ANTIOXIDATIVE STRESS

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Objective: The aim of this short review is to provoke focuses on the antioxidant-induced stress. Although there are studies documenting that supplementation with antioxidants appears to reduce lipid peroxidation and oxidative stress, it is still unknown exactly what amounts are needed to have a beneficial antioxidant effect and which dose reflects the safe and appropriate limit for use. Many of antioxidant vitamins and the other antioxidants can cause pathologic changes to the exposed tissues and to the organs of the bodies by initiating different mechanisms. These harmful and undesired effects are created by prooxidant, antioxidant or some other unknown ways. Although the most important point related to the use of antioxidants is not their dosages, the term hypervitaminosis is commonly used referring to the negative effects of the overdoses of the vitamin antioxidants. The question which level of the antioxidants may lead to stress is unanswered yet though this is vital in determining antioxidative stress. This article uses the term "antioxidative stress" for the first time for the negative effects of antioxidants. In our opinion, focusing on antioxidative stress is essential as it is on oxidative stress by the medical disciplines. For this purpose, close collaboration between the triad of molecular biochemist, physiologist and the pharmacologist is required to develop new, specific, and more effective antioxidants and therapy modulations. We believe that further studies are needed to elucidate the factors and ways creating the antioxidative stress, as well as its consequences together with an "insurance policy" containing appropriate measures against to it.

Key words: *Antioxidative stress, oxidants, antioxidants, vitamins.*

In recent years, very much attention has been paid to the issue of oxidant-antioxidant balance and its effects. These studies are largely focused on the argument that taking antioxidants or augmenting antioxidant defense system can prevent several diseases. However, it seems that a significant fact has been ignored in most of these studies. Some of the questions related to this ignored fact can be given as follows;

"Is oxidant-antioxidant balance always broken in favor of radicals and oxidants?",

"May an over-increased antioxidant level always be an antioxidative stress state?",

"Which indicators can be antioxidative stress markers". The existence of these questions, and many of others, marks the essentiality of forming a new approach on antioxidants.

Accepted For Publication: 22 June 2000

Supplementation of organisms with antioxidants generally appears to reduce oxidative stress (1). Although this is an important point, the issue of whether to supplement with antioxidants and how much to supplement them still remains unsolved because of the fact that taking antioxidants in little, normal or megadoses could lead to antioxidative stress in prooxidant way or in some yet undiscovered mechanisms (2,3).

We know that, under physiological conditions, free radicals are part of the normal cellular redox state (4). This balance is tightly controlled by antioxidants (5). The term "oxidative stress" is often used to refer to the effects of increased free radical formation in the body (6,7). A similar term to "oxidative stress" can be used to define the stressor effects of antioxidants. Because several unanswered questions which derive from enhanced use of antioxidants make the use of the term "antioxidative stress" possible.

Antioxidative stress

Antioxidants play the role of blocking free radical production processes and oxidative stress (5,7). An antioxidant cannot distinguish among radicals that play a physiological role and those that cause damage. Moreover, it is often disregarded by the authors who advocates for the general use of antioxidants that these compounds not only function as an antioxidant, but also have pro-oxidant action (3). For example, vitamin C is a well-known antioxidant. It is less known that it may also act as a distinct prooxidant. Addition of vitamin C up to a concentration of 0.2 mM potentiated 10 mM increase in Fe- induced lipid peroxidation, due to increased Thiobarbitüric acid reactive substances in a maximal amount. The reduction of Fe^{3+} appears to be a possible explanation for the prooxidant action of vitamin C. Vitamin C does not have an effect by it self, but the combination of vitamin C with Fe causes intense oxidation of polyunsaturated fatty acid (PUFA's). The degree of iron reduction may, therefore, determine the prevalence of vitamin C to act as either a threatening factor or scavenging agent (2, 3, 8). Silifka et al (9) also reported that Fe/vitamin C combinations are used therapeutically to enhance the intestinal absorption of iron in its reduced form. Theoretically, it might be anticipated that this combination causes intestinal damage via lipid peroxidation observed in rodents. With high concentrations of vitamin C, no lipid peroxidation may be observed. In contrast, a relatively high concentration of vitamin E may cause radical formation, functioning as a prooxidant (10,11).

reaction A: Vit E + LOOH $\rightarrow$ vit E· + LO· + H_2O

reaction B: Vit E + LOO· → LOOH + vit E·

Aalt et al. (3) note that the reaction B is an equilibrium reaction. Propagation increases during a closed lipid peroxidation. Since a membrane contains excess fatty acid (LH) over vitamin E molecules, it implies that vitamin E is consumed while the LH concentration remains constant during peroxidation. A decline in vit E / LH increases the LOOH/ vit E ratio. Accumulation of LOOH reverses reaction C,

reaction C: LOOH + Vit E· → vit E + LOO·

and stimulates the propagation reaction (D)

reaction D: LH + LOO· → LOOH + L·

An optimal concentration of vitamin E should be given at such a dose that the propagation will be inhibited effectively. However, this dose is not exactly known at the present.

Superoxide dismutase (SOD) is occasionally used to prevent the damage caused by radicals. We know that intraarticular administration of SOD appears to be useful. On the other hand, some authors report that in the presence of H_2O_2, SOD acts as a pro-oxidant (3,12).

As these examples demonstrates, generally accepted antioxidants such as vitamin C, vitamin E, SOD and Glutothione (GSH), may also posses antioxidative stress potential under certain conditions. (1,2,3,7,13). Therefore, interaction of antioxidants should also be reconsidered.

Ideally antioxidant therapy contains specific acting drugs. Targeting of antioxidants to locations having undesirable excessive radical formation not only could impair specificity but also prevents physiologically important radical-mediated processes. (3,7)

Until recent, popular belief has been that no dose of antioxidant drugs and micronutrients is harmful. Taking different doses of antioxidants, particularly vitamin C, could cause prooxidative risk in the body, even it could have serious consequences including increased rate of heart attack. Moreover, there is some evidence that low or megadose of vitamin C could lower vitamin B12 level by adversely affecting the absorption of vitamin B12 from nutrients. (13).

High doses of tocopherols can interfere with the absorption of vitamins A and K, though amounts of 200 to 600 mg/d appear innocuous (1). Doses of 1 mg/day and 5 mg/day of selenium for an extended period have been shown to have negative effects (14).

In using antioxidants, it should be addressed that the question of how these agents are commensurate with existing integrated physiologic radical defense. Although there is data documenting that antioxidants reduce oxidative stress, it is still uncertain exactly what amounts are needed to have a beneficial effect. Herbert (13) reports that vitamin C and beta carotene act as antioxidants at physiologic levels, but at pharmacological levels they have increasing pro-oxidant effects. The relevant question of whether the antioxidative stress capacity is also expressed in a delicately integrated physiologic system still remains unanswered.

The assumption that the reactive species and free radicals are merely pernicious is incorrect, since they play a vital role in many physiologic reactions, such as killing microorganisms, mitochondrial oxidations, and regulation of the tone of smooth muscle. Oxidant-antioxidant imbalance contains many pathologies. In attempting to alleviate these pathologies with antioxidants, it should be taken into account that these agents are neither specific nor mere antioxidants. As Bast et al state "the biochemical interplay of the radical scavenging system may obviate the prooxidant action of the separate parts" (3).

These are also serious questions and anxieties about antioxidant drugs and substances. What biomolecule is the compound supposed to protect? For example, an inhibitor of lipid peroxidation is unlikely to be useful if the oxidative damage is mediated by an attack on proteins of DNA. Will the compound be presented at or near the biomolecule in sufficient concentration? How does the compound protect: by scavenging radicals, by preventing their formation, or by repairing damage? If the antioxidants act by scavenging radicals, can the resulting antioxidant-derived radicals do biological damage? Can the antioxidants cause damage in biological systems besides protection? For example, several inhibitors of lipid peroxidation have the potential to accelerate free radical damage to other molecules (7,15,16).

Conclusion

It should be noted that little is known about the long term effects of different doses of the antioxidant micronutrients and supplements. When one considers that the body operates on a finely tuned homeostatic state, it would appear that uncleared doses of any antioxidant could interfere with a delicate balance and cause negative effects whose discovery may take a long time. In the developing new antioxidant agents and therapy modulations, the important question of how these drugs are incorporated into or commensurate with existing integrated physiologic radical-defense systems should be addressed.

The acceptance and common use of the term "antioxidative stress" may be a significant stage in the formation of a scientific consciousness against unbalanced and non-specific use of antioxidants. Further studies are needed to determine the ways and factors causing the antioxidant induced stress and its consequences, together with the "insurance policy" against it. It is hoped that this review will stimulate further research on antioxidative stress in animals and human beings.

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