Antioxidants: Friend or foe for tuberculosis patients

Rajasri Bhattacharyya1, Dibyajyoti Banerjee2*

1Department of Biotechnology, Maharishi Markandeshwar University, Mullana, Ambala, India
2Department of Experimental Medicine and Biotechnology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
Email: *dibyajyotis200@yahoo.co.in

Received 22 August 2013; revised 22 September 2013; accepted 15 October 2013

Copyright © 2013 Rajasri Bhattacharyya, Dibyajyoti Banerjee. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Respiratory burst induced bacteria killing by oxidants are important mechanism of host defence. However, it is impaired in tuberculosis due to inhibition of respiratory burst by Mycobacterial factors. Antioxidants are compounds that cause chelation of reactive oxygen species. So, antioxidants are expected to play a negative role in the management of active tuberculosis. But, oxidative stress is a proved fact that invariably happens in tuberculosis patients which is known to cause immunosuppression. Immunosuppression in turn is expected to augment tuberculosis. Hence, antioxidant supplementation is expected to benefit tuberculosis patients by minimising oxidative stress induced immunosuppression. Therefore, the role of antioxidants in tuberculosis appears to be paradoxical and urgent. Understanding of the role of antioxidant supplementation in tuberculosis is warranted. It is in this context that we have reviewed the recent literature and addressed the problem for its solution.

Keywords: Tuberculosis; Antioxidants; Reactive Oxygen Species; Clinical Trial; Mycobacterial tuberculosis

1. INTRODUCTION

Antioxidants are among the most popular health-protecting products, sold worldwide without prescription. At the present moment, there is majority opinion that antioxidants are good for human health but very recently some researchers are in the opinion that it may not be good for human health universally [1].

In case of infections intracellular generation of ROS/RNS plays an important role in pathogen clearance.

Phagocytosis is the process by which all pathogens are engulfed by the macrophages. In the process of phagocytosis, a membrane bound vesicle is formed containing the pathogen. This membrane bound vesicle, is popularly known as phagosome. Phagosome generally contains various subunits of NADPH oxidase, the respiratory burst enzyme (that generates superoxide), iNOS (that generates peroxynitrite), and many other proteins that generally undergoes a maturation process by which internalized particles (such as bacteria and dead cells etc.) are trafficked into a series of increasingly acidified membrane-bound structures (endosomes, lysosomes), leading to particle degradation [2,3]. It is also now proved that if the phagosomal ROS is not produced or less produced the host becomes susceptible to intracellular infections. The classical example of the above statement is chronic granulomatous disease which is characterized by diminished capacity of intracellular ROS production leading to tuberculosis very often [4].

The role of extracellular antioxidants may be critical in functioning of intracellular ROS. It is expected that the available extracellular antioxidant will percolate inside the cell and neutralize the nascent ROS. In that case antioxidants should be harmful in the scenario of active infections. However, some antioxidants behave as pro-oxidants in specialized situations. Below an example is elaborated for explanation of the above mentioned fact.

α-tocopherol (α-TC, Vitamin E) produces α-tocopheroxyl radical when it reacts with reactive species such as peroxynitrite [5] or superoxide [6]. α-TC radical is then recycled to α-TC by other antioxidants such as ascorbic acid (Vitamin C) and glutathione [7-9]. As soon as ascorbic acid recycles Vitamin E, it is transformed to the ascorbyl radical, which has a lower reactivity than α-TC radical [7]. α-TC radical is also recycled to α-TC by β-carotene [9,10]. So, for proper antioxidant effect Vitamin E should be administered with another antioxidant and excess amount of vitamin E may be pro-oxidant...
per se. Therefore, it is important to understand the role of vitamin E in various concentrations in presence and absence of other antioxidants, on the re-ox capacity of intracellular nascent ROS. Similar examples may be cited with all the commonly used antioxidants and the role of commonly used antioxidants in intracellular ROS production/function is unclear as on date. Such knowledge is important keeping in mind the prevalence of the infectious diseases and the consumption habit of antioxidants of public at large. In this article the same will be attempted to be reviewed in the context of tuberculosis.

2. PHAGOSOMAL NICHE FOR Mycobacterium tuberculosis

Mycobacterium tuberculosis is engulfed by host macrophages. It resides inside a stable phagosome which does not fuse with lysosome for effective bacterial killing. Such maturation arrest of phagosomes containing Mycobacterium tuberculosis is thought due to defective recruitment of rab proteins in such phagosomes [11]. Mycobacterial factor like secreted acid phosphatase is also thought to be important for inhibition of phagolysosome biogenesis [12]. As a result the tuberculosis bacterium resides inside the phagosome without experiencing the adverse environment produced by lysosomal acid hydrolases. Moreover Mycobacteria containing phagosome recruits cellular iron into the phagosome which is utilized for bacterial sustenance [13]. The phagosome is supposed to posses subunits of NADPH oxidase, the key enzyme for respiratory burst which in turn is expected to generate superoxide. Further myeloperoxidase in phagosome is known to form hypohalites. Both superoxide and hypohalites are known agents that kill intraphagosomal parasites. Inducible nitric oxide synthase is also known to be recruited in phagosomes which generates peroxynitrite, the toxic free radical and mediates bacterial killing. However, Mycobacterial factors are known to inhibit the function of inducible nitric oxide synthase and NADPH oxidase and thus less oxidants are produced in Mycobacterium tuberculosis containing phagosome, making the phagosomal pathogen to stay inside a protective cover [14,15].

3. TUBERCULOSIS AND THE ANTIOXIDANT PARADOX

Mycobacterium tuberculosis is an intracellular pathogen and currently infected more than one third of global population. Like all intracellular pathogens it resides successfully inside phagosome of macrophages. Mycobacterial factors inhibit phagosome maturation so that the intraphagosomal bacterium is not assaulted by lysosomal hydrolases [12]. Various bacterial antioxidants are also proved to counter phagosomal respiratory burst causing safe stay of the tuberculosis bacterium inside the phagosome [16-18]. In case of atypical Mycobacterium species bacterial antioxidants are thought to modulate host derived oxidative killing mechanisms [19]. In Mycobacterium species new antioxidant mechanisms that protect the bacterium from the phagosomal respiratory burst is an established phenomenon [20,21]. Even recombinant BCG over-expressed with superoxide dismutase A confers less protection for development of tuberculosis [22]. Pathogen derived antioxidant mediated escape from phagosomal oxidative burst is not unique for tuberculosis bacterium and proved to be true in other successful intracellular pathogen as well [23,24]. Host derived antioxidants are also recently proved to be beneficial for persistence of intracellular pathogens [25]. Therefore it is appearing that availability of antioxidants at the phagosome play a negative role for the host in cases of active tuberculosis infection.

On the other hand antioxidants like N-acetyl cysteine is shown to inhibit growth of tuberculosis bacteria inside tubercular abscess [26]. Such observations are also confirmed with other antioxidants like manganese (II) mesotetraakis-(N-methylpyridinium-2-yl) porphyrin [27]. Further, glutathione is known to modulate the T cell mediated immune response in a manner that reduces the intracellular stability of the tuberculosis bacterium [28]. This fact is observed to be true for many other intracellular infection and so may be considered as a general phenomenon [29]. Extra cellular superoxide dismutase is shown to augment phagocytic killing of bacteria [30]. There is evidence in in-vivo studies that control of oxidative stress by supply of antioxidants is beneficial for prevention and treatment of tuberculosis [31]. In living human tuberculosis patients oxidative stress is also proved beyond any doubt [32]. The activities of antioxidant enzymes are observed to be comparatively less in blood samples in subjects suffering from active tuberculosis along with corroborative increase in concentration of protein carbonyl [33].

Therefore antioxidants if neutralize the phagosomal oxidants has the chance to augment active form of tuberculosis. In other hand if antioxidants are expected to modulate the immune response to combat intracellular infection then it may act as a preventive armor for tuberculosis. In the context of tuberculosis supplementation of antioxidants will play beneficial role or not needs a solution of the paradoxical evidences so far accumulated.

4. SOLUTION OF THE PARADOX

Clinical effect of vitamin E is not observed in recipients who consume less vitamin C containing diet [34]. It has been observed that vitamin E supplementation transiently
increases the risk of active tuberculosis in heavy smokers if co-supplemented with vitamin C [35]. Similar conclusions are arrived in clinical cases of pneumonia [36]. Therefore vitamin C and vitamin E co-supplementation may be harmful for any infectious disease including tuberculosis. It is possible that vitamin C neutralizes tocopheryl radical that may have microbiocidal role.

Oxidative stress is a proved fact associated with tuberculosis [31,32]. Oxidative stress is a phenomenon that may cause immunosuppression [37]. Oxidative stress results into defective T cell mediated immunity [38] which in turn may accelerate tuberculosis infection. Therefore antioxidant supplementation in tuberculosis patients along with recommended chemotherapy may help to combat the oxidative stress mediated defective cell mediated immunity. In the context of tuberculosis management, treatment of the cause of the disease is important since now it is a recognized fact that in the scenario of oxidative stress the management must address the cause of genesis of the primary disease [39]. However both endogenous and exogenous antioxidants are observed to be protective against antitubercular drug induced toxicity [40,41]. Therefore co-administration of antioxidants and anti-tubercular drugs has the potential to serve benefit to tuberculosis patients for multiple causes. But blind supplementation of antioxidants with anti-tubercular drugs in tuberculosis patients may cause more harm than benefit. We believe that if oxidative stress develops in a particular case of tuberculosis appropriate antioxidant supplementation along with antitubercular therapy will accelerate the healing process. Therefore clinical trials in this direction are warranted to document objective data to formulate rational antioxidant combination therapy as an adjunct to antitubercular drug therapy in proved cases of tuberculosis.

5. ACKNOWLEDGEMENTS

DB acknowledges Department of Biotechnology, Govt. of India for financial assistance.

REFERENCES


Copyright © 2013 SciRes.
Advances in Microbial Physiology, 60, 263-324. http://dx.doi.org/10.1016/B978-0-12-398264-3.00004-8


Copyright © 2013 SciRes.

