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Review

Exercise and the endothelial cell

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Abstract

Regular exercise is known to be effective in the prevention and treatment of cardiovascular disease. Among the cardioprotectant mechanisms influenced by exercise, the endothelium is becoming recognised as a major target. Preservation of endothelial cell structure is vital for frictionless blood flow, prevention of macrophage and lipid infiltration and, ultimately, optimal vascular function. Exercise causes various kinds of mechanical, chemical and thermal stresses, and repeated exposure to these stresses may precondition the endothelial cell to future stresses through a number of different mechanisms. This review discusses stress-induced changes in endothelial cell morphology, biochemistry and components of platelet activation and cell adhesion that impact on endothelial cell structure. An enhanced understanding of the effects of exercise on the endothelial cell will assist in directing future research into the prevention of cardiovascular disease.

Keywords: Exercise; Endothelium; Apoptosis; Oxidative stress

1. Introduction

Regular exercise is known to protect against cardiovascular disease [1,2]; however, previous research has predominantly focused on the effect of exercise on endothelial function, myocardial protection and risk factors such as blood pressure, lipids and obesity. The structural integrity of the endothelium is compromised in atherosclerosis, and it is unclear if regular exercise increases endothelial cell protection. As the endothelium is constantly exposed to various chemical and mechanical stresses, the endothelial cell possesses a variety of defences; however, the development of various pathologies associated with cardiovascular disease can overwhelm these defences causing structural damage and subsequent functional impairment. The complexity and importance of the endothelium in cardiovascular pathology would suggest that multiple processes are involved in exercise-induced endothelial adaptations. Therefore, this review examines various factors induced by exercise that are known to influence the structure and biochemistry of the endothelial cell, primarily focusing on in vitro and animal studies due to the lack of research in human populations.

2. Exercise-induced stresses

Exercise induces several different types of physiological stress yet, paradoxically, is known to confer protection against diseases such as atherosclerosis [2,3]. These stresses are well documented and include increases in heat production, reactive oxygen species and shear stress. It is difficult to examine the impact of each stress in isolation in vivo due to the myriad cause and effect relationships involved; however, of these, shear stress is the stress most closely associated with the endothelium rather than vascular smooth muscle in vivo. Shear stress increases during exercise as a result of an increased oxygen demand in the working muscles, which elicits a subsequent increase in cardiac output. In vitro application of laminar shear stress to cultured endothelial cells elevates free radical production, up-regulates protective mechanisms such as antioxidant enzymes and heat-shock proteins and down-regulates proapoptotic factors [4–8]. Furthermore, shear stress is known to influence the in situ morphology of endothelial cells that is dependent upon location as cells lining the arterial system tend to be elongated as opposed to the more round or oval

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shapes seen in the venous circulation [9]. As shear stress is known to increase with exercise and has a direct impact on endothelial cell structure, in vitro studies of shear stress and cultured endothelial cells are a relevant and necessary inclusion when examining the effects of exercise on the endothelial cell.

3. Morphological changes

Few studies have examined the effect of exercise on morphological changes within the endothelium. Increases in capillary luminal areas [10,11] and plasmalemmal vesicle numbers [10] have been reported following exercise training in rats. Interestingly, Cosmas et al. [10] also observed thinner endothelial walls in myocardial capillaries which could facilitate the formation of more transendothelial channels, thus allowing enhanced transport of ions and molecules to the tunica media [12]. Immediately following an intensive bout of exercise in untrained rats, thickness of the basement membrane and endothelium of skeletal muscle capillaries were decreased, but returned to control levels 6 h post-exercise [12]. Interestingly, there was no change in interendothelial cleft parameters following a single exhaustive exercise bout [12].

The influence of shear stress on endothelial cell morphology is well documented and is most evident in the morphology of cells lining regions of high and low stress regions of the circulation. Artery lumens are typically lined by elongated endothelial cells, whereas cells lining the venous circulation are of a more rounded appearance [9]. In vitro application of physiological levels of shear stress to cultured endothelial cells causes similar changes with elongation of the cells and alignment longitudinally to the flow [8,13–15]. Low levels of shear stress do not effect such changes [8,13,14,16]. These morphological changes are due to an alignment of F-actin filaments that is both time- and dose-dependent [15]. Interestingly, when physiological levels of shear stress are applied to cultured vascular smooth muscle cells, no morphological changes are evident [14].

4. Protective pathways

Several pathways exist that provide protection against cellular damage, including up-regulation of various anti-apoptotic and heat-shock proteins. Several studies have shown that moderate exercise training results in elevated levels of myocardial heat-shock proteins [17–20], but none have demonstrated an effect on the endothelial lining of the coronary circulation in healthy subjects. Bao et al. [21] reported that single bouts of shear stress cause a transient increase in phosphorylated extracellular signal-regulated kinase-1/2 (pERK-1/2), the antiapoptotic form of ERK-1/2. Sustained exposure to similar stresses results in sustained elevation of pERK-1/2, and both of these increases were diminished but not totally inhibited by the administration of the antioxidant *N*-acetylcysteine [21], suggesting that oxidative stress is one mediator of ERK-1/2 activation. Similarly, Rush et al. [22] reported a decrease in pERK-1/2 pathway in the aortic endothelium with an up-regulation of antioxidant enzymes. De Keulenaer et al. [4] showed an increase in mRNA expression of haemoxygenase-1, a redox-sensitive heat-shock protein, in cultured endothelial cells exposed to laminar shear stress with marked attenuation after 24 h of constant exposure. Phosphorylation of protein kinase B (Akt) is induced in vitro by physiological levels of shear stress and protects cells from subsequent apoptosis induced by serum deprivation [23]. Exercise training in patients with coronary heart disease activates the antiapoptotic Akt via an increase in the level of Akt phosphorylation [24]. Similarly, in vitro application of shear stress to cultured endothelial cells inhibits apoptosis via activation of eNOS and Cu/Zn SOD pathways [5] in addition to inhibition of caspase-3 [6]. NO has also been shown to increase with exercise [25], and such increases have been shown to inhibit endothelial cell apoptosis in vitro [26] in addition to regulating vascular tone.

5. Antioxidant protection

Paradoxically, exercise is a known protector against atherosclerosis, but is also known to induce oxidative stress. This occurs primarily as a result of the inefficiency of the mitochondrial respiratory chain and the increase in fluid shear stress against the endothelium [4]. Exercise training results in an up-regulation of antioxidant defences in various tissues, presumably due to increased exposure to oxidative stress. Several studies have shown this increase in the myocardium [22,27–32]; however, few have investigated changes in the endothelium. Rush et al. [22] demonstrated that protein levels of SOD, but not catalase, were increased in aortic endothelial cells with exercise training. While Meilhac et al. [31] found increases in catalase in the aortic wall of trained mice, subsequent immunohistochemical analyses found this to be localised to the subendothelial region of the intima media. Thus, in vitro studies currently provide the best insight into the potential effects of exercise on the antioxidant defences of the endothelium. Shear stress applied to endothelial cells increases both SOD [5,7] and glutathione peroxidase [8] activity. Interestingly, SOD activity remained at baseline levels in cultured human aortic smooth muscle cells [7], suggesting a cell-specific response. De Keulenaer et al. [4] reported increases in superoxide production following laminar shear stress in cultured endothelial cells that was also accompanied by an increase in SOD mRNA and protein. Mehta and Li [33] proposed that changes seen with exercise might result from increased circulating levels of catecholamines and found that the application of epinephrine to cultured endothelial cells increased superoxide anion generation and SOD activities.