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Effect of Iodine Supplementation on Antioxidant Status of Normal and Alloxan Monohydrate in Toxicated Rats

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Abstract: Oxidative stress is implied in numerous pathologies, including obesity, type 2 diabetes, atherosclerosis, inflammatory disorders and ageing. Antioxidants are known to neutralise the effects of oxidative stress. Hence, the present study was designed to evaluate the effect of iodine supplementation on the antioxidant status of alloxan monohydrate intoxicated rats. Two groups (A and C) of Wistar rats were kept normal (were not induced oxidative stress), while other two groups (B and D) were induced oxidative stress by alloxan monohydrate (150 mg kg^{-1}) intoxication. Group A and B animals were fed normal rodent diet while group C and D animals' diet was supplemented with iodine (KI, 25 mg kg^{-1} diet). The feeding lasted 6 weeks and the animals were sacrificed and the plasma and red blood cells hemolysate prepared from whole blood samples were used for biochemical analysis. Alloxan monohydrate intoxication induced a collapse in the antioxidant system characterized by a significant drop ($p<0.05$) in antioxidant enzyme activity and ferric reducing antioxidant power as seen in group B animals. However, iodine supplementation tends to prevent this effect with significant increases ($p<0.05$) in belirubin concentration, Ferric reducing antioxidant power and superoxide dismutase and catalase activities. A significant ($p<0.05$) reduction in the Thiobarbituric Acid Reactive Substance (TBARs), carbonyl and the thiol functionalities that were originally increased by alloxan monohydrate intoxication, further substantiate the antioxidant status of iodine. Thus, iodine has an antioxidant potential. The antioxidant potential of iodine obtained in this study is informative of the important role iodine plays in the human diet.

Key words: Oxidative stress, catalase, superoxide dismutase, carbonyl, thiol, TBARs

INTRODUCTION

Iodine is an antiseptic soluble in alcohol. The first living cells to produce oxygen earlier considered to be toxic were the algae containing high amount of iodine (Venturi and Venturi, 1999). Thus, the high iodine content played a protective antioxidant role in the algea. Iodine deficiency has been reported to activate antioxidant genes and cause DNA damage in the thyroid gland of rats and mice. Antioxidative enzymes in iodine deficient rats and mice showed increased mRNA expression. Thus, indicating increased radical burden that could lead to accumulation of oxidized adducts as seen in the thyroidal genomic DNA (Maier *et al*., 2007). Dietary iodides have earlier been reported to defend brain cells from lipid peroxidation (Wang *et al*., 2004). The antioxidant action of iodide has also been described in isolated rabbit eyes. Potassium iodide supplementation at normal dose had a significant antioxidative ability in the retina of the rat eye (Wu *et al*., 2003). As an essential element, iodine is derived from the diet and humans require a daily intake of iodine (as iodide) of about one tenth of a milligram. It has earlier been reported that iodine deficiency is still a problem in Cameroon (Taga *et al*., 2004, 2008, 2009). Similar results have also been observed in Bangladesh (Ara *et al*., 2010). Lack of proper nutrition limits the body's ability to properly develop, protect and work at its capacity. However, earlier observations suggested that

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long and un-necessary use of iodized salt may produce sub clinical hyperthyroidism and thyrotoxicosis (Khan *et al*., 2003).

Diabetes has been related to oxidative stress either as a causative factor or as its consequence (Qia *et al*., 2008). Oxidative stress is known to cause tissue damage occurring in several diseases, including diabetes (El-Missiry *et al*., 2004). Several research results have established Alloxan monohydrate at a single dose regiment of 150 mg kg^{-1} body weight as a standard method for induction of experimental diabetes (Ananthan *et al*., 2003; Ekor *et al*., 2010; Manoharan *et al*., 2007; Mohamed and Faddah, 2007). Alloxan oxidizes glutathione (GSH) to form hydrogen peroxide (Nakazaki *et al*., 2000; Bromme *et al*., 2001) which though a stable molecule but can be dangerous in the presence of a metal ion. Induction of diabetes mellitus by alloxan in animals has been associated with lipid peroxide levels (Nishikawa *et al*., 2000) and a corresponding depression in the antioxidant defense mechanism characterized by decreased super oxide dismutase, catalase and glutathione (El-Missiry *et al*., 2004).

The role of iodine supplementation on the antioxidant status of normal and alloxan monohydrate intoxicated rats was evaluated in this study.

MATERIALS AND METHODS

Reagents: All reagents were of analytical grade purchased from Sigma Chemical (St Louis, MO).

Experimental animals: This piece of research was conducted from July, 2009 to December 2009 in the Laboratory of Pharmacology in the Centre of Research on Medicinal Plants and Traditional Medicine, Institute of Medical Research and Medicinal Plants Studies. Twenty female Wistar albino rats raised in the Institute of Medical Research and Medicinal Plants Studies, Yaoundé Cameroon were used for this study. The experiment was carried out in accordance with the 1996 Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act that pertains to research of this nature. The rats were divided into 4 groups of 5 rats each and housed in wire meshed cages. The groups A and C were not induced oxidative stress (kept normal), while oxidative stress was provoked in groups B and D by intraperitoneal injection of a solution of alloxan monohydrate (150 mg kg^{-1} animal weight single dose) as earlier described (Ekor *et al*., 2010). Animals with hyperglycemia (blood glucose = 200 mg dL^{-1}) were considered as stressed. The group A and B animals were fed the normal rodent diet while the group C and D animals were fed the normal rodent diet supplemented with potassium iodide (KI 25 mg kg^{-1} of food). The feeding lasted 6 weeks and the animals were sacrificed after an overnight fast by cervical dislocation and blood (4 mL) collected by cutting the jugular vein immediately. The plasma prepared from the blood was stored at -20°C until analyzed. The red blood cells were then washed using physiological saline (0.9% NaCl). The resulting red blood cells were then haemolysed by the addition of cold distilled water. The hemolysate was then stored at -20°C until analysed.

Biochemical analysis: Biochemical parameters analysed from the plasma were total protein (Bradford, 1976), protein thiols groups (SH) (Ellman, 1959), protein Carbonyl Groups (CO) (Reznick *et al*., 1992) and bilirubin (Friedman and Young, 2004). Blood glucose was analysed from whole blood using Glucometer (one touch ultra2). Antioxidant markers such as Superoxide dismutase (SOD) (McCord and Fridovich, 1969) and catalase (Beers and Sizer, 1952) were analyzed from the hemolysate. FRAP (Ferric Reducing Antioxidant Power) was analysed by employing the method of Benzie and Strain (1996).

Statistical analysis: All data obtained were subjected to statistical analysis and are presented as Means±Standard deviation. Analysis of Variance on Ranks was employed in groups' comparison. All pair wise multiple comparisons to determine significant difference between groups were carried out using Kruskal-Wallis test. The SPSS software version 10.1 was employed in these analyses. The level of significance was set at $p<0.05$ for all tests.

RESULTS

Table 1 presents the effect of iodine supplementation on antioxidant status of normal and alloxan monohydrate intoxicated rats. Group A and C animals (normal rats) were not intoxicated with alloxan monohydrate. However, Group C animals received iodine supplementation. The iodine supplementation improved the antioxidant status of the Group C rats significantly ($p<0.05$) as seen in the belirubin concentration (89.73±23.13 μmol L^{-1}), FRAP (420.71±17.57 μM) and catalase activity (24.0±11.56 UI mg^{-1} protein) but did not alter the SOD activity significantly ($p>0.05$). Alloxan monohydrate intoxication induced a collapse in antioxidant status of group B animals by significantly ($p<0.05$) decreasing the FRAP (292.15±35.52 μM) and the activities of SOD (118.22±0.16 UI mg^{-1} protein) and CAT (10.69±6.69 UI mg^{-1} protein). However, supplementation with iodine maintained the antioxidant status as seen in group D animals with FRAP SOD (129.74±0.11 UI mg^{-1}

Table 1: Effect of Iodine supplementation on antioxidant status of normal and alloxan monohydrate intoxicated rats

Parameters	Group A (Normal rats)	Group B (ALX rats)	Group C (Normal+iodine)	Group D (ALX+iodine)
Bilirubin (μmol L^{-1})	60.43±23.43	42.55±31.45[a]	89.73±23.13[a]	129.50±15.40[b]
FRAP (μM)	397.78±38.41	292.15±35.52[a]	420.71±17.57[a]	335.65±17.75[b]
Total protein (μg L^{-1})	229.32±42.95	218.67±75.53	238.97±21.65	234.99±52.35
Catalase (UI mg^{-1} protein)	13.95±7.57	10.69±6.69[a]	24.00±11.56[a]	22.00±9.01[b]
SOD (UI mg^{-1} protein)	139.80±0.08	118.22±0.16[a]	134.65±0.93	129.74±0.11[b]

Value represented as Mean±SD of 5 rats in each group. [a]indicated significant difference (p<0.05) compared to Group A (normal rats fed normal rodent diet), [b]indicated significant difference (p<0.05) compared to Group B (alloxan intoxicated rats fed normal rodent diet). ALX = Alloxan monohydrate

Table 2: Effect of Iodine supplementation on blood glucose and oxidative stress parameters of alloxan monohydrate intoxicated rats

Parameters	Group A (Normal rats)	Group B (ALX rats)	Group C (Normal+iodine)	Group D (ALX+iodine)
Blood glucose (mg dL^{-1})	96.00±4.69	227.04±69.0[a]	100.50±5.27	206.10±34.58
TBARS (μmol L^{-1})	1.95±1.06	3.06±0.44[a]	1.68±0.25	1.82±0.88[b]
SH (μmol mg^{-1} protein)	45.44±8.79	206.25±20.22[a]	38.79±19.6	180.88±33.92[b]
CO (μmol mg^{-1} protein)	180.64±73.52	252.50±82.5[a]	186.02±32.59	203.03±17.41[b]

Value represented as Mean±SD of 5 rats in each group. [a] indicated significant difference (p<0.05) compared to Group A (normal rats fed normal rodent diet), [b]Indicated significant difference (p<0.05) compared to Group B (alloxan intoxicated rats fed normal rodent diet). ALX: Alloxan monohydrate

protein) values turning toward normal. Table 2 presents the effect of iodine supplementation on blood glucose and oxidative stress parameters of normal and alloxan monohydrate intoxicated rats. Intoxication of experimental animals with alloxan monohydrate induced hyperglycemia (227.04±69.0 mg dL^{-1}) which was not significantly reduced (p>0.05) following supplementation with iodine. Supplementation of normal rats with iodine did not alter the blood glucose concentration either. Carbonyl (CO), thiol (SH) and lipid peroxidation represented by Thiobarbituric Acid Reactive Substances (TBARS) were assessed as markers of oxidative injury. TBARS, SH and CO were significantly (p<0.05) increased in alloxan intoxication 3.06±0.44 μmol L^{-1}, 206.25±20.22 μmol mg^{-1} protein and 252.5±82.5 μmol mg^{-1} protein, respectively. The increase in TBARS concentration in the plasma of rats in Group B is an indication of lipid peroxidation. These increases in TBARS, SH and CO were prevented in the iodine supplemented group 1.82±0.88 μmol L, 180.88±33.92 μmol mg^{-1} protein and 203.03±17.41 μmol mg^{-1} protein, respectively.

DISCUSSION

Alloxan monohydrate treatment is an established method for induction of diabetes. The mechanism of action has been attributed to DNA fragmentation in pancreatic islets and cell damage free radicals (Takasu *et al*., 1991). Diabetes has been related to oxidative stress either as it is a causative factor or because of its consequence (Qia *et al*., 2008). Oxidative stress and tissue damage are common phenomena in several diseases especially those linked to toxic agents' exposure (El-Missiry *et al*., 2004). Thus, controlling oxidative stress may either help prevent development of diabetes or control its consequence which may lead to further harmful effects. The present study evaluated the effect of iodine supplementation on the antioxidant status of alloxan monohydrate intoxicated rats. A mark oxidative stress effect was induced by alloxan administration evidenced by the significant decline of endogenous antioxidant enzymes (SOD and CAT) activities, in the erythrocytes of experimental animals studied (Group B). Similar results have been obtained in isolated pancreatic islets (Fisher and Humburger, 1980), erythrocytes (Yadav *et al*., 1996), liver and testis (Soto *et al*., 1998; El-Missiry and El-Gendy, 2000); brain (El-Missiry *et al*., 2004) and forebrain (Kosenko *et al*., 1999) of experimental animals.

Catalase has the function of detoxification of H_2O_2, an effective inhibitor of SOD (De Duve and Baudhuin, 1996). Catalase scavenges the active oxygen metabolites, and protects the cells from toxic oxidation (Marklund *et al*., 1982). The decreased catalase activity in alloxan intoxicated animals (Group B) served as an indicator of increased reactive oxygen species generation in diabetic rats (Makni *et al*., 2010; Farombi and Ige, 2007). Alloxan in a single injection destroys the insulin-producing islet β-cells in order to cause diabetes in experimental animals (Rerup, 1970). This is mediated by redox reaction which produces superoxide radicals in or near the β-cells (Deamer *et al*., 1971; Heikkila *et al*., 1976; Grankvist *et al*., 1979). Thus, superoxide dismutase, enzyme removing superoxide anion radicals, may acts prophylactically against alloxan-induced diabetes (Grankvist *et al*., 1981). In the present study alloxan induced a collapse in the SOD activity. Similar decline in SOD activity in alloxan treated animals has been reported by Makni *et al*. (2010) and Farombi and Ige (2007). Supplementation with iodine reinstated the antioxidant status of alloxan intoxicated animals (Group D) suggesting that iodine may have a superoxide anion radical scavenging activity.

Diabetes may induce increased systemic oxidative stress which is the underlying cause of dysregulation of adipocytokines and development of metabolic syndrome and pathogenesis of various diseases (Brownlee, 2001).

Oxidative stress impairs glucose uptake in muscle and adipose tissue in diabetic conditions (Maddux *et al*., 2001; Rudich *et al*., 1998) and decreases insulin secretion from pancreatic B cells (Matsuoka *et al*., 1997). This results to a hyperglycemic environment which may impair radical scavenging activity and hence exposing proteins and lipids to peroxidation. Earlier studies have reported increases in lipid (TBARS) and protein oxidation (CO) products in diabetic patients (Telci *et al*., 2000; Kesavulu *et al*., 2001; Farombi and Ige, 2007). This is in conformity with the results obtained in the present study characterized by a significant rise in TBARS, CO and SH concentrations in alloxan inoxication. The increase in thiol and carbonyl concentrations may be due to the oxidation of the side chains of certain amino acids resulting to the liberation of the thiol and carbonyl groups in the plasma (Pincemail *et al*., 1999). The evaluation of protein carbonyls as a useful marker of oxidative stress is based on its long half life in circulating blood (Trombetta *et al*., 2006; Dalle-Donne *et al*., 2003). This suggests that iodine supplementation to prevent the rise in oxidative stress.

CONCLUSION

Iodine functions as an antioxidant by increasing antioxidant enzyme activity in both normal and alloxan intoxicated rats there by reversing the effect of alloxan intoxication and fortifying the antioxidant defense mechanism. Reducing the accumulation of oxidative stress markers such as carbonyl and thiol functionality and lipid peroxidation (collapse of antioxidant function) is also an important property of iodine observed in this study. It will be important to evaluate the oxidative stress and antioxidant statutes in iodine deficient endemic areas so as to have an understanding of the risks involved and a better intervention program.

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