *et al.* 1993). The result of this study based on the rising creatinine and urea levels (Table 3) due to consumption of Power Horse gives an insight into the possible nephrotoxic effects of energy drinks when taken in excess. However, this position cannot be offered with certainty as no histopathological examination of the kidney was performed in this study. The rising levels of plasma urea and creatinine due to the consumption of Red Bull and Power Horse has been previously reported by earlier studies (Taiwo and Adesokan, 2018; Akande and Banjoko, 2011; Khayyat *et al.*, 2012, 2014) thus giving credence and justification to the observations made in this study.

In high cases of metabolic stress, there also arises greater crave and need for the clearance of generated reactive oxygen species. The observed rise and further depletion of the oxidative enzymes AO and SO (Tables 5 and 6) by the different brands of the energy drinks may be due to the needed clearance of the several aromatic oxides arising from energy drink consumption. It is important to note that the justification for these findings have been previously given by Ichipi-Ifukor *et al.* (2013) and Asagba (2010) who reported that a rise in oxidative enzyme activities are significant markers for tissue metabolic stress conditions which further triggers the depletion of tissue proteins and the continual production of heterocyclic compounds that may over time contribute to the inhibition of oxidative enzyme activities such as the aldehyde and sulphite oxidases.

Table 5: Effect of Energy Drinks on Sulphite Oxidase activities in Tissues of Rats

	Group I	Group II	Groups III	Group IV
Brain	346.75±2.37 ^a	396.27±4.50 ^b (14.28%)	336.75±1.59 ^a (-2.88)	343.75±4.55 ^a (-0.86%)
Heart	496.02±1.32 ^a	394.06±3.85 ^b (-20.56%)	389±1.95 ^b (-21.57%)	431.8±1.39 ^c (-12.94%)
Kidney	406.45±1.95 ^a	259.52±2.96 ^b (-36.15%)	371.0±1.64 ^{ac} (-8.72%)	374.75±1.28 ^{ac} (-7.79%)
Liver	387.14±1.18 ^a	382.8±1.18 ^a (-1.08)	346.0±1.05 ^b (-10.59)	447.36±5.24 ^c (15.53)

All values are expressed as Mean ± SD. Values followed by different alphabet superscripts in the same row indicate a significant difference while values in brackets indicate percentage change relative to control.

Table 6: Effect of Energy Drinks on Tissues Activities of Aldehyde Oxidase in Rats

	Group I	Group II	Groups III	Group IV
Brain	183.21±2.67 ^a	203.27±6.88 ^a (10.95)	131.5±0.50 ^b (-28.14)	156.25±9.09 ^c (-14.72)
Heart	143.25±2.81 ^a	160±7.04 ^b (11.92)	181±1.46 ^{bc} (+26.35)	158.75±96.92 ^{ac} (10.82)
Kidney	143.50±6.70 ^a	128.25±9.52 ^b (10.62)	127.44±1.29 ^b (11.49)	210.75±18.82 ^c (46.86)
Liver	171.5±4.67 ^a	145.25±8.84 ^b (15.30)	162±1.9 ^a (5.53)	161.5±0.89 ^a (5.83)

All values are expressed as Mean ± SD. Values followed by different alphabet superscripts in the same row indicate a significant difference while values in brackets indicate percentage change relative to control.

Conclusion

Findings from this study gives ample evidences that the uncontrolled consumption of energy drinks may overtly be unsafe as it had the capability of inducing metabolic stress in experimental rats via the induction of tissue lipid peroxidation and eventual depletion and increase of tissue and plasma amino transferases respectively, increased plasma urea and creatinine nitrogen, and the reduced activities of the aldehyde and sulphite oxidative enzymes in the tissues.

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