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Effect of Vitamin E on Ethanol-induced Increase in Some Cardiovascular Parameters and Blood Uric Acid Levels in Man

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Abstract: Alcohol metabolism has been reported to generate Reactive Oxygen Species (ROS) which initiate series of oxidative reactions that culminate in hyperuricemia and accompanying cardiovascular dysfunction. Present study investigates the effect of a free radical scavenger-vitamin E, on alcohol-induced increase in serum uric acid, triacylglycerol and blood pressure. One hundred consenting undergraduates (60 males and 40 females) in apparent good health and who were matched in age, weight and body build were selected and tested on four different occasions separated by 14 days. On the first day of testing, the subjects were randomly separated into Groups A (0.75 mL fruit juice/kg + 100 mg tapioka dried cassava product: n = 25), Group B (0.75 ml ethanol/kg+ 100 mg tapioka: n = 25), Group C (0.75 mL ethanol/kg + 100 mg vitamin E:n = 25) and Group D (0.75 mL fruit juice/kg + 100 mg vitamin E: n = 25) and were treated as indicated. The ethanol administered was diluted to 30% with fruit juice. Each participant was rotated every forthnight until he/she completes the four rounds of testing. The data obtained show that the co-administration of ethanol and vitamin E significantly reduced ($p<0.05$) the level of serum uric acid and the proportion of subjects in the prehypertension and stage 1 hypertension classes induced by ethanol consumption alone. Apart from confirming the recent proposal that links ROS to hyperuricemia and secondary cardiovascular disorders, this study suggests that boosting the level of antioxidant vitamins in the body could alleviate the ethanol-induced hyperuricemia and perhaps, associated disease conditions.

Key words: Hyperuricemia, vitamin E, free radical, hypertension, alcohol

INTRODUCTION

Most urinary uric acid appears to be derived from tubular secretion (Wang *et al*., 2001), since about 98-100% of the amount filtered is reabsorbed. The presence of organic acids like lactic acid and ketoacids have been reported to impair the proximal secretion of uric acid (Fahlen and Agraharkar, 2003), consequently, elevating the level of plasma uric acid. The chief risk of uric acid elevation include gout and kidney stones (Fields, 2003). Increase in blood uric acid has been associated with hypertension and renal disease (Johnson *et al*., 2003), however, there is no proven, causative role of hyperuricemia for these group of diseases.

Alcohol consumption has been demonstrated to increase plasma uric acid level by several workers (Faller and Fox, 1982; Beghi *et al*., 1995; Onyesom, 2003). Increase in the NADH:NAD^+ ratio produced during the oxidation of ethanol, elevates plasma lactate (Tygstrup *et al*., 1965) which in turn decreases the sensitivity of the tubular epithelial cells to uric acid secretion and consequently, the ability of the kidneys to excrete uric acid is reduced.

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In addition, the ethanol-induced increase in NADH:NAD^+ ratio has been observed to stimulate mitochondrial respiratory chain (Bailey *et al*., 1999). Such stimulation causes the generation of reactive oxygen species (Bailey and Cunningham, 1998) which has been connected to hyperuricemia (Houston *et al*., 1998). In view of this, we investigated the effect of vitamin E, (a lipophilic antioxidant capable of reducing the level of free radicals and their mediated actions in the body) on the changes in serum uric acid, triacylglycerol and blood pressure measures induced by ethanol in humans.

MATERIALS AND METHODS

Subjects

One hundred consenting undergraduates (60 males and 40 females) in apparent good health, between the ages of 20 and 30 years were screened for drug use and selected for the study. Their mean±SD body weight is 60.2±10.5 kg (range: 50-70 kg). The volunteers were light drinkers of alcohol (between 1-2 drinks/day) and they neither smoke cigarette nor snuff tobacco or other addictive agents. They were not on any medication and they remained so throughout the period of the investigation. The participants were asked not to drink alcohol or take medications the night prior to testing, but were advised to eat a light breakfast at about 7 am and then not to eat, drink or smoke from that time until reporting to the laboratory at 8:30 am, because food in the stomach might influence alcohol effects in the body.

Experimental Groups and Testing Exercise

On arrival to the laboratory as scheduled, the participants willingly endorsed the Human Rights and Ethics form provided as a means of seeking their consent. They were then weighed and randomly separated into four groups: group A (control group), Group B (ethanol group), group C (ethanol + vitamin E group) and Group D (Vitamin E group). Subjects' participation was approved by our Faculty's Ethics Committee.

On the first occasion, Group A subjects were given 0.75 mL fruit juice/kg body weight and 100 mg tapioka- a placebo. Tapioka is a dried cassava product. It contains starch and fibre mainly and is commonly eaten between meals. Group B participants orally received 0.75 mL (80 proof USP) ethanol/kg body weight after diluting to 30% with fruit juice and 100 mg tapioka. Proof is the common unit used to express the amount of ethanol in spirits and is double the concentration of ethanol in per cent (%). The volunteers in group C drank the same dose of ethanol 0.75 mL kg^{-1} and 100 mg vitamin E (made by PROCAPS Barranquilla, Colombia: NAFDAC Reg No. 04-3796) and Group D members took fruit juice (0.75 mL kg^{-1}) and 100 mg vitamin E.

Each participant was rotated every forthnight until he/she went through the four rounds of testing. The rotation was important in order to limit the effect of intra-individual factor(s) that may likely influence the results of a particular group. The results of the four rounds of tests for each group were pooled and the mean±SD was derived.

The data of each group obtained during the four rounds of testing were pooled and mean±SD was then determined. The dosing regimen was based on previous study on blood alcohol and plasma urate (Onyesom, 2003).

Collection of Blood Sample

At different specified post administration time intervals (0, 3, 6 and 9 h), intravenous whole blood sample was collected into plain sterile tube, then centrifuged after allowing to clot, at 1, 200 x g for 5 min at room temperature in order to separate the serum which was decanted into bijou bottle. Sera samples were analyzed fresh within the hour of collection. The specified time intervals were based on earlier report (Onyesom and Anosike, 2004).

Serum Uric Acid and Triacylglycerol Assays

The serum uric acid level was measured on a spectrophotometer (Spectronic 21: Milton Roy Co., USA) by the uricase method (Caraway, 1963) using a Randox kit (ref. Randox UA 230, Randox Laboratories, Ardmore, United Kingdom). Serum triacylglycerol was determined by a spectrophotometer (Spectronic 21: Milton Roy Co., USA) using the end-point colorimetric method (Searcy, 1961) and reagent kit supplied by Teco Diagnostics, USA.

Measurements of Blood Pressure

This was measured shortly before blood sample collection in a well-seated position after about 10 min of rest using Digital Aneroid Sphygmomanometer (ACCOSSON MERCURY, CE 0120) as previously described by Moreira *et al*. (1998).

The study was conducted in 2006 between August and September in the Alcohol Research Laboratory, Department of Medical Biochemistry, Delta State University, Abraka, Nigeria.

Classification of Blood Pressure Measurements and Serum Triacylglycerol Values

Blood pressure was classified according to current guidelines (Chobanian *et al*., 2003) and triacylglycerol levels were classified according to the National Cholesterol Education Program guidelines (NCEP, 2001).

Statistical Analysis

Analysis of variance (ANOVA) was used to compare mean values followed by Dunett's test for multiple comparison to determine statistical significance between the groups. (Winer *et al*., 1991). EPI computer software package was used and the level of statistical significant difference was established at the 5% probability level.

RESULTS

Figure 1 and 2, show that overall, the level of serum uric acid is higher in males compared with females and the ingestion of 0.75 mL ethanol/kg by male subjects significantly increased ($p<0.05$) their serum uric acid levels after about 3 and 6 hours, when compared with basal (0h) and corresponding control values. But the 9th h post administration value was not significantly different from both basal and corresponding control value ($p>0.05$).

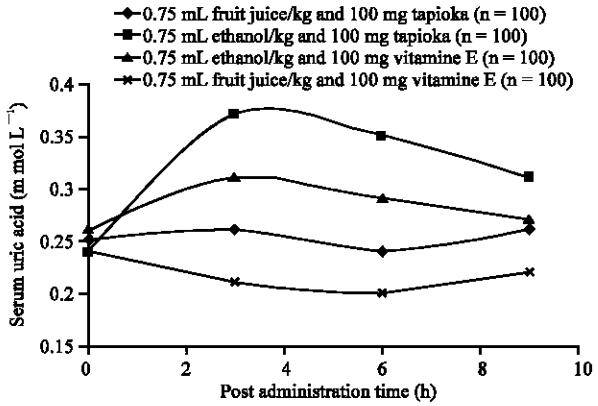

Fig. 1: Changes in serum uric acid induced by ethanol and ethanol + vitamin E co-administration in male subjects

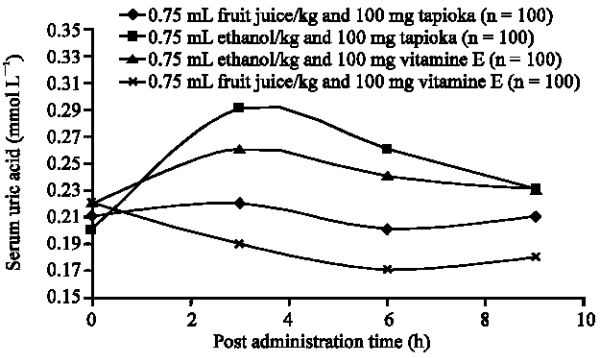

Fig. 2: Changes in serum uric acid induced by ethanol and ethanol + vitamin E co-administration in female subjects

Table 1: Classification of blood pressure measures and serum triacylglycerol values based on experimentally derived data

	Post administration time (h)							
	Male				Female			
Temperature	0	3	6	9	0	3	6	9
Group A								
Normal	98	99	100	99	100	100	99	100
Prehypertension	2	1	-	1	-	-	1	-
Stage 1 hypertension	-	-	-	-	-	-	-	-
Stage 2 hypertension	-	-	-	-	-	-	-	-
Group B								
Normal	100	92	74	83	100	96	82	91
Prehypertension	-	8	24	17	-	4	18	9
Stage 1 hypertension	-	-	2	-	-	-	-	-
Stage 2 hypertension	-	-	-	-	-	-	-	-
Group C								
Normal	100	94	89	94	100	98	93	96
Prehypertension	-	6	11	6	-	2	7	4
Stage 1 hypertension	-	-	-	-	-	-	-	-
Stage 2 hypertension	-	-	-	-	-	-	-	-
Group D								
Normal	100	100	100	100	100	100	100	100
Prehypertension	-	-	-	-	-	-	-	-
Stage 1 hypertension	-	-	-	-	-	-	-	-
Stage 2 hypertension	-	-	-	-	-	-	-	-
Classification of serum triacylglycerol values								
Group A								
Normal	99	100	100	99	100	99	100	99
Borderline high	1	-	-	1	-	1	-	1
High	-	-	-	-	-	-	-	-
Group B								
Normal	100	93	89	86	100	96	92	88
Borderline high	-	7	11	13	-	4	8	12
High	-	-	-	1	-	-	-	-
Group C								
Normal	100	97	94	93	100	98	96	95
Borderline high	-	3	6	7	-	2	4	5
High	-	-	-	-	-	-	-	-
Group D								
Normal	100	100	100	100	100	100	100	100
Borderline high	-	-	-	-	-	-	-	-
High	-	-	-	-	-	-	-	-

Values are expressed as percentage of n (100) subjects Group A: 0.75 mL fruit juice/kg + 100 mg tapioka, Group B: 0.75 mL ethanol/kg + 100 mg tapioka, Group C: 0.75 mL ethanol/kg + 100 mg vitamin E, Group D: 0.75 mL fruit juice/kg +100 mg vitamin E, [a]NCEP (2001)

Vitamin E intake generally reduced ($p>0.05$) the level of serum uric acid in both genders and ethanol + vitamin E administration was observed to attenuate the serum uric acid level induced by ethanol in both male and female participants.

Table 1 shows that ethanol (0.75 mL kg^{-1}) increased the risk of high blood pressure. The proportion of male and female volunteers in the prehypertension and stage 1 hypertension classes were increased by alcohol consumption and this was significant ($p<0.05$) after about 6 h of the alcohol intake. Similar trend was observed for serum TAG, though the highest increase in proportion occurred at about the 9th h of alcohol post consumption.

Vitamin E, whether taken alone or co-administered with alcohol was seen to ameliorate the increased proportion in blood pressure and serum TAG induced by alcohol administration alone (Table 1). Intake of Vitamin E supplements may improve the cardiovascular disorders and hyperuricemic condition elicited by alcohol abuse.

DISCUSSION

Present results (Fig. 1, 2 and Table 1) indicate that vitamin E, an antioxidant having the ability to quench free radical (oxidation) reactions, appears to reduce the increase in serum uric acid induced by ethanol. This hyperuricemic-ameliorating potential of vitamin E seems to suggest that the Reactive Oxygen Species (ROS) generated during the oxidation of ethanol could contribute to the hyperuricemic condition already established among alcoholics (Bartimaeus and Eno-Eno, 2002).

The oxidation of ethanol to ethanal and ethanal to ethanoate, alters the $NADH/NAD^+$ redox state and in order to maintain this redox condition, the electron flow along the respiratory chain is increased and this generates ROS. Besides eliciting cell injury (Bailey *et al*., 1999), ROS has been implicated as a risk factor of ethanol-induced hyperuricemia (Houston *et al*., 1998). ROS could oxidize endothelial nitrogen (II) oxide, NO to NO_3^- and the latter possibly activates xanthine oxidase via sulfhydryl oxidation (Houston *et al*., 1998). Xanthine oxidase in turn catalyzes the conversion of hypoxanthine to xanthine and then to uric acid sequentially.

The resulting hyperuricemic condition has been reported to exhibit an increase in juxtaglomerular rennin and a decrease in macula densa neuronal Nitic Oxide (NO) synthase enzyme activity (Mazzali *et al*., 2001). Synergistically, the hyperuricemia-induced inhibition of NO synthase and ROS-initiated oxidation of endothelial NO to NO_3^- could significantly deplet the levels of NO, a potent regulator of vasoreactivity (Koppenol, 1998). This may be another mechanism by which alcohol consumption affects blood pressure (Table 1). However, present study demonstrates that Vitamin E supplements could improve the hyperuricemic condition (Fig. 1 and 2) and disturbances in serum TAG and blood pressure (Table 1) elicited by alcohol consumption.

From this study, it appears reasonable to conclude that ethanol-induced generation of ROS may elicit some biochemical processes that could lead to hyperuricemia and possibly, hypertension. Thus, increasing the level of vitamin E to augment natural antioxidants in the body, possibly via enriched diet (or supplements) may be a good nutritional support (or intervention therapy) if the purpose is to reduce the effects of ROS on serum uric acid and cardiovascular dysfunction elicited by ethanol metabolism.

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