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Review Article

Reactive oxygen species in cardiovascular disease

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ABSTRACT

Based on the "free radical theory" of disease, researchers have been trying to elucidate the role of oxidative stress from free radicals in cardiovascular disease. Considerable data indicate that reactive oxygen species and oxidative stress are important features of cardiovascular diseases including atherosclerosis, hypertension, and congestive heart failure. However, blanket strategies with antioxidants to ameliorate cardiovascular disease have not generally yielded favorable results. However, our understanding of reactive oxygen species has evolved to the point at which we now realize these species have important roles in physiology as well as pathophysiology. Thus, it is overly simplistic to assume a general antioxidant strategy will yield specific effects on cardiovascular disease. Indeed, there are several sources of reactive oxygen species that are known to be active in the cardiovascular system. This review addresses our understanding of reactive oxygen species sources in cardiovascular disease and both animal and human data defining how reactive oxygen species contribute to physiology and pathology.

Contents

Abbreviations: 5-LO, 5-lipoxygenase; 5-MTHF, 5-methyltetrahydrofolate; 12-LO, 12-lipoxygenase; 12/15-LO, 12/15-lipoxygenase; ACS, acute coronary syndrome; ApoA-I, apolipoprotein A-I; ApoE, apolipoprotein E; BH_4, 5,6,7,8-tetrahydrobiopterin; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; eNOS, endothelial nitric oxide synthase; GCH, GTP-cyclohydrolase; GPX-1, glutathione peroxidase-1; HDL, high-density lipoprotein; HF, heart failure; iNOS, inducible nitric oxide synthase; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; LV, left ventricular; MI, myocardial infarction; Mn-SOD, manganese superoxide dismutase; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate; nNOS, neuronal nitric oxide synthase; NOS, nitric oxide synthase; ox-LDL, oxidized low-density lipoprotein; PROBE, prospective randomized open blinded end-point; RCT, randomized controlled trial; ROS, reactive oxygen species.

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Introduction

In the early 20th century, the "rate-of-living hypothesis" was derived from observations that animals with higher metabolic rates were characterized by shorter life spans, implying that a species' metabolic rate ultimately determines its life expectancy. In 1956, Denham Harman proposed a "free radical theory" that endogenous oxygen radicals were generated in cells over time, resulting in cumulative cellular damage targeting DNA, protein, lipids, and other components of the cell [1]. Because cardiovascular disease is a manifestation of aging, researchers have attempted to elucidate the relation between cardiovascular disease and oxidative stress caused by free radicals.

Clinical studies of antioxidants in vascular disease

Initially, these studies focused on how antioxidants may influence the clinical course of atherosclerosis and cardiovascular disease. Numerous clinical trials have been performed to examine the potential for preventing cardiovascular disease using antioxidant therapies (please see Table 1). The term "cardiovascular disease" encompasses the major clinical end-points related to the heart and vascular system, including myocardial infarction (MI; heart attack), ischemic heart disease (MI and angina), stroke, and peripheral arterial disease (ischemia of the limbs). The most common manifestations of cardiovascular disease are MI and stroke. Thus, a predominance of studies investigating antioxidant status focus on cardiovascular disease (CVD) with combined end-points of stroke and MI, whereas some focus on MI using the term coronary heart disease (CHD).

Primary prevention of vascular disease

Some antioxidant studies have focused on the primary prevention of CVD, meaning the prevention of CVD in patients that do not already have the disease. Observational studies of vitamin C in the primary prevention of CVD have been conflicting, with only some suggesting a benefit with the consumption of vitamin C supplements [2–8]. Large-scale randomized trials evaluating vitamin C indicate no effect on the primary end-point of CVD and no meaningful impact on all-cause mortality [9,10]. In contrast, observational studies of vitamin E supplementation predominantly found that vitamin E was associated with a lower risk of CHD [6,7,11,12]. These findings were of considerable interest, but had to be interpreted with caution as observational trials are subject to unintended bias and confounding. Thus, several randomized, double-blind, placebo-controlled trials were conducted to investigate the impact of vitamin E supplementation on CVD and none have found a benefit for the primary prevention of CVD [9,13–16]. In fact, evidence from some of these trials found that vitamin E treatment was associated with increased heart failure [17] and hemorrhagic stroke [9]. β-Carotene has also been investigated and randomized trials of this antioxidant failed to show any effect on the primary prevention of CHD or the risk of death from CVD [13,18–20]. Thus, it has been difficult to demonstrate that antioxidant supplementation (vitamin C, vitamin E, and β-carotene) has an impact on the primary prevention of CHD or CVD.

Secondary prevention of vascular disease

Secondary prevention refers to inhibiting manifestations of CVD in those patients who already have the disease. Because the risk of a second cardiovascular event (MI, stroke, angina) is high in patients that have already had a first event, established prevention measures (e.g., cholesterol lowering, smoking cessation, etc.) are most effective in secondary prevention. Thus, if antioxidant therapy were to be of benefit, it would be expected to be most effective in secondary prevention. However, treatment of postmenopausal women with CHD using vitamins C and E showed no benefit on CHD and even demonstrated excess death compared to placebo [21]. Similarly, in women with CHD or at high risk for CHD, treatment with vitamin C, vitamin E, and β-carotene, either alone or combination, did not show any benefits on cardiovascular events [22]. With regard to vitamin E alone, there are two trials that suggested a benefit. The Cambridge Heart Antioxidant Study demonstrated a benefit for vitamin E in patients with coronary disease, but no impact on mortality [23], and in patients with kidney disease the administration of vitamin E significantly reduced the incidence of cardiovascular events [24]. However, in other large-scale randomized trials, vitamin E administration alone or in combination had no effect on cardiovascular outcome [25]. With β-carotene, there is no convincing evidence of a benefit on angina [26], and it may be harmful for patients with previous MI because of increased cardiac death [27]. Thus, on balance, these results lead to the conclusion that there is no consistent evidence of benefit from vitamin C or E or β-carotene for the secondary

Table 1
Selected clinical studies of antioxidant therapy associated with cardiovascular disease.

Antioxidant	Study design	Study subjects	Findings	Interpretation	Reference
Primary prevention					
Vitamin C	Prospective cohort	—	Associated with lower cardiovascular disease risk	Effective	[2–8]
Vitamin C	RCT	—	No effect on composite cardiovascular events	Ineffective	[9,10]
Vitamin E	Prospective cohort	—	Associated with lower cardiovascular disease risk	Effective	[6,7,11,12]
Vitamin E	RCT	—	No benefit to prevention of cardiovascular events, but increased HF	Ineffective or harmful	[9,13–17]
β-Carotene	RCT	—	No impact on cardiovascular death or MI	Ineffective or harmful	[9,18–20]
Secondary prevention					
Vitamin C	RCT	Women with CAD	Increased mortality	Ineffective or harmful	[21,22]
Vitamin C	RCT	CAD patients	Reversed endothelial dysfunction	Effective	[281]
Vitamin C	Prospective cohort	Variant angina	Attenuated abnormal vasomotor reactivity	Effective	[282]
Vitamin E	RCT	CAD patients	Reduced CAD events	Effective	[23]
Vitamin E	RCT	Hemodialysis patients	Reduced cardiovascular events	Effective	[24]
Vitamin E	RCT	Patients after MI	No benefit to prevention of cardiovascular events	Ineffective	[25]
Vitamin E	PROBE	Variant angina	Reversed endothelial dysfunction	Effective	[283]
Vitamin E	RCT	Patients with HF	No improvements in prognostic or functional indexes of HF	Ineffective	[284]
β-Carotene	RCT	Patients after MI	Increased CAD risk	Harmful	[27]
Probucol	RCT	Patients after PCI	Prevented restenosis	Effective	[32–34]
Succinobucol	RCT	Patients after ACS	No benefit to prevention of cardiovascular events	Ineffective or harmful	[37]
Edaravone	PROBE	Patients with acute MI	Decreased infarct size, RI, and cardiac events	Effective	[242,243]
Coenzyme Q10	PROBE or RCT	Patients with HF	No improvement of outcome or important cardiac function	Ineffective	[285]
Allopurinol	RCT	Patients with HF	Reversed endothelial dysfunction	Effective	[278]
Oxypurinol	RCT	Patients with HF	No clinical improvements	Ineffective	[279]

For abbreviations please see the text.