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Endothelin-1 in peripheral arterial disease: A potential role in muscle damage

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ABSTRACT

The evidence for the role of endothelin-1 (ET-1) in endothelial dysfunction and atherosclerosis has been growing since its discovery. However most studies have focussed on cardiac disease and its role in peripheral arterial disease (PAD) is less clear. In addition to its role in the development and progression of atherosclerotic lesions in lower limb arteries, there is evidence that ET-1 adversely affects microvessels within the muscle and the viability of the ischemic muscle itself. This review summarises some of these findings which underscore the potential use of ET antagonists as an adjunct in the treatment of PAD.

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1. Introduction

The pathophysiological role of endothelin-1 (ET-1) in atherosclerosis is established with the majority of studies focusing on coronary artery disease [1]. Peripheral arterial disease (PAD) where atherosclerotic lesions result in lower limb ischemia receives less attention despite its increasing prevalence in the West and its potentially devastating consequences. Patients with PAD may suffer from intermittent claudication, with exercise-induced pain in the affected muscle groups which could become disabling as the disease progresses. In severe PAD, critical limb ischemia (CLI) occurs, where viability of the limb is threatened and 20% of patients face limb loss within a year [2].

There is evidence that ET-1 is involved in the pathophysiology of PAD, contributing to atherosclerotic narrowing of the lower limb arteries as well as microvascular dysfunction. This review summarises this evidence and discusses the potential role of ET-1 within the affected ischemic muscle itself.

2. Potential role of ET-1 in PAD

2.1. Raised ET-1 levels in patients with PAD

Evidence implicating ET-1 in atherosclerosis includes raised plasma levels of the peptide in patients with symptomatic atherosclerosis such as ischemic heart disease [3] and stroke [4,5]. In a heterogeneous group of patients with symptomatic atherosclerosis including PAD, ET-1 plasma concentrations were found to correlate positively with the number of sites of atherosclerotic lesions [6].

In PAD, raised ET-1 levels have been demonstrated in both patients with claudication and CLI [7]. Mangiafico et al. found that whilst no correlation between plasma ET-1 levels and pain-free walking distance in patients with claudication was found, treating claudicants with prostaglandin E1 resulted in improved walking distances which were associated with decreases in ET-1 plasma levels [7,8]. In their study, patients with CLI ($n = 10$) had higher plasma ET-1 levels than claudicants ($n = 14$) [7] possibly to be due to greater and more sustained activation of the ET-1 pathway in more advanced disease. Recently, de Haro Miralles et al. confirmed that raised ET-1 plasma levels occurred in patients with PAD compared to controls but in their study with larger numbers (66 patients with intermittent claudication and 37 with CLI), they found higher ET-1 plasma levels in patients with claudication compared to those with CLI [9]. They suggested that in later disease as vessel damage progresses, potential sources of ET-1 such as endothelial cells may be lost, leading to reduced ET-1 secretion. Despite the use of clinical classification for patients with PAD, it is likely that these groups remain heterogeneous with varying degrees of co-morbidities including atherosclerosis in other vascular beds which might also influence systemic levels of ET-1. Newton et al. studied markers of endothelial function in patients with CLI before and after lower limb amputation and found that ET-1 plasma levels, unlike those of vascular endothelial growth factor (VEGF) and von Willebrand factor, did not reduce following amputation [10]. Moreover, higher levels of ET-1 in these patients were associated with poorer prognosis in terms of all cause mortality and cardiovascular mortality [11].

Abbreviations: CLI, critical limb ischemia; ET-1, endothelin-1; ET_AR, endothelin type A receptor; ET_BR, endothelin type B receptor; PAD, peripheral arterial disease; VEGF, vascular endothelial growth factor.

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2.2. Raised ET-1 and its receptors in diseased human arteries

ET-1 immunoreactivity [12], mRNA levels [12] and ET receptor binding [13] have been found in atherosclerotic plaques and diseased coronary arteries where ET-1 was associated with medial vascular smooth muscle cells and luminal endothelial cells. ET_A receptors were found predominantly on smooth muscle cells and ET_B receptors on microvascular endothelial cells [14].

In diseased femoral and popliteal arteries obtained from patients with CLI, a similar pattern has been shown with ET-1 binding to ET_A and ET_B receptors on medial vascular smooth muscle cells and further ET_B receptors located on microvessels and vascular nerves [15,16].

These atherosclerotic lesions are significant sources of ET-1. Whilst ET-1 is known to be a paracrine factor being released abluminally to act on ET receptor bearing cells locally, overspill of the peptide into the systemic circulation is likely to contribute to raised plasma levels and enables the peptide to also exert its effect further downstream.

2.3. Role of ET-1 in diseased arteries

The effects of ET-1 on vessels and blood flow are well established. Infusion of ET-1 into femoral arteries in dogs resulted in an initial increase followed by a gradual decrease in femoral blood flow [17,18]. In humans, ET-1 infusion reduced blood flow in the legs of young healthy volunteers [19]. In older subjects, ET antagonism resulted in greater increases in blood flow than in younger subjects, suggesting that ET-1 may play a role in the age-related raised baseline vascular tone [20]. However there is currently little evidence on the direct effect of ET-1 on femoral blood flow in patients with PAD.

PAD is characterised by endothelial dysfunction and atherosclerosis in the lower limb arteries [21] and ET-1 is likely to contribute to both of these processes. ET-1 activation is associated with atherogenic risk factors such as hypertension, hyperlipidemia [22] and diabetes [23] where as a potent vasoconstrictor it acts to antagonize endothelium-derived vasodilators such as nitric oxide contributing to endothelial dysfunction [24–26]. Endothelial dysfunction in turn promotes leucocyte adhesion, thrombosis, inflammation and cell proliferation leading to the development of atherosclerotic plaques. Once developed, these lesions provide further sources of ET-1 which acts in a paracrine fashion to contribute to the progression of the disease [27]. As the atherosclerotic lesions progress, flow-limiting stenoses or even occlusions occur, compromising perfusion to the distal tissue.

3. Microvascular involvement and ET-1 in PAD

In addition to large vessel disease, microcirculatory disturbances also occur in PAD where microvessels have been shown to be structurally [28,29] and biochemically [30] abnormal. We have previously demonstrated increased ET-1 expression in muscle biopsies taken from patients with CLI with binding of the peptide to ET_A and ET_B receptors on microvessels within the tissue [31].

The effect of ET-1 on microvessels has been demonstrated in animal studies where infusion of ET-1 into cremaster muscle of spontaneously hypertensive rats led to pronounced arteriolar constriction which was dose-dependently blocked by the ET_A receptor antagonist LU13525 [32]. Using the same model in non-hypertensive rats, exogenous ET-1-induced vasoconstriction was also effectively blocked by the mixed $ET_{A/B}$ receptor antagonist PD142893 [33]. In a mouse model of critically perfused musculocutanous flap, selective antagonism of the ET_B receptor using BQ788 increased arteriolar blood flow and reduced flap necrosis whilst neither non-selective ET nor selective ET_A receptor antagonism had any significant effect [34]. In contrast, both the mixed $ET_{A/B}$ receptor antagonist bosentan and the selective ET_A receptor antagonist LU13525 increased tissue blood flow as measured by laser Doppler flowmetry 14 days after critical hind limb ischemia in rats [35].

In humans, the effect of ET_A receptor blockade on skin microcirculation was studied in patients with type 2 diabetes and albuminuria since this group of patients have documented functional microangiopathy [36,37]. Infusion of the ET_A receptor antagonist BQ123 improved nutritive skin microcirculation as measured by capillary blood velocity in nailfold capillaries [38]. This group of researchers also assessed the effects of ET_A receptor blockade in a small group of patients with type 2 diabetes and CLI who were not eligible for revascularisation procedures. They found that an infusion of BQ123 led to an increase in mean transcutaneous oxygen tension and toe blood pressure indicating improved local tissue perfusion [39].

In addition to its role in microcirculatory function, a potential role of ET-1 in ischemia-induced angiogenesis has also been suggested. In a rat hindlimb ischemia study, the mixed ET receptor antagonist bosentan led to increased microvessel density in the ischemic limb which was abolished by co-administration of a nitric oxide inhibitor or a VEGF-neutralizing antibody [40]. These findings are in contrast to evidence supporting a pro-angiogenic effect of ET-1 in *in vitro* [41] and *in vivo* models [42], reflecting the complex pathways involved in angiogenesis.

4. Potential role of ET-1 on muscle damage

In our analyses of muscle biopsies from patients with CLI, we found significant upregulation of ET-1 and ET_A receptor mRNA in addition to increased ET-1 immunoreactivity associated with muscle fibres as well as microvessels and macrophages within the tissue [31]. Similarly, in the rat critical hind limb ischemia model mentioned above [35], upregulation of preproendothelin-1, endothelin converting enzyme-1, ET_A and ET_B receptor mRNA was found in the ischemic muscle together with increased ET-1 tissue concentrations. Since muscle fibres constitute the majority of the heterogeneous lower limb ischemic tissue, they may represent a significant source of ET-1 and may themselves be paracrine targets of the peptide.

In vitro experiments using cultured myotubes allow the specific effects of ET-1 on muscle to be studied. Using the L6 rodent skeletal cell line, Fekete et al. demonstrated that there is an abundance of ET_A receptors in skeletal muscle with ET_B receptors accounting for less than 10% of the total ET receptor density [43]. We have found that ET-1 and its receptors are also expressed by C2C12 myotubes and that exposing C2C12 myotubes to 24 h of simulated ischemia results in upregulation of ET-1 and ET_A receptor protein expression (Fig. 1). These findings suggest that skeletal muscle may be both a significant source and a target tissue for ET-1.

There is evidence that ET-1 plays a role in skeletal muscle metabolism and function. ET-1 has been found to impair glucose uptake in cultured skeletal muscle [44]. It also attenuated function in mouse skeletal muscle preparations *ex vivo* [45]. Upregulation of ET-1 and its precursors was also found in diaphragmatic muscle fibres in a rat sepsis model and may contribute to the respiratory compromise in sepsis [46].

Preliminary results from our group suggest that ET-1 may modulate part of the ischemia-induced changes that occur in C2C12 myotubes since bosentan reduced hypoxia-induced collagen gel contraction by C2C12 myotubes (Fig. 2). The effect of ET-1 on skeletal muscle damage has also been studied in models of ischemia-reperfusion. Hvaal et al. [47] used a rat model of tourniquet-induced hindlimb ischemia (3 h) and reperfusion

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