

Vitamin E Modulates the Oxidant-Antioxidant Imbalance of BPA induced Oxidative Stress in Albino Rats

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Abstract: Bisphenol A (BPA) is one of the world's highest production volume chemicals used in polycarbonate plastics in many consumer products and epoxy resins lining food and beverage containers. Study on the oxidative stress and antioxidant enzyme defense system in BPA induced rats blood sample revealed an augmented oxidative stress due to BPA level in rat blood sample and decreased antioxidant enzyme defense which might decrease the blood pumping efficiency and leading to the probable increase of oxidative stress in blood. the supplementation of vitamin E is an important lipid soluble antioxidant *in vivo*, and it is presumed that its principle role is to protect membrane lipids from lipid peroxidation *in vivo*, by scavenging lipid alkoxy or peroxy radicals which are capable of abstracting hydrogen from adjacent polyunsaturated lipid molecules to propagate a lipid peroxidation reaction and thus prevent the serum damage due to oxidative stress.

Keywords: Oxidative stress, BPA, Vitamin E, Antioxidants

1. Introduction

Oxygen as an essential element is critical for energy production and existence of all organisms on earth. However, there are potentially damaging effects also associated with it leading to production of oxygen centered free radicals. These radicals are highly reactive and can cause damage to various biomolecules. Presence of a physiological antioxidant defense system keeps these free radicals in check. Any imbalance in the levels of free radicals or reactive oxygen species (ROS) leads to oxidative stress in the body and may culminate in various patho-physiological conditions.

In recent years, considerable attention has been focused on endocrine disrupting compounds and their impacts on the environment and human health, raising questions about their levels of exposure. Bisphenol A (BPA) is one of the world's highest production volume chemicals (Ritter 2011) used in polycarbonate plastics in many consumer products and epoxy resins lining food and beverage containers (EU 2008). BPA is a kind of potential endocrine disruptor. It is a ubiquitous xeno estrogen that can leach into the contents during processing and storage. Moreover, BPA-based resins are commonly used in dentistry. Therefore the Human population is continuously and inevitably exposed to low doses of BPA in daily life. Importantly, BPA has been detected in amniotic fluid, cord blood and human breast milk, which demonstrates the potential of this compound to pass from mother to fetus. Evidence suggests that conditions experienced during early development play an important role in determining the long term health of individuals.

The global population is subjected to repeated exposure to BPA, primarily through packaged food but also through

drinking water, dental sealants, dermal exposure and inhalation of household dusts (Lakind and Naiman 2008) with detectable concentration of metabolites in the urine of >90% of the population worldwide (Calafat *et al.* 2005; Ye *et al.* 2008). Heat, repeated washing of polycarbonate products and contact with either acidic or basic compounds accelerate hydrolysis of the ester bond linking BPA molecules in polycarbonate plastics and resins resulting in an increase in the rate of leaching of BPA (Lim *et al.*2009). In addition, another potential source of human exposure is water used for drinking or bathing. Studies conducted in Japan (Kawagoshi *et al.*2003) and in the united (coors *et al.*2003) shown that BPA accounts for most estrogenic activity that leaches from landfill into the surrounding ecosystem.

Increasing evidences shows that adverse effect of BPA on health are miscellaneous, varying with duration, doses and route of BPA Exposure, as well as sex difference. In humans, increased levels of BPA in adults have been correlated with various diseases, health outcomes and medical conditions. To date, reported health complications associated with increased level of BPA exposure include diabetes (Lang *et al.*2008), cardio vascular diseases (Lang *et al.*2008; Melzer *et al.*2010) altered liver enzymes as increase in alanine amino transferase and aspartate aminotransferase (Lang *et al.*2008;mourad and khadrawy 2012) and obesity promoting effects (Ropero *et al.*2008, tracavengesande *et al.*2012;Harley *et al.*2013) contributing to the potential for altered metabolic homeostasis, BPA has been shown alter glucose homeostasis, increase pancreatic insulin content and induce insulin resistance in adult male mice (Alonso-magdalena *et al.*2006).

BPA can cause liver, kidneys, brain, and other organs injury by forming Reactive oxygen species (ROS). ROS are

Volume 7 Issue 1, January 2018

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cytotoxic agents causing oxidative damage by attacking cell membrane and DNA. The liver has a range of antioxidant defense system. ROS are scavenged by the endogenous antioxidant defense system, including superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) in cells. When the capacity of this antioxidant system decreases, the level of inactivated ROS rises.

Reactive oxygen species (ROS) are involved in the pathogenesis of several diseases and tissue damages (Slater *et al.* 1987; Wei, 1998; Lee *et al.* 1999; Calabrese *et al.* 2005). These reactive species include superoxide anion (O₂⁻), hydrogen peroxide (H₂O₂) and hydroxyl radical (·OH). ROS may cause cell injuries such as lipid peroxidation, enzyme inactivation, changes in intracellular redox state and DNA damage (Halliwell and Gutteridge 1985; Bejma and Ji, 1999; Zhang *et al.* 2005; Rubio-Gayosso *et al.* 2006). Oxidative stress can be defined as state of disturbance in the prooxidant/antioxidant balance in favour of the former leading to potential damage. Cells possess enzymatic defense system to reduce the risk of oxidative injury to the cells that can cause cellular malfunction and even cell death.

Vitamin E (α-tocopherol) is considered one of the most important dietary antioxidant in biological systems due to its association with cell membrane and its ability to act directly on reactive oxygen species (ROS) preventing peroxidation. Besides the well characterized function of vitamin E as antioxidant alternative roles such as that of a membrane stabilizer, and a regulation of membrane fluidity have been proposed. The protective role of vitamin E on the oxidative stress develops due to antileprosy chemotherapy in leprosy patients was recorded. In the present study is carried out to evaluate the impact of vitamin E supplementation on the oxidative stress during BPA administration.

Vitamin E (α-tocopherol) is considered one of the most important dietary antioxidant in biological systems due to its association with cell membrane and its ability to act directly on reactive oxygen species (ROS) preventing peroxidation (Burton and Traber 1990; Azzi *et al.* 2000; Xu *et al.* 2003; Kir *et al.* 2005). Besides the well characterized function of vitamin E as antioxidant alternative roles such as that of a membrane stabilizer (Urano *et al.* 1989; Kim, 2005) and a regulation of membrane fluidity (Ohyashiki *et al.* 1986; Ohyashiki *et al.* 1998) have been proposed. The protective role of vitamin E on the oxidative stress develops due to antileprosy chemotherapy in leprosy patients was recorded (Srinivasan *et al.* 2004; Das *et al.* 2004; Vijayaraghavan *et al.* 2005).

In the present study is carried out to evaluate the impact of vitamin E supplementation on the oxidative stress during BPA induced in albino rats blood (Jeff *et al.* 2002). The BPA induced rats kept for 20 days were fed with vitamin E (α-tocopherol) of 200mg/kg body wt. (Tang 1989; Bauersachs *et al.* 1993; Ibrahim *et al.* 1997; Venkatraman *et al.* 1998) for 15 days (Tang 1989; Shukla *et al.* 1997; Manju *et al.* 2005).

2. Literature Survey

Huang YF *et al.* (2017) investigate urinary NP and BPA levels in relation to biomarkers of oxidative /nitritative stress and inflammation and to explore whether changes in oxidative/nitritative stress are a function of prenatal exposure to NP/BPA and inflammation in 241 mother-fetus pairs. The results support a role for exposure to NP and BPA and possibly inflammation in increasing oxidative/ nitritative stress and decreasing antioxidant activity during pregnancy

3. Materials and Methods

Animals

Male albino rats of Wistar strain weighing around 160 to 180gms were purchased from Tamilnadu Veterinary and Animal Sciences University, Chennai. The Animals were acclimatized to the laboratory conditions, fed with commercial pelleted rats chow (Hindustan Lever Ltd, Bangalore, India) and had free access to water. The experiments were designed and conducted in accordance with the guidelines of institutional animal ethics committee.

Experimental Protocol

The rats were divided into 4 groups comprising of 6 animals in each group.

Group I Control-sham operated animals (C)

Group II BPA induced (by oral) 20 days animals-Control (EC)

Group III BPA induced animals after 20 days given Vitamin E (ET vitE₁₅)

The study was carried out to assess the oxidative stress, antioxidant enzymes, TSH, LDL and Protein in the BPA induced animal blood and under the influence of BPA induced and vitamin-E and tablet Thyronorm supplementation.

BPA induction

BPA was given to the albino rats by oral 20mg/ kg body weight for 20 days.

Vitamin E supplementation

Rats were fed with vitamin E (-tocopherol) of 200mg/Kg body weight, as reported earlier (Tang, 1989; Bauersachs *et al.* 1993) for 15 days (Manju *et al.* 2005).

Sample Preparation

The experimental animals were sacrificed by cervical dislocation at the end of the appropriate experimental period. The various experimental groups viz. C, EC, ET vitE, ETvitE₁₅&THY₁₅ were dissected and heart punctured and blood sample were collected for analysis.

Oxidative damage assay

Oxidative damage in the muscle tissue was assessed by measuring the levels of TBARS in all the blood samples viz C, EC, ET vitE, ETvitE₁₅&THY₁₅ were estimated according to the standard procedures described below.

TBARS (MDA)

TBARS (MDA) was measured in all the blood samples viz. C, EC, ET vitE, ET vitE₁₅&THY₁₅ animals using the method of Ohkawa (1979).

Antioxidant enzyme assay

Super oxide dismutase, Catalase, Glutathione reductase enzymes were measured in all the blood samples viz. C, EC, ET vitE, ET vitE₁₅&THY₁₅ animals according to the standard procedures described below.

Super oxide dismutase (EC. 1.151.1)

Super-oxide-dismutase enzyme was assayed in all the blood samples viz. C, EC, ET vitE, ET vitE₁₅&THY₁₅ animals by using the method of Beauchamp and Fridovich (1974).

Super-oxide-dismutase (SOD) enzyme activity was expressed as Units / mg protein / min (one unit of SOD activity is defined as the enzyme reaction, which give 50% inhibition of NBT reduction in one minute under the assay condition).

Catalase (EC. 1.11.1.6)

Catalase was measured in all the blood samples viz. C, EC, ET vitE, ET vitE₁₅ &THY₁₅ animals by using the method of Chance and Machly (1955).

Catalase (CAT) enzyme activity was expressed as μ moles of H₂O₂ consumed / min / mg protein.

Glutathione reductase: (EC. 1.6.4.2)

The activity level of glutathione reductase was measured in all the blood samples viz. C, EC, ET vitE, ET vitE₁₅ &THY₁₅ animals by using the method of Racker, (1955).

Glutathione reductase (GR) enzyme activity was expressed as μ moles of NADPH oxidized/min/mg protein.

Statistical Analysis

The statistical analysis of the various parameters of the present study in all animal groups was carried out. Student's 't' test was conducted to test the difference between two sample means by using given formula as suggested by Gupta (1978)

4. Result and Discussion

The activity levels of thiobarbituric acid reactive substances was significantly elevated to 10% when compared to that of control (Table-2; Figure-2) The activity levels of antioxidant enzymes viz. super oxide dismutase (SOD), catalase (CAT), and glutathione reductase (GR) reduced to -14.28%, -13.51%, -12.63% respectively in the BPA induced albino rats when compared to that of control (Table -1; Figure -1)

TBARS was recorded a significant decrement 42.85% (Table-2; Figure2 -) indicating lowered lipid peroxidation in the BPA induced albino rat blood supplemented with vitamin E. The study on the antioxidant defense enzyme revealed a significant elevation of the activity levels of enzymes viz. SOD, CAT and

GR in the blood samples of vitamin E fed BPA induced animals, the elevation of activity levels of enzymes ranges 37.5%, 62.5% and 71.08%. (Table-1; Figure-1a).

The oxidative stress leading to increased lipid peroxidation in the BPA induced albino rat was indicated by elevated levels of TBARS. Small amounts of malondialdehyde were produced during peroxidation and can react in the thiobarbituric acid test to generate a coloured product for photometric measurement. The measurement of level of TBARS which is the marker of oxidative stress induced lipid peroxidation reveal significant elevated levels in the BPA induced albino rats blood. Similar observations, where the free radicals generated lipid peroxidation were recorded in previous studies during BPA induction in albino rats blood sample. The increased levels of TBARS in the BPA induced rats blood sample indicating elevated lipid peroxidation which might be due to increased oxidative stress and/or decreased levels of antioxidant enzyme defense mechanism in the blood sample.

Further probe into the antioxidant defense mechanism of the BPA induced rats blood sample was carried out. The activity level of the cytosolic enzyme super-oxide-dismutase (SOD) recorded a significant decrease indicating decreased inhibition of formation of hydroxyl ion (\cdot OH) from hydrogen peroxide, thereby increasing the free radical concentration leading to oxidative stress. The enzymes catalase (CAT) [Whose activity levels recorded depletion in the present study] prevent the formation of hydroxyl radicals that can initiate lipid peroxidation by converting the hydrogen peroxide into water and diatomic oxygen. The enzymatic antioxidant viz. superoxide dismutase (SOD), which catalyses the conversion of the oxygen radical (O₂ \cdot) to H₂O₂ (Somani *et al.* 1996; Husain and Somani 1997, 1997a, b, c) and H₂O; the enzyme catalase (CAT) which then converts H₂O₂ to H₂O and oxygen (O₂); Further catalase (CAT) is involved in detoxification of high concentration of H₂O₂. The enzyme glutathione reductase (GR) catalyze the reaction to reconvert the GSSG to GSH. Hence working in concert, the peroxidase/reductase couple counter act oxidative stress in the blood.

The decreased levels CAT in BPA induced rats blood sample in the present study might suggest reduce detoxification of H₂O₂ and other peroxides which might lead to production of hydroxyl and peroxyl radical in the presence of iron (Gutteridge and Halliwell 1994; Rice-Evans and Burdon, 1994; Halliwell, 1996; Mares-Perlman *et al.* 1996; Bast and Barr 1997). The depleted activity levels of glutathione reductase (GR) in the BPA induced rats blood sample, which is an important enzyme for the maintenance of intra cellular concentration of reduced glutathione (Chandra, 1992; Gutteridge and Halliwell 1994; Rice-Evans and Burdon, 1994; Diplock, 1995; Halliwell, 1996).

Thus the study on the oxidative stress and antioxidant enzyme defense system in BPA induced rats blood sample revealed an augmented oxidative stress due to BPA level in rat blood sample and decreased antioxidant enzyme defense which

might decrease the blood pumping efficiency and leading to the probable increase of oxidative stress in blood.

The increased lipid peroxidation in the BPA induced in albino rats blood might be due to increased generation of reactive oxygen species (ROS) in the muscle (Chapter I) thereby disturbing both enzymatic and non enzymatic antioxidant defense system in the blood. Vitamin E (α -tocopherol) serves as potent peroxy radical scavenger. Excess generation of ROS may overwhelm natural antioxidant defenses such as serum vitamin E leading to lipid peroxidation in further contributing to serum damage (Ohyashiki *et al.* 1986; Bowles *et al.* 1991; Meydani *et al.* 1993; Ohyashiki *et al.* 1998).

The decrease levels of TBARS in the present study indicate the reduced lipid peroxidation which might be due to the non enzymatic antioxidant vitamin E impact on the BPA induced in albino rats blood. Similar studies where vitamin E reduced lipid peroxidation were recorded (Ohyashiki *et al.* 1986; Bozkurt, 2002). The deranged antioxidant enzymatic defense system with the depleted activity levels of SOD, CAT and GR were significantly restored indicating the elevated activity levels of SOD, CAT and GR in the blood of BPA induced animals supplemented with vitamin E. This might be due to the free radicals scavenging act of vitamin E, thus reducing the free radical concentration and the probable regain of the antioxidant enzymatic defense system.

5. Conclusion

The above results envisage that the supplementation of vitamin E is an important lipid soluble antioxidant *in vivo*, and it is presumed that its principle role is to protect membrane lipids from lipid peroxidation *in vivo*, by scavenging lipid alkoxy or peroxy radicals which are capable of abstracting hydrogen from adjacent polyunsaturated lipid molecules to propagate a lipid peroxidation reaction and thus prevent the serum damage due to oxidative stress.

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Table 1: Parameters of antioxidant enzymes in control and BPA & Vit E induced of male albino rats. Values are mean \pm SD (n=10). Values with different letters are significantly different (P < 0.001).

| Parameter | Control (C) | % of changes | BPA Induced EC* | % of changes | BPA & Vit E Induced ET VitE15** |
|--|----------------|--------------|-----------------|--------------|---------------------------------|
| SOD Unit ¹ /mg protein/min | 0.56 \pm 0.8 | -14.28 | 0.48 \pm 0.4 | +37.5 | 0.66 \pm 0.7 |
| CAT Unit ² /mg protein/min | 0.37 \pm 0.1 | -13.51 | 0.32 \pm 0.1 | +62.5 | 0.52 \pm 0.02 |
| GR Unit ⁴ /mg protein/min | 0.95 \pm 0.1 | -12.63 | 0.83 \pm .001 | +71.08 | 0.24 \pm .001 |

Unit¹ SOD = Superoxide dismutase activity, expressed as Units / mg protein / min (one unit of SOD activity is defined as the enzyme reaction, which give 50% inhibition of NBT reduction in one minute under the assay condition); **Unit² CAT** = Catalase activity, expressed as μ moles of H₂O₂ consumed / min / mg protein; **Unit³GR** = Glutathione reductase activity, expressed as μ moles of NADPH oxidized/min/mg protein;

*Group compared between control(C)and bpa induced (EC *)**Group compared between bpa induced (EC*) and bpa & vit E induced (ET vitE15) ‘¥’ denotes statistical significance (P< 0.001)

Table 2: Parameters of oxidative damage in control and BPA & vitE induced of male albino rats. Values are mean \pm SD (n=10). Values with different letters are significantly different (P < 0.001).

| Parameter | control (C) | % of changes | BPA induced EC* | % of Changes | BPA & Vit E Induced ET VitE15** |
|--------------------------------------|---------------|--------------|-----------------|--------------|---------------------------------|
| TBARS μ moles /mg protein | 0.7 \pm 0.5 | +10 | 0.63 \pm 0.05 | -42.85 | 0.36 \pm .001 |

TBARS = content in tissue, expressed as μ moles Malondialdehyde (MDA) /mg protein;
Group compared between control(C)and bpa induced (EC *)**Group compared between bpa induced (EC*) and bpa & vit E induced (ET vitE15) ‘¥’ denotes statistical significance (P< 0.001)

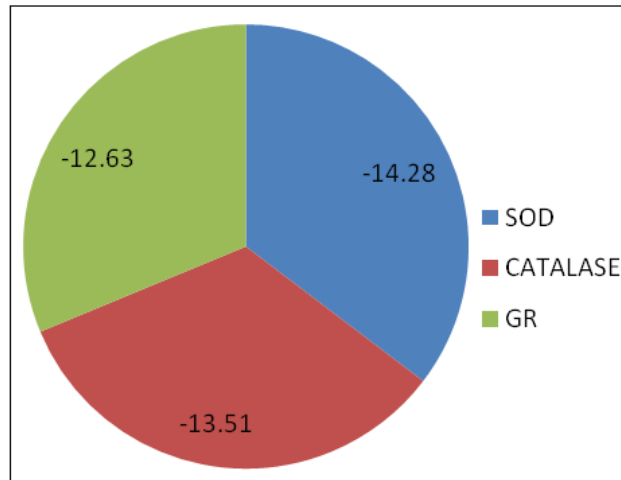


Figure 1 (a): Percentage change of activity levels of antioxidant enzyme viz. SOD, CAT and GR in control compared with BPA induced albino rats

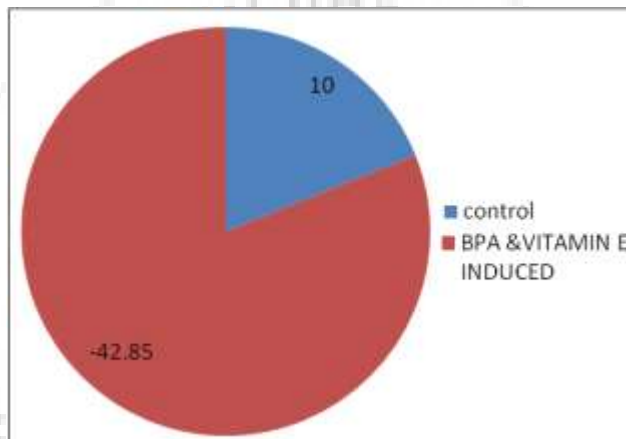


Figure 1 (b): Percentage change of activity levels of antioxidant enzyme viz. SOD, CAT and GR in BPA induced compared with Vitamin E supplemented albino rats

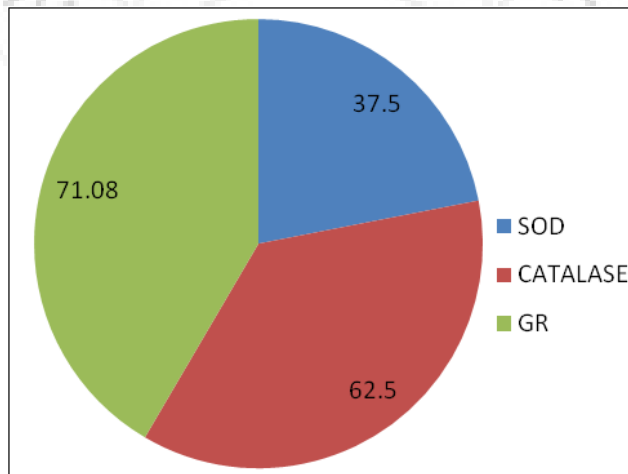


Figure 2: Percentage change in the Levels of thiobarbituric acid reactive substances (TBARS) in control and BPA & Vitamin E induced albino rats .