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A diet high in cholesterol and deficient in vitamin E induces lipid peroxidation but does not enhance antioxidant enzyme expression in rat liver

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Abstract

Expression of antioxidant enzymes (AOE), an important mechanism in the protection against oxidative stress, could be modified by the redox status of the cells. The aim of this project was to evaluate the role of vitamin E deficiency in association with a high-cholesterol diet in the hepatic lipid peroxidation and the expression of AOE. Two groups of 6 male rats were fed with a high-cholesterol or a high-cholesterol vitamin E-deficient diet. All animals were sacrificed at 72 days of treatment. Liver lipid peroxidation index (Malondialdehyde ; MDA) and hepatic AOE were evaluated. Total liver RNA was extracted, and the steady state messenger RNA (mRNA) levels of glutathion peroxydase, manganese superoxide dismutase, Cu/Zn superoxide dismutase and catalase were examined by northern blot. After 72 days on the diet, a significant increase in the lipid peroxidation index was observed in the vitamin E deficient group (MDA : 4.45 ± 0.29 nmol/mg protein versus 3.65 ± 0.1 nmol/mg protein in vitamin E normal group). Despite this oxidative stress, the activities and mRNA levels of liver AOE were not significantly different in the 2 groups. These preliminary results show that chronic vitamin E deficiency associated with high cholesterol diet is able to increase lipid peroxidation without modulation of AOE expression and activity in the liver. This suggests that beneficial effects of dietary vitamin E are due to a plasma antioxidant effect or a cell mediated action, rather than to a specific modulation of cellular enzymes.

Keywords: Vitamin E; Oxidative stress; Liver; Glutathion peroxidase; Superoxide dismutase; Catalase

1. Introduction

Reactive oxygen species (ROS) produce tissue injury by initiating lipid, protein and DNA oxidative modifications, which could be involved in hypercholesterolemia-induced vasculopathies. In order to protect tissues from these damaging effects, the organism possesses enzymatic and non enzymatic antioxidant systems [1]. Enzymatic systems are composed of cytosolic enzymes such as Copper/Zinc superoxide dismutase (Cu/Zn SOD), catalase (CAT), glutathione peroxidase (GPx) and mitochondrial enzymes such as manganese superoxide dismutase (Mn SOD). SOD convert superoxide anion into H_2O_2 and O_2 [2], while catalase and GPx reduces H_2O_2 to H_2O [3]. It has previously been reported that *in vitro* oxidative stress could regulate the expression and activity of specific antioxidant enzymes (AOE) [1,4–7]. In rat liver, oxidative stress induced by toxic substance administration, such as alcohol or cocaine, results in variations of mRNA content and enzymatic activity [8,9].

In addition to these enzymatic systems, non enzymatic mechanisms also protect against oxidative stress. These mechanisms include natural lipophilic antioxidants such as vitamin E, beta-carotene, and hydrophilic substances such as vitamin C, glutathione (GSH) which could act synergistically. For example, vitamin E acts as a peroxyl radical scavenger and could be further regenerated by vitamin C and GSH. In addition to this chain propagation breaking

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effect, cell mediated vitamin E effects have recently been described and could be in part independent of the antioxidant potency. Indeed, vitamin E could regulate smooth muscle cell proliferation [10] and ROS monocyte production [11,12] by mechanisms involving protein kinase C (PKC) inhibition, largely dependent on vitamin E isoforms and stereoisomers [13,14]. Alternatively, modulation of transcriptional factor activity such as activator protein-1 (AP-1) and nuclear factor κB *(NF-κB)*, could be directly related to vitamin E antioxidant potency [15,16] and/or linked to the direct modulation of kinase cascades or DNA binding [15].

Interestingly, AP-1 and NF-κB DNA binding sites have been located to regulatory regions of inflammatory genes such as adhesine molecules, cytokines and AOE [17].

Thus, it could be postulated that vitamin E *per se* or indirectly, by altering the cell redox status, could modulate AOE expression and activity. However, *in vivo* modulation of AOE gene expression by an oxidative stress, not related to toxic drug administration remains poorly investigated. In a vitamin E–and selenium–deficiency model of liver oxidative stress, Fraga et al. [18] reported an isolated decrease of selenium-glutathione peroxidase activity. The present study was designed to evaluate the modulation of hepatic AOE expression and activity during oxidative stress induced by vitamin E deficiency associated with a high cholesterol diet in rats.

2. Materials and methods

2.1. Animals and diets

Male Sprague Dawley rats ($n=12$) weighing approximately 147 g were divided randomly into two dietary groups of six animals, which received an experimental semi-synthetic diet. Group 1 was fed with a high-cholesterol-vitamin E-sufficient diet (192 mg/kg). Group 2 received a high-cholesterol-vitamin E-deficient diet (22 mg/kg). The composition of the two diets is shown in Table 1. The rats were weighed every 4 days and sacrificed at 72 days of diet. The French instructions 88–123 concerning ordinance 87–848 about rules of animal experimentation were followed.

2.2. Experimental protocols and tissue preparation

At the end of this experimental period, the animals were fasted overnight and then anesthetized with intraperitoneal thiobarbital (60 mg/kg) injection, and sacrificed by exsanguination. Livers were perfused with RNAse-free cold 1.15% KCl solution, then rapidly excised and weighed.

In order to determine liver enzyme activities and global lipid peroxidation index, liver tissue homogenization was performed at 4°C as previously described [19]. Tissue was homogenized in 5 vol ice cold 0.1M potassium phosphate (pH 7.4) and centrifuged at 13,000 x g for 15 min. The post-mitochondrial supernatant was spun at 105,000 x g for 60 min and the resulting cytosol was stored at −80°C until analysis. The protein content was determined according to Smith et al. [20].

Table 1
Composition of the experimental diets (g/kg diet)

Ingredient	Vitamin E-sufficient diet (Group 1)	Vitamin E-deficient diet (Group 2)
Casein	217	217
Cornstarch	433	433
Sucrose	50	50
Vegetable oil[a]	20	20
Lard	150	150
Mineral mix[b]	110	110
Vitamin mix[c]	10	0
Vitamin E-free vitamin mix[a]	0	10
Added cholesterol	10	10
Total vitamin E (mg/kg diet)	170	22

[a] Maize oil:soybean oil (1:1).

[b] Mineral mix (g/kg mix): $CaHPO_4$, 430; KCl, 100; NaCl, 10; $MgCl_2$, 50; $MgSO_4.7H_2O$, 50; Fe_2O_3, 30; $MnSO_4.H_2O$, 2,5; $ZnSO_4.H_2O$, 2; $CuSO_4.5H_2O$, 0,5; $CoSO_4$, 0,004; KI, 0,008; cellulose Q.S.P. 1000 g.

[c] Vitamin mix (mg/kg mix): retinol, 600; cholecalciferol, 300; all-*rac*-α-tocopheryl acetate, 17000; menadione, 200; thiamin, 2000; riboflavin, 1500; nicotinic acid, 10000; pantothenic acid, 7000; pyridoxine, 1000; inositol, 15000; biotin, 30; folic acid, 500; cyanocobalamin, 0.5; para amino benzoic acid, 5000; choline, 136000; cellulose Q.S.P. 1000 g.

[d] In the Vitamin E-free vitamin mix, all-*rac*-α-tocopheryl acetate was replaced by an equal amount of cellulose.

In order to determine GPx, CAT, MnSOD and Cu/Zn-SOD mRNA levels, aliquots of 30 mg were immediately frozen in liquid nitrogen and stored at -80°C until mRNA extraction.

2.3. Lipid peroxidation measurement

Liver lipid peroxidation was evaluated by linked-malondialdehyde (MDA) determination using the thiobarbituric acid (TBA) test according to the Esterbauer and Cheeseman procedure [21]. TBA-reactive substances (TBARS) were expressed as nmoles of MDA per mg of protein.

2.4. Antioxidant enzymes activities

Glutathione peroxidase (GPx) activity was measured by the glutathione reductase coupled oxidation of NADPH using hydrogen peroxide as the substrate according to the method of Wendel et al. [3] and including 1.0 mM azide to inhibit catalase [22]. One unit of GPx enzyme activity is defined as μmol of NADPH oxidized/min/mg protein. Total superoxide dismutase (SOD) activity was assayed by the method of Paoletti et al. [2,23]. The assay is based on the inhibition of a superoxide-driven NADH oxidation. One unit of the enzyme is the amount of SOD capable of inhibiting the rate of NADH oxidation observed in the control (absence of SOD) by 50% and is expressed per mg protein.

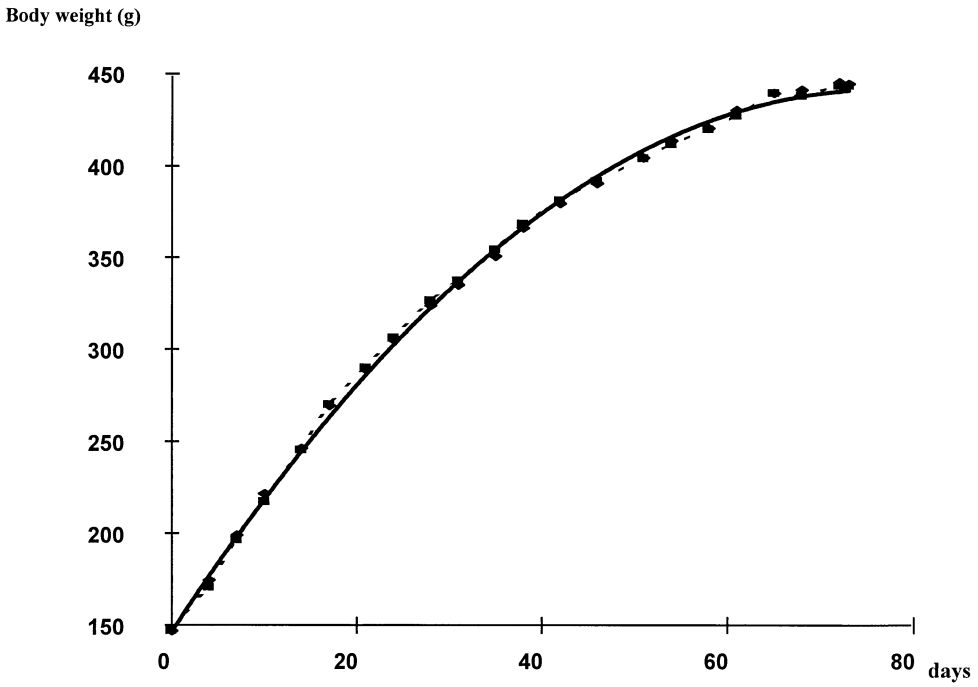

Fig. 1. Growth of rats during the 72 days of diet. Group 1 (—) Group 2 (····).

Catalase activity was measured according to Aebi et al. [24] following the rate of H_2O_2 consumption. Catalase activity was measured spectrophotometrically at 240 nm.

2.5. Determination of antioxidant enzymes mRNA levels

2.5.1. Probes synthesis

Probes specific for the antioxidant enzymes were obtained by reverse transcription followed by a polymerase chain reaction. One μg of total RNA extracted from a rat liver was reverse transcripted with an oligo-dT primer using 2 UI of reverse transcriptase (Promega, Charbonnière, France). The reaction was carried out at 37°C for 1 hr and 2 min at 99°C. A polymerase chain reaction was performed using 7.5 μl of the cDNA obtained, and the PCR product was purified with the Quiaquick kit (Quiagen, Courtaboeuf, France). Oligonucleotides were chosen by using an informatical program and the published cDNA sequences of the rat ; CuZnSOD [25], MnSOD [26], GPx [27], catalase [28].

2.5.2. Northern blot analysis

Total RNA was extracted from frozen livers using the RNeasy minikit (Quiagen, Courtaboeuf, France) and was stored at -80°C. Ten μg of total RNA were separated by electrophoresis on a 1% agarose denaturing gel, and transferred to a nylon membrane (HYBOND $N^{+,}$ Amersham, Les Ullis, France). The absence of RNA damage was checked before transferring by visualization of the bands with ethidium bromide. The membrane was hybridized overnight with (32P)-labeled specific probe at 42°C, in 50% of formamide. After stringency washes, the intensity of bands were quantified using a Phosphorimager (FUGIX BAS 1000), and blots were subsequently exposed at -80°C to a Biomax film for 48 hr. Glyceraldehyde 3-phosphate deshydrogenase (GAPDH) was used as an internal control as it is expressed constitutively in the liver. Blots revealed with GPx or MnSOD specific probes were dehybridized and subsequently rehybridized with GAPDH probe for normalization. Hybridizations with specific probes for the catalase, GAPDH and Cu/ZnSOD were done on the same blot.

2.6. Statistical analysis

Data are shown as the mean ± SEM for six observations per group. The statistical significance of differences between treatments was established by ANOVA using a stat VIEW 512+ microcomputer program (Brain Power, Calabasas, CA) incorporating a calculation of Fisher's least significant difference between groups. Differences were considered significant when $P < 0.05$. The analysis of autoradiographic bands obtained for catalase, GPx, MnSOD and Cu/ZnSOD were normalized against GAPDH expression and statistically analyzed by the same statistical procedure.

3. Results

3.1. Body weights

The body weights of the 2 groups of rats up to 72 days are presented in Figure 1. At the end of the experimental

Table 2
Lipid peroxidation index (MDA) and liver activities of superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) in rats fed with the experimental diets

	Group 1	Group 2
MDA (nmol/mg protein)	3.65 ± 0.1[a]	4.45 ± 0.29*
SOD (U/mg protein)	266.0 ± 23.1[a]	247.6 ± 13.1[a]
GPx (mU/mg protein)	344.8 ± 35.5[a]	334.0 ± 35.0[a]
CAT (U/mg protein)	152.9 ± 6.8[a]	151.1 ± 20.0[a]

[a] Values are means ± SEM of six observations per group; values in a row with different superscript letters are significantly different ($P < 0.05$).

diet, we did not observe any difference in body weight : (446 ± 0.86 g) for the group 1 versus (445 ± 0.82 g) for the group 2. Moreover the growth of rats *consuming* a high cholesterol diet was constant and independent of the vitamin E supply (4.73 ± 0.01 g/day).

3.2. Liver lipid peroxidation index

Table 2 shows the effects of vitamin E deficiency on liver lipid peroxidation in rats submitted to a high cholesterol diet. Linked MDA, expressed as MDA (nmol/mg protein), was significantly higher (21%) in vitamin E deficient animals (group 2) compared to animals receiving the vitamin E sufficient diet (group 1).

3.3. Liver antioxidant enzymes activities

The activity of the liver antioxidant enzymes GPx (mU/mg proteins), SOD and catalase (U/mg proteins) are reported in Table 2 for the two groups. These results show that vitamin E deficiency associated with high cholesterol diet did not induce any modification of liver antioxidant enzymes activities.

3.4. Expression of antioxidant enzymes mRNA

One representative track of the autoradiogram corresponding to each diet condition is represented in Fig. 2 and shows that vitamin E deficiency in rats fed high cholesterol diet did not modify the expression of GPx, CAT, Cu/Zn-SOD and MnSOD. Quantitative analysis was performed using the ratio of specific blots/GAPDH (Table 3). Clearly, vitamin E deficiency did not induce any modification of mRNA levels between the two groups tested. The data reporting the lack of alteration in the transcriptional level are in agreement with those concerning specific enzymatic activities.

4. Discussion

Our study shows that a high-cholesterol vitamin E-deficient diet was able to increase the level of peroxidized lipids in the liver. However, this oxidative stress did not induce any modulation of hepatic AOE gene expression and enzymatic activities.

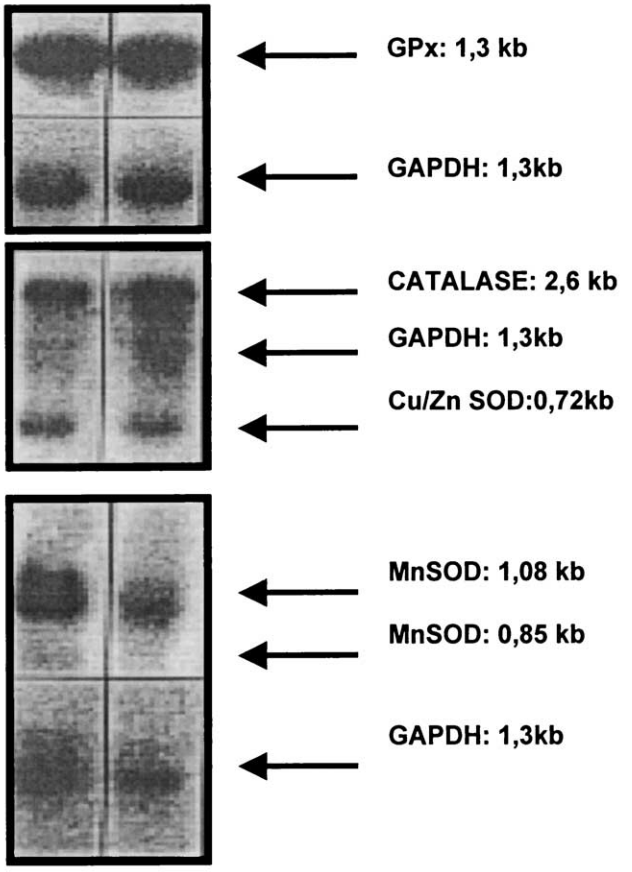

Fig. 2. Northern blot : qualitative analysis A: mRNA from rats belonging to group 2 (high cholesterol-vitamin E deficient diet) B: mRNA from rats belonging to group 1 (high cholesterol-vitamin E adequat diet).

These observations confirm and extend previous reports on the oxidative stress in the liver resulting from nutritional antioxidant deficiency. It is now well known that high cholesterol diet induces ROS overproduction which could in turn initiate lipid peroxidation [29,30]. *As* vitamin E is one of the main chain breaking antioxidant [31], propagation of oxidative stress could be enhanced in vitamin E deficient

Table 3
AOE/GAPDH mRNA ratio: superoxide dismutases (SOD), glutathione peroxidase (GPx) and catalase (CAT) in rats fed with the experimental diets

	Group 1	Group 2
Cu/ZnSOD	1.19 ± 0.03[a]	1.14 ± 0.05[a]
MnSOD	1.15 ± 0.16[a]	1.4 ± 0.07[a]
GPx	1.2 ± 0.03[a]	1.25 ± 0.04[a]
CAT	2.5 ± 0.06[a]	2.46 ± 0.03[a]

[a] Results of AOE are normalized against liver GAPDH expression. Values are means ± SEM of six observations per group; values in a row with different superscript letters are significantly different ($P < 0.05$).

animal. The significant increase in TBARS observed in our high-cholesterol vitamin E-deficient rats is in total agreement with this hypothesis and with previous report in vitamin E-deficient Syrian Hamster [32]. Fraga et al. [18] first reported that vitamin E and selenium-deficiency could enhance oxyradical generation and oxidative stress as determined using in situ chemiluminescence. Associated deficiency led to a hepatic necrosis while isolated vitamin E deficiency resulted in oxidative stress without necrosis. Interestingly, AOE activities were not increased in this model. The absence of increase in AOE activities and mRNA levels observed in this study strongly suggests that oxidative stress resulting from a high-cholesterol-vitamin E-deficient diet does not modulate AOE gene expression.

In vitro studies have suggested that oxidative stress could be crucial in the regulation of specific AOE activities mainly mitochondrial Mn SOD, cytosolic GPx and CAT [4–7]. In rat cultured hepatocytes, MnSOD gene expression and activity could be enhanced by different oxidative stress conditions including H_2O_2 exposure [33] cocaine or ethanol administration [9,34], hepatitis virus infection [35] or oltipraz administration [36]. A strong correlation has been found between the amount of mRNA and the activity of MnSOD in rat glomerular, adenocarcinoma or $3T_3$ cell lines submitted to oxidative stress, suggesting that the regulation of AOE activity is dependent on the modulation of gene expression [37–39]. Catalase and GPx genes could be also enhanced by oxidative stress including PMA stimulation [40], H_2O_2 exposure [33] or excessive H_2O_2 generation by SOD gene transfection [41]. By contrast Cu/Zn SOD does not appear to be regulated by oxidative stress [33,37] in all *in vitro* models.

Meanwhile the AOE regulation appears more complex, *in vivo.* The regulation seems to be dependent on several environmental factors, such as the origin of the oxidative stress mainly due to infection or toxic substance administration. MnSOD activity and expression are up-regulated by acute or chronic alcohol administration [8] or oxidative stress induced by influenza virus infection in rat lung [42]. By contrast, MnSOD could be decreased in rat liver after endotoxin administration [43]. Nutritional factors are another critical point for AOE regulation. Copper deficiency induces hepatic MnSOD transcription [44] but not GPx and catalase expression. Dietary polyunsaturated fatty acid intake, which increase the lipid peroxidation, modulates the detrimental effect of chronic alcohol administration. Indeed, a greater amount of polyunsaturated fatty acid in the diet was associated with a reduced effect of ethanol on hepatic induction of MnSOD gene expression. By contrast, polyunsaturated fatty acid diet results in a dramatic increase in GPx and CAT [45]. As far as we know, the direct effect of oxidative stress on *in vivo* regulation of AOE remains poorly investigated, especially when associated with a high cholesterol diet. Fraga et al. [18] reported that oxidative stress associated with vitamin E deficiency did not modulate the activities of catalase, glutathione peroxidase or superoxide dismutase, but AOE gene expression was not documented. In addition, since Mn SOD activity was enhanced after acute irradiation without changes in mRNA levels, a post transcriptional regulation could be postulated *in vivo* [46]. Our results show clearly that oxidative stress due to a high cholesterol vitamin E deficient diet did not induce any modulation of enzyme activities and mRNA levels. Thus our data are in total agreement with those previously reported by Fraga et al. [18] and strongly suggest that vitamin E deficiency when associated with a high cholesterol diet could not induce de novo AOE expression.

Although, oxidative stress *per se* did not modify AOE expression, it could act synergistically with toxic substances acting as enzymatic inducers such as alcohol or cocaine. This action could be mediated by activation of the responsive element of transcription factors AP-1 and NF-κB which have been located on regulatory region of AOE genes [47]. It is generally assumed that NF-κB and AP-1 expression or activity are up-regulated by oxidative stress. Their transcriptional activities could be largely prevented by lipophilic antioxidant such as tocopherols, tocopherol derivatives and phenolic acids [16,48 ,49].

In conclusion, vitamin E deficiency enhances the lipid peroxidation related to a high cholesterol diet. This increment in cellular levels of oxidative stress index was not associated with upregulation of AOE expression or activity.

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