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THE ROLE OF ALCOHOL IN THE OXIDANT ANTIOXIDANT BALANCE IN HEART

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1. ABSTRACT

The myocardium, like other tissues, has enzyme and non-enzyme systems to neutralize free radicals. The enzymes superoxide dismutase, catalase and glutathione peroxidase and glutathione reductase as well as the non-enzyme antioxidants vitamin E and ascorbic acid are the main antioxidants. Oxidants are produced by the mitochondria under normal conditions and by other sources under pathologic conditions. The quantity of antioxidants present in the myocardium is matched to the production of oxygen free radicals that may be produced under basal physiological conditions. However, the myocardium can be exposed to increased levels of oxygen free radicals under conditions in which myocardial metabolism, i.e. mitochondrial oxidative phosphorylation, is accelerated to match the adenosine triphosphate utilized to support the increased work load on the heart or can be exposed to oxygen free radicals under pathologic conditions such as ischemia and reperfusion, inflammation, and cardiotoxic drugs such as anti-cancer agents. Under such circumstances the normal heart has been shown to increase its antioxidant production and to be, with time, protected from further sources of oxygen free radicals. In particular, hearts previously exposed to a stimulus to produce greater antioxidant levels show less damage during ischemia reperfusion injury presumably because of neutralization of oxygen free radicals. This review will present several situations in which the myocardium increases its tolerance to ischemia reperfusion injury as a result of an initial oxidative stress.

2. INTRODUCTION

Oxidant balance in the heart has a very important role in protecting the heart and in allowing normal cardiac contractile performance. In general the amount of antioxidants is sufficient to protect the heart from any oxidant production that might occur under normal circumstances. However, the antioxidant reserves can be inadequate under pathological situations such as ischemia and reperfusion, inflammation, and administration of cardiotoxic drugs. In these situations, the antioxidant status can be compromised and thus oxidant injury can occur and compromise cardiac performance. Since the function of the heart is to pump a cardiac output that is adequate to meet the blood flow requirements of the peripheral tissues both at rest and at varying levels of tissue activity, a compromise in cardiac function can lead to ischemia and injury of other organs in the body. As such then the heart must balance oxidant production under varying levels of activity. Since the heart requires a continuous supply of high energy phosphate compounds for support of its constant contractile activity, mitochondrial "leak" of oxygen free radicals is a potential problem for which the myocardial cell has developed very effective protective, i.e. antioxidant, mechanisms. These mechanisms include superoxide dismutase and catalase, glutathione and vitamin E which are also found in most other tissues.

Not only is the myocardium optimally designed to neutralize normal levels of production of oxygen free radicals, the myocardium is also able to generate increased levels of antioxidants when it is stressed by an oxidant injury. Interestingly the stresses that induce increased production of antioxidant protective mechanisms can be very different, some related to increased work demand on the heart and others related to impaired blood supply, sepsis or bacteremia, or drug toxicity. All of these forces that induce enhanced production of antioxidants in the heart may do so by one mechanism or by several different mechanisms. Each will be discussed keeping in mind what is causing the increase antioxidant capacity and how the antioxidant capacity is increased.

In the remainder of this discussion, ischemia reperfusion injury will be used primarily as a functional test of the antioxidant capacity of the heart and protection will be correlated with the biochemically determined increase in the antioxidant capacity of the heart subsequent to an initial

stress. Prior to discussion of the studies that have shown induction of antioxidant levels in the heart, we will briefly discuss the role of oxygen free radicals in myocardial ischemia reperfusion injury.

3. DISCUSSION

3.1. Ischemia Reperfusion Injury

Ischemia and reperfusion are both of potential importance in oxygen free radical production (1,2). Radicals can be formed intracellularly, in the interstitial space and in the vascular space. Most cells in the heart, i.e. myocytes, vascular smooth muscle and endothelial cells, as well as mast cells and infiltrating neutrophils, can produce oxygen radicals. Although the source of oxygen radicals may be different at various time points during reperfusion, in general, it would appear that the major radicals that cause injury are superoxide, hydrogen peroxide and the hydroxyl radical as demonstrated by both direct and indirect methods. Electron resonance spectroscopy and spin trapping agents (3-5) and enhanced chemiluminescence (6) have been used to demonstrate the presence of the superoxide radical during reperfusion. Salicylate, which reacts with hydroxyl radicals to form a stable compound that can be detected in the coronary effluent by high performance liquid chromatography (7), has been used both to show that hydroxyl radicals are produced during reperfusion and also to protect the heart from oxygen radical damage (8). Hydrogen peroxide is probably very important in contributing to myocardial injury in that it is a substrate for iron dependent production of the hydroxyl radical. Efforts have thus been made to block or neutralize these oxygen radicals with more or less specific agents. Superoxide dismutase has been used to convert O_2^- to H_2O_2; catalase to convert H_2O_2 to water; a combination of these two enzymes and a variety of agents to neutralize the hydroxyl radical or prevent its formation by chelating iron which is required for the conversion of hydrogen peroxide to the hydroxyl radical. Many studies have been performed in various models of ischemia reperfusion injury with most showing some protection of the myocardium when oxygen radical scavengers are provided during early reperfusion (9). It would appear that at least one component of the injury due to ischemia and reperfusion is the very early production of oxygen radicals at the initiation of reperfusion.

Interestingly, although the provision of oxygen radical scavengers during reperfusion generally improves recovery from ischemic injury, there is usually some residual damage suggesting that not all injury is due to oxygen free radicals. However, since ischemia reperfusion injury is at least attenuated by the provision of exogenous oxygen radical scavengers, the benefit of increased endogenous antioxidant capacity seems reasonable. Such an induction of antioxidant capacity had originally been demonstrated in lung injury due to hyperoxia. Pretreatment with endotoxin was shown to protect the lungs from oxygen toxicity (10). Application of this pretreatment in order to protect the heart from oxygen toxicity came soon after. At least four different conditions have been shown to protect the heart from ischemia reperfusion injury by increasing endogenous antioxidant balance: hypertrophy, exercise, sepsis or endotoxin or cytokine administration and heat shock.

3.2. Hypertrophy

Myocardial hypertrophy in response to a pressure overload due to constriction of the aorta leads to increased levels of several antioxidative enzymes (11-14). Six to 12 weeks after aortic constriction, a stable hypertrophic state exists and superoxide dismutase activity, measured as the inhibition of autoxidation of dopamine, was significantly elevated (11). Glutathione peroxidase activity was also elevated and tissue malondialdehyde, an index of lipid peroxidation, was approximately 25% lower in hypertophied hearts than in control hearts. In a functional assessment of antioxidant capacity, hypertrophied hearts showed a smaller decrease in left ventricular developed pressure and a smaller increase in resting tension when hearts were perfused with an oxygen radical generating system - xanthine plus xanthine oxidase. In another study of hearts in which pressure overload hypertrophy had been induced, levels of reduced glutathione (GSH) and oxidized glutathione disulfide (GSSG) were measured as an index of oxidative stress due to ischemia and reperfusion (12). Total glutathione (GSH + GSSG) was significantly increased in hypertrophied hearts. Glutathione was significantly decreased in control hearts after ischemia and reperfusion and GSSG was increased. Although absolute levels of GSH and GSSG were greater in the hypertrophy group, they did not significantly change with ischemia and reperfusion. In addition, the decrease in myocardial adenosine triphosphate and total adenine pool measured in control hearts at the end of ischemia and after reperfusion did not occur in the hypertrophy group suggesting that ischemia and reperfusion were less of a stress in hearts that had undergone pressure induced hypertrophy. Similar observations have been made in guinea pig hearts after induction of pressure overload by constriction of the aorta (14). At 10 weeks after constriction, myocardial superoxide dismutase and glutathione peroxidase activity were increased as were the levels of GSH and the GSH to GSSG ratio. Interestingly, in this study the levels of superoxide dismutase and the GSH to GSSG ratio decreased below control levels by 20 weeks after aortic constriction, a time point at which evidence of heart failure was present. Thus the development of myocardial hypertrophy was associated with an increased antioxidant status of the heart whereas the transition to heart failure was associated with the decline in antioxidant balance. Whether the decline is the initiating factor in progression from stable hypertrophy to failure remains to be determined.

3.3. Exercise

Rigorous exercise has also been shown to stimulate an antioxidant response in the heart. Treadmill running at three different intensities (55, 65 and 75% of maximal oxygen uptake) and three different durations (30, 60 and 90 min /day) induced an increased superoxide dismutase activity in the left ventricle by 10 weeks of training (15). Catalase and glutathione peroxidase did not show a similar increase. The authors speculated that the

increase in SOD is in the mitochondria (the cytosolic form of the enzyme is not inducible in heart) and may be important in neutralizing superoxide radicals formed during the elevated mitochondrial activity needed to support the elevated workload of the heart during aerobic exercise. Other investigators have shown that treadmill running for 11 weeks resulted in changes in the heart such that ischemia and reperfusion caused less severe alterations in cardiac performance, diastolic stiffness and adenine nucleotides (16). Swimming exercise, rigorous enough to induce cardiac hypertrophy, also protects hearts from ischemia reperfusion injury (12). Myocardial levels of ATP are better preserved in hearts from trained rats than in hearts from controls and the ratio of GSH to GSSG remains unchanged during reperfusion whereas in control hearts the ratio significantly decreases after ischemia and reperfusion.

3.4. Endotoxin, cytokines and sepsis

Administration of a bolus of endotoxin (17), a component of the cell wall of gram negative bacteria, has been shown to protect the heart from ischemia reperfusion injury. This protection is coincidental with an increase in catalase activity whereas superoxide dismutase, glutathione peroxidase, glutathione reductase and glucose-6-phosphate dehydrogenase levels were unaltered. Protection from ischemia reperfusion injury could be demonstrated 24 hr after administration of endotoxin but not at 1 hr after giving endotoxin. Nor could endotoxin given in the perfusate elicit protection. Inhibition of catalase activity with aminotriazole (given 12 hr after endotoxin and therefore 12 hr before the heart study) reversed the endotoxin-induced protection of the heart from ischemia reperfusion injury. In subsequent studies this same group of investigators demonstrated that pretreatment of rats with monophosphoryl lipid A, a derivative of endotoxin that apparently is non-toxic but does cause the production of cytokines, could also induce protection of the heart from ischemia reperfusion injury and increase catalase activity (18). Administration of the cytokines tumor necrosis factor (TNF) and interleukin 1 (IL-1), both of which are produced in animals after the administration of endotoxin, also induced protection of the heart (19-21). Studies with IL-1 indicated that protection found 36 hr after administration of IL-1 correlated with accumulation of neutrophils in the heart and increased levels of glutathione disulfide (an index of oxidative stress) 6 hr after giving IL-1 (21). As with endotoxin, protection required time to be elicited, i.e., hearts were not protected from ischemia reperfusion injury 1 hr after giving IL-1 or with IL-1 in the perfusate. In this study none of the antioxidant enzymes, including catalase, were elevated compared to control although glucose-6-phosphate dehydrogenase activity was increased. Depletion of neutrophils by 4 days of treatment with vinblastine, prevented the induction of protection by IL-1 suggesting that the early neutrophil infiltration may have induced an initial oxidative stress that resulted in induction of an increased antioxidant balance in these hearts. The significance of increased glucose-6-phosphate dehydrogenase (G6PDH) correlating with protection from ischemia reperfusion is suggested by the fact the G6PDH activity, which is necessary for the regeneration of glutathione (GSH) from oxidized glutathione (GSSG), was increased when protection was seen but not increased when protection was not seen, e.g. after vinblastine treatment.

We have recently shown that sepsis, induced by the administration of gram negative bacteria into the dorsal subcutaneous space, can result in protection of the heart from ischemia reperfusion injury 24 hr later (22,23). The mechanism of this protection may be different from that elicited by endotoxin or a cytokine because bacteremia is a continuous insult, i.e. there is bacteremia probably throughout the 24 hr septic episode whereas the endotoxin or cytokines are administered as a bolus. In addition the cytokine profile in sepsis is very different from that found after a bolus dose of endotoxin. Endotoxin administration causes an increase in TNF which peaks at approximately 90 min but declines by 3 hr, and the other cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8) increase and decrease sequentially (24-26). In sepsis, as measured in human septic patients, TNF levels and IL-1 levels may or may not be increased but IL-6 and IL-8 may remain elevated for prolonged periods during the septic episode (27,28). Whether the cytokine network in sepsis generates the same pattern of myocardial oxidative stress that is initiated by a bolus of cytokine or if neutrophils mediate the oxidative stress as they apparently do after endotoxin or cytokine administration, remains to be determined. It has been determined though that the myocardial catalase levels are elevated the day after the induction of sepsis - the time at which protection from ischemia reperfusion injury is present. Interestingly, sepsis induced protection of the heart from ischemia reperfusion injury occurs in spite of the fact that sepsis itself has caused a decrease in myocardial performance. This contrasts to the observations made with the bolus administration of cytokines in which myocardial performance appears to be unimpaired by cytokine administration. Also of interest is the fact that sepsis also protects the heart of the 8-10 week alcoholic rat from ischemia-reperfusion injury.

3.5. Heat shock

Heat shock has been found to induce changes in isolated cells as well as in organs from animals exposed to hyperthermia (29,30). Exposure of rats to a 42^{o}C environment for as short a period as 30 min has been shown to cause dramatic changes in the inducible heat shock protein 72 (HSP 72) in the myocardium within 24 hr (30). Hearts of animals exposed to the heat shock showed less damage or infarction after 35-min coronary artery occlusion and also showed a better recovery of left ventricular pressure during reperfusion after ischemia. In another study, exposure of rats to hyperthermia for 15 min resulted in elevated levels of catalase as well as improved recovery of the isolated heart and less loss of creatine phosphokinase from the heart after 30 min of global ischemia and reperfusion (29). Although catalase levels were increased, myocardial levels of several other antioxidant enzymes, superoxide dismutase and glutathione peroxidase, were not altered 24 hr after heat shock. The authors postulate that even though the total capacity of catalase to neutralize H_2O_2 is less than the total capacity of glutathione peroxidase to neutralize H_2O_2, the beneficial effect of catalase may reside in the fact that: 1) catalase

appears to be the major mechanism for detoxifying hydrogen peroxide in the rat heart as shown by studies in which catalase is inhibited with aminotriazole (31); 2) catalase does not require a cofactor such as glutathione; and 3) catalase is compartmentalized both in the cytosol as well as in peroxisomes (glutathione peroxidase seems to be located only in the cytosol).

3.6. Alcohol

The response of the body to chronic or acute administration of ethanol has been shown to result in generation of oxygen derived free radicals in many tissues (32,33) and to cause alterations in cardiac muscle (34) . However, in spite of the fact that acute and chronic administration of ethanol has been shown to affect protein synthesis (35,36), excitation contraction coupling (37-39), myocardial function (40), responsiveness to inotropic agents (41,42), and susceptibility to sepsis induced cardiac depression (43), there has been no clear demonstration that oxygen radical injury causes alcohol induced contractile dysfunction or cardiomyopathy. However, several studies suggest that there may be some changes in the oxidant-antioxidant balance due to alcohol administration. Mice given a single dose of ethanol, i.p., (2g/kg) showed myocardial damage as evidenced by loss of lactate dehydrogenase and histologic changes noted by electron microscopy (44). These alcohol-induced alterations were ameliorated by vitamin E. Chronic administration of alcohol may cause similar changes. Rats given ethanol in the drinking water for 6 weeks had increased levels of myocardial conjugated dienes and slightly decreased levels of glutathione (45). Both of these were reversed by supplementing the diet with vitamin E. Rats fed ethanol and a high fat diet also showed evidence of lipid peroxidation in the heart by spin trapping and electron paramagnetic resonance spectroscopy (46). Other investigators have been unsuccessful in showing evidence of oxidative stress due to alcoholism. Turkeys given ethanol in their drinking water for 15 weeks had in vivo indications of left ventricular dysfunction and dilation of the heart but elevated levels of the antioxidant enzymes SOD, catalase and glutathione peroxidase and a moderate (10%) decrease in GSH (47). The authors conclude that oxygen free radicals may not play a significant role in alcohol-induced cardiomyopathy, at least in this species which may have greater antioxidant reserves than in other species. Several other studies have shown that chronic administration of alcohol in a liquid diet in which alcohol is 36% of the caloric intake causes an increase in myocardial catalase levels (48,49). We therefore hypothesized that chronic alcohol consumption would increase the antioxidant status of the heart and decrease the injury induced to the heart by ischemia and reperfusion. Therefore animals were fed a liquid diet for 8-10 weeks in which alcohol made up 36% of the total calories (22,23). After chronic alcohol consumption, hearts were removed and studied in an isovolumic preparation. Hearts from alcoholic rats demonstrated normal ventricular developed pressure (systolic pressure minus diastolic pressure) and left ventricular end diastolic pressure. When hearts were made globally ischemic for 35 or 50 min and then reperfused for 25- 30 min, hearts from alcoholic rats recovered to the same extent, as did hearts from control fed rats. There appeared to be no greater or lesser injury due to ischemia reperfusion injury in alcoholic hearts vs. control hearts. Interestingly however, if alcoholic or control animals were made septic by injecting Escherichia coli into the dorsal subcutaneous space, sepsis induced cardiac depression occurred in both groups of hearts but ischemia and reperfusion caused no further decrease in left ventricular developed pressure in the hearts from septic alcoholic and nonalcoholic rats (100% recovery) whereas recovery of developed pressure was only 80% in the alcohol and control nonseptic groups. Again, alcohol neither potentiated ischemia reperfusion injury nor did it interfere with the mechanisms by which sepsis improves the ability of the heart to recover from oxidant injury imposed by ischemia and reperfusion.

4. CONCLUSION

In studies reported in this review, there is an initial, presumably oxidative, stress that initiates increased production of antioxidants in the heart, however, there seems to be no clear pattern of which enzyme or antioxidant component is induced. In some situations (hypertrophy) superoxide dismutase seems to be induced; in other situations (endotoxin, cytokines or sepsis), catalase seems to be induced. Whether the mechanism initiating induction of antioxidants is different or our ability to assess biochemical and functional indices of antioxidant balance is limited is unknown. In general though, independent of the character of the initial stress, i.e. pressure overload hypertrophy, exercise, sepsis or endotoxemia, or heat shock, the outcome is that the heart is protected from ischemia reperfusion injury probably at least partly due to enhanced capacity to neutralize oxygen free radicals.

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