Disruption of Vitamin E and Butylated Hydroxytoluene Antioxidant Function in Response to Paraquat-Induced Chromosomal Damage in Cultured Anuran Leukocytes

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Abstract

Researchers have reported that the phenolic antioxidants vitamin E and butylated hydroxytoluene (BHT) effect on cultured cells and human low-density lipoprotein is disrupted by various synthetic chemical compounds and Cu^2+ involved in reactive oxygen species (ROS) generation by redox reaction. In this paper, information involved in pro-oxidative action of vitamin E and BHT in cultured anuran leukocytes is provided in attempt to clarify such disruption mechanisms of antioxidant function.

Keywords: Vitamin E; Butylated hydroxy toluene; Antioxidants

Introduction

Researchers have reported that the phenolic antioxidants vitamin E effects on cultured cells and human low-density lipoprotein is disrupted by various synthetic chemical compounds and Cu^2+ involved in reactive oxygen species (ROS) generation by redox reaction [1-8]. Phenolic antioxidants vitamin E effect on cultured cells and human low-density lipoprotein is disrupted by various synthetic chemical compounds and Cu^2+ involved in reactive oxygen species (ROS) generation by redox reaction [1-8]. Phenolic antioxidants vitamin E and BHT have capability to inhibit autodestruction of unsaturated fatty acids (USFAs) followed by a chain reaction of free radical [9-11]. Preventive effect of phenolic antioxidants on autoxidation of USFAs is thought to be induced by two chemical reactions, hydrogen transfer reaction and termination reaction [10-15], shown below.

Antioxidant Action by Phenolic Antioxidants

USFA autoxidation chain reaction

L-H + various stimulations (irradiation, heat treatment, reaction with metal ion and reaction with another free radicals) (→ H•) L-•

L• + O2 → LOO•

LOO• + H - L → LOOH + L•

LOOH + Metal ion (an example, Fe^2+) → LO • + Metal ion (Fe^3+) + CH•

Hydrogen transfer reaction

A-H + LO• → A• + LOH

A-H + LOO• → A• + LOOH

Termination reaction

A• + A• → A-A (Antioxidant dimer)

A• + LO• → A-LO (Lipid-antioxidant copolymer)

A• + LOO• → A-LOO (Peroxidic copolymer)

H, phenolic antioxidant; A•, free antioxidant radical; H^•-, hydrogen transfer reaction; L-H, unsaturated fatty acids; L•, lipid radical; LO•, alkoxy radical; LOO•, peroxy radical; LOH, hydroxy acid; LOOH, lipid hydroperoxides; OH•, hydroxyl radical

Phenolic antioxidants-inhibited mechanism of lipidic free radical production is as follows; hydrogen transfer reaction producing hydroxy acid and lipid hydroperoxides; termination reaction forming lipid-antioxidant copolymers and peroxidic copolymers. Free antioxidant radical generated at the USFA autoxidation also reacts with another free antioxidant radical, and thereby inactivating free antioxidant radical by forming antioxidant dimer. Particularly, representative phenolic antioxidant vitamin E is seen to function as protective compound against lipidic free radicals generated in human and wild life body by such chemical reactions [9, 16-19]. It is a vitamin E synthetic analog, and also has vitamin E-like antioxidant activity, mentioned above [10,13]. Disruption of antioxidant function is therefore thought to promote unexpected accumulation of reactive oxygen species (ROS), resulting in adverse influence [6-8].

This paper focuses on the mechanism involved in antioxidant function-disruption of phenolic antioxidants (vitamin E and BHT).

Vitamin E

Vitamin E is an essential substance which has reproductive health and antioxidant effect on human and wildlife health maintenance [9,16-19]. For example, lipid peroxidation was reported to be caused by vitamin E-deficient-induced rabbit liver mitochondria dysfunction, resulting in an increase in liver damage [18]. Also, in the gastrocnemius muscle and liver of rats fed to vitamin E-depleted diet for 48 weeks, malondialdehyde (lipid peroxidation indicator) was found to increase [20]. With regards to suppression of carcinogenic...
and clastogenic damage by vitamin E, examples are shown below. Vitamin E pretreatment for 24 hours was found to suppress sodium chlorate-induced chromosomal aberrations in Chinese hamster V79 cells [21]. Carcinogenic and clastogenic damage occurred in liver of transgenic mice carrying transforming growth factor-α/c-myc genes was reported to be inhibited by vitamin E [22]. Moreover, Vitamin E succinate (a form of vitamin E with most antitumor activity) was reported to suppress not only proliferation of MCF-7 and MDA-MB-231 cells derived from human breast cancers but also tumor growth of breast cancer in athymic nude mice implanted with MDA-MB-231 cells [23]. The same study [23] indicated suppression of vascular endothelial growth factor gene expression (a potent modulator of tumor growth and angiogenesis) in MDA-MB-231 cells by vitamin E succinate.

On the other hand, Brigelius-Floh [5] indicated that vitamin E has protective function against lipidic free radicals(for example, BHT was reported to suppress aflatoxin B1-induced hepato carcinoma formation in male rats [38]. Bleomycin (antitumor antibiotic)-induced chromosomal damage in cultured Chinese hamster ovary cells has been found to be inhibited by BHT [36]. On the other hand, chronic BHT treatments after exposure to carcinogens promote tumor development in some strains of rodents [39-44].

Another study showed that BHT fails to inhibit high dose-rate gamma (192iridium) rays-induced chromosomal damage in Chinese hamster ovary cells [45]. Moreover, BHT in combination with PQ has been reported to enhance PQ-induced chromosomal damage in cultured anuran leukocytes despite the fact that BHT alone has no genotoxic effect on cultured leukocytes derived from Pelophryx nigromaculatus (P. nigromaculatus) frogs [7-8].The same studies [7-8] have reported that PQ plus BHT-enhanced chromosomal damage is inhibited by combination of Mn(III)Tmppy and catalase. This response of cultured P. nigromaculatus leukocytes to PQ plus BHT has been found to be very similar to that to PQ plus vitamin E [6, 8]. BHT has been further reported to induce PQ•+ formation chemically in PQ•+ formation-test [7-8]. These studies have indicated that BHT reduces PQ•+ chemically to PQ•+, leading to ROS generation, causing chromosomal damage.

Regarding preliminary study involved in induction of acute chromosomal damage in cultured anuran leukocytes through stimulation of BHT in combination with PQ, high level of nitrite was discovered in the tails of Ranarugosa tadpoles exposed to PQ plus BHT [8]. Tanaka [46] reported that nitrite derived from the NO releaser enhances PQ genotoxicity. Moreover, Hanada [8] has reported that sodium nitrite reduces PQ•+ chemically toPQ•+ in PQ•+ formation-test. PQ plus BHT-enhanced endogenous nitrite production has been therefore shown to have ability to induce remarkable free radical generation with concomitant acute increase in chromosomal damage.

Concluding Remarks

Vitamin E and BHT alone are believed to have little mutagenic and clastogenic potential, and has ability to suppress tumorigenic, carcinogenic and clastogenic damage induced by various chemical compounds [34-37]. For example, BHT was reported to suppress aflatoxin B1-induced hepato carcinoma formation in male rats [38]. Bleomycin (antitumor antibiotic)-induced chromosomal damage in cultured Chinese hamster ovary cells has been found to be inhibited by BHT [36]. On the other hand, chronic BHT treatments after exposure to carcinogens promote tumor development in some strains of rodents [39-44].

BHT

BHT is widely used as antioxidant for rubber, plastics, food packaging, cosmetics, hand-washing soap, pet foods, chewing gum etc. BHT alone is believed to have little mutagenic and clastogenic potential, and has ability to suppress tumorigenic, carcinogenic and clastogenic damage induced by various chemical compounds [34-37].
Further study is required for elucidation of phenomena concerning vitamin E and BHT antioxidant function-disruption.

Figure 1: Proposed mechanism of chromosomal damage enhanced by PQ + phenolic antioxidants. $e^{-}$ = electron; $H_{2}O_{2}$ = hydrogen peroxide; $O_{2}^{•-}$ = molecular oxygen; $O_{2}^{-}$ = superoxide; $OH^{-}$ = hydroxyl radical; $PQ^{2+}$ = paraquat cation; $PQ^{+}$ = paraquat monocation radical; Chemical reaction; Enzymatic reaction.

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