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Influence of Angiotensin-Converting Enzyme Inhibitors (ACEi) on Angiogenesis Induced by Physical Exercise

Influência dos Inibidores da Enzima Conversora de Angiotensina (iECA) Sobre a Angiogênese Induzida pelo Exercício Físico

Anderson Geremias Macedo*[ab]; David Michel de Oliveira[c]; André Thiago Rosito Goes[d]; Astor Reis Simionato[d]; Danyelle Siqueira Miotto[e]; Danilo Alexandre Massini[a]; Dalton Müller Pessôa Filho[ab]

[a]Universidade Estadual Paulista Julio Mesquita Filho Stricto Sensu Postgraduate Program in Human Development and Technologies. SP, Brazil.
[b]Universidade Estadual Paulista Julio Mesquita Filho, Department of Physical Education. SP, Brazil.
[c]Universidade Federal de Jataí, Physical Education Course, GO, Brazil.
[d]Faculdade Anhanguera, Physical Education Course. SP, Brazil.
[e]Universidade Federal de São Carlos, Interinstitutional Stricto Sensu Graduate Program in Physiological Sciences. SP, Brazil.
*Email: andersongmacedo@yahoo.com

Abstract

Angiotensin-converting enzyme inhibitors (ACEi) are used to reduce blood pressure and vascular resistance by modulating the ACE activity responsible for the angiotensin II formation. However, different ACEi seem to influence exercise-induced angiogenesis. The objective of this review was to investigate the effects of different ACEi on vessel growth in skeletal muscle induced by exercise training. The present study is characterized by a narrative literature review design, the databases of Scielo, Google Scholar and PubMed were consulted. There are different groups of ACEi , sulfhydryl group such as captopril and a carboxyl group such as perindiporil and enalapril that can influence their effects on ACE activity. It is already known that exercise promotes the increase of vessels from vessels already existing in the skeletal musculature, a process known as angiogenesis and contributes to the blood pressure reduction (BP). Although these different responses are still scarce, vessel endothelial growth factor (VEFG) and nitric oxide (NO) may participate. Thus, the use of different ACEi can influences the angiogenesis responses induced by exercise, being one of the important mechanisms for BP reduction. The choice of ACEi group should be carefully analyzed for hypertensive individuals who practice physical exercise.

Keywords: Physical Education and Training. Microcirculation. Hypertension.

Resumo

Os inibidores da enzima conversora de angiotensina (iECA) são utilizados para redução da pressão arterial e resistência vascular modulando a atividade da ECA responsável pela formação da angiotensina II. Entretanto, diferentes iECAs parecem influenciar a angiogênese induzida pelo exercício físico. Desta maneira objetivo desta revisão foi investigar os efeitos de diferentes iECA sobre o crescimento de vasos no musculo esquelético induzido pelo exercício físico. O presente estudo caracteriza-se um delineamento de revisão de literatura narrativa, foram consultadas as bases de dados do Scielo, Google acadêmico e PubMed. Existem grupos distintos dos iECAs, grupo sulfidrila como o captopril e o grupo carboxila como o perindiporil e grupo que pode influenciar seus efeitos sobre a atividade da ECA. Já é sabido que O exrcício promove o aumento de vasos a partir de vasos já existentes na musculatura esquelética, processo conhecido como angiogênese e colabora para redução da pressão arterial (PA). Entretanto os iECAs parecem influenciar esta resposta do aumento da densidade capilar no músculo esquelético. Embora ainda sejam escassos estas diferentes respostas podem ter as participações do fator de crescimento endotelial de vasos (VEFG) e o óxido nítrico (NO). Desta maneira o uso dos grupos do iECAs podem influenciar as resposta da angiogênese induzido pelo exercício sendo um dos mecanismos importantes pela redução da PA. A escolha do grupo de iECA deve ser analisada com cautela para indivíduoS hipertensos que praticam exercício físico.

Palavras-chave: *Educação Física e Treinamento. Microcirculação. Hipertensão*

1 Introduction

Angiotensin-converting enzyme inhibitors (ACEi) are used to reduce blood pressure(BP) and vascular resistance by modulating the ACE activity responsible for the angiotensin II (Ang II) formation. This class of drug has been prescribed as pharmacological treatment mainly for hypertension and congestive heart failure[1]. However, there are different ACEi groups, such as the sulphydryil carboxyl group represented by captopril, carboxyl group represented by perindopril and phosphoryl group represented by phosphinopril, these differences in ACEi groups may lead to differences in plasma concentration and plasma half-life[2,3].

It has been demonstrated that physical exercise (PE), more specifically in skeletal musculature, promotes the increase in vessel numbers, a process known as angiogenesis [4]. This process seems to occur quickly and remains for the duration of physical training[5]. This increase in the number of vessels in the skeletal musculature induced by PE seems to contribute to the BP reduction[6]. It has been shown that Ang II seems to influence angiogenesis in skeletal musculature and the blockade of Ang II formation through treatment with ACEi seems to attenuate angiogenesis induced by PE or electric stimulation[4,7]. ACEi are used as pharmacological treatment for arterial hypertension and its use affects or attenuates exercise-induced angiogenesis, affecting one of the factors

that contribute to BP reduction promoted through PE.

However, ACEi present different groups, which may influence angiogenesis in the skeletal musculature induced by the PE in different ways. Thus, the objective of this review was to demonstrate the effects of different ACEi groups on PE induced angiogenesis in the skeletal musculature.

2 Development

2.1 Methodology

This study has a design the narrative literature review. Scientific articles published in SciELO, Google Schoolar and Pubmed databases were selected. Search was carried out in February 2021 and the following English terms were used: "ACE inhibitors", "exercise traning", "angiogenesis", "skeletal muscle". For inclusion criteria, original scientific articles involving animal and human experimental models and published revisions up to the year 2021 were used, derived from subjects related to physical exercise, angiogenesis and angiotensin-converting enzyme inhibitors. Articles with incomplete information and/or did not meet the criteria of the selected themes were excluded.

2.2 Angiogenesis

The formation process of new blood vessels from preexisting vessels is known as angiogenesis and this process may occur in physiological and pathological conditions. The process of developing new capillaries begins through factors that will act on the abluminal surface of already existing capillaries and/or venules, promoting the basal membrane degradation[8]. After the basal membrane degradation, migration of endothelial cells and proliferation will occur, forming abluminal sprouts that will become functional through the new capillaries formation entering into connection with the capillary network segments[8,9].

In order for the angiogenesis process to occur, endothelial cells should be stimulated, for example through PE. The endothelium will release triggers that initiated the degradation process of the basal membrane and extracellular matrix by means of enzymes known as proteases[10]. The basal membrane degradation occurs by metalloproteinases belonging to the class of proteases, enzymes responsible for the proteins degradation present in the basal membrane,thus allowing the endothelial cell migration and sprouts expansion and development and formation of new vessel network[8,10].

2.2.1 Physical exercise and Angiogenesis

During the PE practice, there is an increase in oxygen and nutrients demand by the muscles, generating acute responses such as increased heart rate, increased blood flow and increased pulmonary ventilation. The increase in energy and oxygen needs by active muscles will promote adaptations in blood flow regulation[8]. Local oxygen deficit will result in hypoxia being an important stimulus for the vessel growth process , the reductions in oxygen levels will promote the release of hypoxia-induced transcription factor (HIF) by endothelial cells, inducing an increase in vascular endothelial growth factor (VEGF), and this protein plays an important role in the angiogenesis process in skeletal musculature[8,11]. In addition, the mechanical stimulation induced by PE can also stimulate angiogenesis in muscle tissue, since increased blood flow will promote increased stress in the capillary wall (shear stress), occuring the Nitric oxide (NO) production which is another factor also important for the growth of the number of capillaries[8,12].

Literature has shown that chronic PE promotes the increase in the number of capillaries in the skeletal musculature and this process can contribute to the BP reduction, as seen by Hansen et al.[12] verifying that hypertensive patients, after performing 16 weeks of PE with a cycle ergometer, there was a reduction in BP associated with an increase in the number of vessels in the vastus lateralis muscle. In agreement with these findings, Gliemann et al.[13] observed that 20 PE sessions in a treadmill and a cycle ergometer promoted an increase in the capillary/fiber ratio of the vastus lateralis muscle associated with the BP reduction in patients with obstructive pulmonary disease. In animal models, Amaral et al.[6] demonstrated that spontaneously hypertensive rats after 13 weeks of PE presented increased capillary density in gracilis muscle contributing to BP attenuation.

2.3 Molecular aspects

One of the possible molecular mechanisms responsible for the angiogenesis process in skeletal musculature is VEGF and this protein binds to VEGF specific receptors. Several studies have shown that VEGF is involved in the angiogenesis regulation process, which will stimulate metalloproteinases enzymes, promoting the degradation of the endothelial cell membrane and subsequently stimulating a cascade of intracellular signaling resulting in the endothelial cells migration locally leading to sprouting and later the formation of new capillaries[2]. VEFG glycoprotein is considered one of the main mitogenic factors responsible for the formation of new vessels from existing vessels[1,2]. Currently, five isoforms of VEGF, composed of 121, 145, 165, 189 and 206 amino acids, have already been identified, whereas the VEGF receptor family is subdivided into three subtypes: VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1) and VEGFR-3 (Ferrara). Several studies have shown that VEGF is involved in the angiogenesis regulation process, both in animal and human models[14-16].

Some studies have demonstrated that VEFG is involved in the angiogenesis process induced by PE, Olfert et al.[17] showed that knouckout mice of VEGF did not show an increase in capillary density after six weeks of PE in the treadmill. In another study, Amaral et al.[5] observed that exercise-induced protein production of VEGF occurs rapidly between 1-3

days training collaborating to increase the number of vessels, however VEGF production returns to baseline values at 12 weeks, even with capillary density remaining increased.

In addition to VEGF, NO can also contribute to the angiogenesis process in the skeletal musculature[18,19]. Endothelial nitric oxide synthase (eNOS) plays a fundamental role in the nitric oxide formation, eNOS is located in endothelial cells and uses L-arginine as substrate producing citrulin and NO[20]. The main function of NO is to promote vasodilation of the smooth musculature of endothelial cells by increasing blood flow locally[20]. However, some authors such as Hudlicka et al.[18] and Milkiewicz et al.[19] observed that electric stimulation for 2 to 7 days in rats, together with eNOS inhibitor (L-NNA) , had vascular growth in inhibited skeletal muscles. Whereas Fernandes et al.[21] demonstrated that trained rats presented an increase in the capillary/fiber ratio of the soleus muscle accompanied by the increased values of the eNOS protein production.

2.4 Angiotensin-Converting Enzyme Inhibitors

2.4.1 Renin-Angiotensin-Aldosterone System

The renin-agiontensin-aldosterone sytems (RAAS) plays an important role in the BP regulation. RAAS starts from renin which is released into the blood stream by juxtapagellular cells in the kidneys which cleave the angiotensin released by the liver, producing angiotensin I (Ang I) which on ACE action being converted to Ang II[22,23]. This process of transforming Ang I (decapeptide) into Ang II (octapeptide) occurs when Ang I binds to the zinc ion site of ACE, from this proteases enzymes are activated, with the cleavage of two peptides occurring at terminal C of Ang I forming Ang II. Ang II acts through its AT1 and AT2 receptors. The interaction of Ang II with AT1 receptors present in blood vessels will promote vasoconstriction, causing changes in blood pressure. Other factors such as increased blood volume induced by Ang II through increased intake and water reabsorption via ADH and aldosterone also contribute to hemodynamic changes. For all these factors, Ang II is considered the main peptided effector of RAAS[22,23].

In addition to BP control, RAAS seems to be also involved in the vessel growth process[24,25]. Some studies have shown that Ang II is involved in the vessel growth process in skeletal musculature[14,26,27], because the SARS blockade seems to attenuate the growth of vessels induced by electric stimulation and PE.

2.4.2 ACEi Classes

ACEi have been used to reduce blood pressure, being a drug responsible for modulating ACE activity. This enzyme has the function of converting angiotensin I (Ang I) into Ang II. ACE enzyme or kinase II is a bivalent dipeptide metopeptidase that is bound to the membrane in endothelial and epithelial cells and also in blood-soluble form, and is also found in body fluids and tissues[3]. The process of transforming Ang I (decapeptide) into Ang II (octapeptide) occurs when Ang I binds to the zinc ion site of ACE, from this proteases enzymes are activated, and hence, there is the cleavage of two peptides occurring at terminal C of Ang I forming Ang II. ACEi inactivates the ACE, binds to the zinc ion bond site of ACE, occupying this bond site and thus there is not the conversion of Ang I to Ang II[1,2,3].

However, there are different groups of ACEi, which differ by their ligand terminal to the active ACE sites. Currently, they are divided into 3 groups: sulfhydryl, carboxyl and phosphoryl, which present differences in bioavailability, dosage, duration of action, plasma half-life and elimination pathway[1-3]. The sulfhydryl group contains a drug called active drug, which is the most indicated by *sistema único de saúde*, captopril, among the others there are zophenopril, alacepril and moveltipril. On the other hand, the dicarboxylate group is the largest group, including enalapril, ramipril, quinapri, perindopril, lisinopril also considered an active drug, benazepril, cilazapril, delapril and spirapril. And finally, we have phosphonate that contains fosinopril[2,3,28]**.** The groups differ when their N-ring should contain a carboxylic acid to mimic the C-terminal carboxylate of ACE substrates. Large hydrophobic heterocyclic rings (i.e. N-ring) increase the potency and change the pharmacokinetic parameters. ACE zinc ion binding groups may be sulfibril, carboxylic acid or phosphoric acid. Among these groups, the sulfibril group seems to have a higher binding than the zinc ion compared to the other groups[2,3].

2.5 Physical exercise and ACEi

As demonstrated PE promotes the increase in the number of capillaries contributing to the BP reduction[6,13,16]. ACEi have been used as a form of pharmacological treatment for BP reduction. However, it seems that RAAS is involved in the angiogenesis process induced by PE[4,7]. Thus, inhibition or blockade of RAAS through ACEi may influence angiogenesis induced by PE[4]. Amaral et al.[4] demonstrated that treatment with ACEi attenuated the increase in muscle vessel growth in rats after three days of training. However, there are different groups of ACEi and due to their different characteristics, they may have distinct effects on capillary growth in skeletal musculature promoted by PE. Amaral et al.[4] demonstrated that treatment with captopril of sulfhydryl group reduced the increase of the number of vessels in the muscle in rats after three days of PE. On the other hand, perindopril of the carboxyl group, Minami et al.[29] verified that PE in a chronic manner, together with the perindopril treatment, did not impair the increase in capillary density in the muscle of hypertensive rats. Similarly, Guo et al.[30] showed that female elderly rats that received perindopril treatment and performed PE had a higher capillary density increase in the soleus muscle compared to the group that performed only PE. Recently, Miotto et al.[31] demonstrated PE combined with perindopril treatment only attenuated capillary density in the soleus muscle of

hypertensive rats. Thus, it seems that ACEi as a perindopril belonging to the carboxyl group do not seem to influence or influence in a discreet manner the angiogenesis induced by PE, differently from the captopril of the sulfibril group that significantly attenuates it.

Studies investigating possible molecular mechanisms involving angiogenesis induced by PE and ACEi are still insufficient, some authors through animal experimentation, have shown ACEi (captopril) attenuated the increase in gene expression of VEGF receptor and protein production of VEGF[32,4]. Although there are no investigations about eNOS, PE and AECi, Silvestre et al.[33] demonstrated that the treatment with perindopril did not inhibit angiogenesis submitted to ischemic surgery, this result was accompanied by an increase in eNOS.

3 Conclusion

According to the review performed and the findings found, PE promotes angiogenesis in skeletal musculature and this factor contributes to BP reduction. However, RAAS is involved in the capillary growth process in the muscle tissue induced by PE and the blockade of the Ang II formation by AECi seem to attenuate the increase in capillary density promoted by PE, however these responses may be different in relation to the different groups of AECI. In addition, the possible molecular mechanisms involved in these different responses may have the involvement of VEGF and eNOS. Thus, future studies are necessary to investigate the responses of different AECi and PE and possible molecular mechanisms involved in this process.

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