Effects of exercise training on smoking-induced cardiopulmonary diseases. A review of the physiological mechanisms

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ABSTRACT

Objective: Cigarette smoking triggers a plethora of biological mechanisms that promote the development of cardiovascular and respiratory diseases. Some preclinical studies have shown that exercise training could be effective in blunting oxidative stress and inflammatory response induced by cigarette smoking. Therefore, we aim to analyze the effect of exercise training on pulmonary and cardiovascular system in experimental models of cigarette smoking.

Methods: A systematic search was performed in order to identify studies addressed to evaluate the effects of exercise training on pulmonary and/or cardiovascular damage induced by cigarette smoking in animal models.

Results: fourteen articles were identified, all of them performed in rats or mice. Running and swimming were the only training methods and whole-body smoke exposition was the most prevalent smoking protocol used in the studies.

Conclusion: The studies support the hypothesis that exercise training performed before, concurrently or after smoking can blunt or even revert the oxidative stress and inflammatory response in animals exposed to cigarette smoke, which could contribute to recovering its cardiovascular and respiratory function.

Keywords: Tobacco; Nicotine; Inflammation; Mediators of inflammation; Oxidative stress; Lung; Blood vessels; Endothelium; Exercise; Physical effort.

Efectos del entrenamiento físico en la enfermedad cardiopulmonar inducida por el tabaquismo: revisión de los mecanismos fisiológicos

RESUMEN

Objetivo: El tabaquismo desencadena diversos mecanismos biológicos que producen el desarrollo de enfermedades cardiovasculares y pulmonares. Algunos estudios preclínicos han demostrado que el entrenamiento físico puede ser eficaz en la reducción del estrés oxidativo y de la respuesta inflamatoria inducida por el tabaquismo. Por tanto, nuestro objetivo ha sido analizar el efecto del entrenamiento físico en los sistemas pulmonar y cardiovascular en modelos experimentales de tabaquismo.

Método: Se realizó una búsqueda sistemática para localizar estudios orientados al análisis de los efectos del entrenamiento físico sobre los daños pulmonares y/o cardiovasculares inducidos por el tabaquismo en modelos animales.

Resultados: Se identificaron catorce estudios, todos realizados en ratas o ratones. Correr o nadar fueron los únicos métodos de entrenamiento y la exposición de cuerpo entero al humo del tabaco fue el protocolo de tabaquismo mas frecuentemente usado en los estudios.

Conclusión: Los estudios sustentan la hipótesis de que el entrenamiento físico realizado antes, durante o después del tabaquismo, puede reducir o incluso revertir el estrés oxidativo y la respuesta inflamatoria en animales expuestos al humo del tabaco, lo que podría contribuir en la recuperación de la función cardiovascular y respiratoria.

Palabras clave: Tabaco; Nicotina; Inflamación, Mediadores de la inflamación; Oxidativo stress; Lung, Blood vessels; Endotelio; Ejercicio; Esfuerzo físico

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Efeitos do treinamento físico na doença cardiopulmonar induzida pelo tabagismo: A revisão dos mecanismos fisiológicos

RESUMO

Objetivo: O tabagismo desencadeia uma diversidade de mecanismos biológicos que promovem o desenvolvimento de doenças cardiovasculares e respiratórias. Alguns estudos pré-clínicos demonstraram que o treinamento físico (TE) pode ser eficaz na redução do estresse oxidativo e da resposta inflamatória induzida pelo tabagismo. Portanto, objetivamos analisar o efeito do treinamento físico nos sistemas pulmonar e cardiovascular em modelos experimentais de tabagismo.

Métodos: Uma busca sistemática foi realizada para identificar estudos direcionados para avaliar os efeitos do treinamento físico sobre os danos pulmonares e cardiovascular induzidos pelo tabagismo em modelos animais.

Resultados: Quatorze artigos foram identificados, todos realizados em ratos ou camundongos. Correr e nadar foram os únicos métodos de treinamento e a exposição à fumaça de corpo inteiro foi o protocolo de tabagismo mais prevalente nos estudos.

Conclusão: Os estudos sustentam a hipótese de que o treinamento físico realizado antes, concomitantemente ou após o tabagismo pode reduzir ou até revertêr o estresse oxidativo e a resposta inflamatória em animais expostos à fumaça do cigarro, o que poderia contribuir para a recuperação de sua função cardiovascular e respiratória.

Palavras chaves: Tabaco; Nicotina; Inflamação; Mediatoras da inflamação; Estresse oxidativo; Pulmões; Vasos sanguíneos; Endotélio; Exercício; Esforço físico.

Introduction

Smoking is considered a major cause of morbidity and mortality in the general population. In the world, the prevalence reaches 31.1% in men and 6.2% in women and according to the World Health Organization it is projected a partial decline of smoking, which constitutes a public health problem. Cigarette smoke contains nicotine and more than 7000 chemical compounds and oxidizing agents, which are divided into a liquid and gas phase. Several studies have shown that the liquid phase components (water-soluble) are bioavailable in plasma and reach different territories within a few seconds after the exposure to cigarette smoke, promoting various mechanisms associated to the development of pulmonary and cardiovascular disease, such as: oxidative stress, inflammatory response, cardiovascular and lung injury.

Among the most prevalent oxidants in the gas phase are the superoxide anion (O$_2^-$, oxidant) and nitric oxide (ON, free radical), which rapidly reacts to form peroxynitrite (ONOO$^-$); a highly reactive molecule whose effects are mediated by lipid peroxidation and oxidation of sulfhydryl groups. Tobacco tars (aqueous phase) contain oxidants of organic nature (semi-quinones, quinones and hydroquinones) that react with O$_2^-$ to produce high concentrations of hydrogen peroxide (H$_2$O$_2$) and hydroxyl anion (OH-) on the liquid surface of the airway. In lung parenchyma, these oxidant agents cause direct lung damage and increase the oxidative metabolism of macrophages, monocytes, eosinophils and neutrophils, and induce the endogenous production of H$_2$O$_2$, OH$^-$ and O$_2^-$. In addition, an increase in the expression of myeloperoxidases (MPO) in neutrophils of smoking subjects has been observed, which is strongly associated with the magnitude of lung damage. Thus, one of the main consequences of the increased synthesis of oxidant molecules is the oxidation of phospholipids (lipid peroxidation), initiating an inflammatory cascade in lung tissue. Among the principal markers of lipid peroxidation are 4-hydroxy-2-nonenal (4-HNE), malondialdehyde (MDA) and 8-isoprostaglandin F$_2$$\alpha$ (8-isoprostane), which are significantly increased in smokers.

In the cardiovascular system, it has been observed that water-soluble components of cigarette smoke cross the alveoli-capillary barrier and promote the O$_2^-$ and H$_2$O$_2$ synthesis, both in the endothelium and vascular smooth muscle by a mechanism mediated by NAPDH oxidase. These biological changes promote the synthesis of ONOO$^-$ which decreases the endothelial NO bioavailability on vascular beds. In relation to antioxidant mechanisms, some studies have demonstrated that cigarette smoke significantly alters glutathione homeostasis (GSH) in epithelial cells of the respiratory tract. In addition, the plasma levels of vitamin C, E, beta-carotene, as well as, the activity of the superoxide dismutase enzyme (SOD) would be significantly altered, which affects the antioxidant capacity of plasma.

On the other hand, cigarette smoking is strongly associated with the development of a pro-inflammatory phenotype in the pulmonary and cardiovascular system. The results of diverse studies have revealed that smoking promotes the macrophages, neutrophils and lymphocytes recruitment and also induces the synthesis of pro-inflammatory cytokines in the lung parenchyma, such as interleukin (IL) 1$\beta$, 6, 8, 12, 17, tumor necrosis factor (TNF)-$\alpha$ and monocyte chemoattractant protein-1 (MCP-1). Additionally, nuclear factor kappa B (NF-kB) is an important signaling pathway associated to the development of pro-inflammatory phenotype induced by smoking, since this promotes the pro-inflammatory gene transcription. In this context, It has been shown that NF-$\kappa$B is activated by tobacco oxidizing agents and catalyzes the transcription of several cytokines and chemotactic agents such as IL-6, 8, TNF-$\alpha$ and MCP-1 in the pulmonary parenchyma and vascular bed.

Exercise training (ET) is one of the most widely non-pharmacological strategies used for treatment of cardiovascular and respiratory diseases, due to the fact that this promotes a plethora of physiological mechanisms, such as: restoring of reduction/oxydation balance (REDOX), angiogenesis mechanisms, immunomodulatory mechanisms, autonomic balance, among others. Therefore, ET may be potentially important for prevention and/or treatment of pathophysiological consequences associated to cigarette smoke. This review aims to discuss the impact of exercise training (ET) on the smoking-induced cardiovascular and pulmonary damage, with an emphasis on oxidative stress and inflammatory response.

Methods

A systematic search was performed in order to identify studies addressed to evaluate the effects of ET on pulmonary and cardiovascular injury induced by cigarette smoking. The inclusion criteria were: Studies performed in animals exposed to ET and cigarette smoking developed for at least 4 weeks, as well as, studies in which the variables considered were either physiological markers, oxidative stress, inflammatory mechanisms or physiological responses of the cardiovascular and / or respiratory system. The studies performed in humans, review articles and letters were excluded.

The articles were identified in Medline, SciELO and Tripdatabase with the following medical subjects heading: Cigarette Smoking; Exercise; Oxidative Stress; Inflammation; Inflammation Mediators; Cardiovascular System; Respiratory...
System. Additionally, Boolean terms were “AND”, and “OR”. The systematic search was performed between July 2017 and May 2018. Then it was updated in September 2019.

After systematic search, titles matching the inclusion criteria were selected. Abstracts from the selected articles were read, followed by an extensive reading of the texts selected. The article searching and the evaluation of eligibility criteria were performed by 2 reviewers (XN and IRN).

Results

Fourteen articles were identified by the search, all of them were performed in rodents. Six studies used C57BL/6 mice, two used A/JolaHsd mice, three Sprague-Dawley rats and three studies used Wistar rat. In relation to the smoking protocol, in twelve studies the animals were treated with cigarette smoke and in two with nicotine alone. In regard to the exercise protocol, running was the most used ET mode followed by swimming. In eight studies the ET was performed concurrently with smoking protocol and in four studies after smoking protocol. Finally, in two studies the ET was performed before smoking protocol. In the Table 1 are shown the general characteristics of the articles included in the review.

Table 1. Summary of articles identified

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Animal specie</th>
<th>Cigarette smoking protocol</th>
<th>Training mode</th>
<th>Exercise protocol</th>
<th>Physiological effects of ET in smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menegali et al. (2009)</td>
<td>Male C57BL/6 mice, 8 weeks old.</td>
<td>Secondary stream, 300 ppm CO. 12 cigars/day, 7 days/week, 4 weeks.</td>
<td>Swimming performed after cigarette smoking protocol.</td>
<td>5 days/week for 8 weeks, 2 sessions 30 minutes a day.</td>
<td>↑Superoxide production ↓CAT ↓MDA</td>
</tr>
<tr>
<td>Manyhan et al. (2010)</td>
<td>Male Sprague-Dawley rat, weight 250 - 300 g.</td>
<td>Nicotine infusion by minipump, 2 mg/kg/day, for 4 weeks.</td>
<td>Running performed concurrently with nicotine treatment protocol.</td>
<td>5 days/week for 4 weeks. 1st week a speed of 15–20 m/min, 0° inclination, 10 min. Subsequently &gt; 25 m/min, 10° inclination, 60 min.</td>
<td>↑NRF2, ↓MDA, ↓HMOX1</td>
</tr>
<tr>
<td>Toledo et al. (2012)</td>
<td>Male C57BL/6 mice, 6–8 weeks old.</td>
<td>Secondary stream, 250 – 300 ppm CO. 30 min/day, 5 days/week, 24 weeks.</td>
<td>Running performed concurrently with smoking protocol.</td>
<td>Exercise test in weeks 1, 8, 16, 24 before exposure. 50% maximum speed, 60 min/day.</td>
<td>↑NRF2, ↓MDA, ↓HMOX1</td>
</tr>
<tr>
<td>Al Obaidi et al. (2012)</td>
<td>Male Wistar rat, weight 150 – 200g</td>
<td>Subcutaneous nicotine 1.5 mg/kg for 4 weeks.</td>
<td>Swimming performed concurrently with nicotine treatment protocol.</td>
<td>5 days/week for 4 weeks. Progressive increased on duration and intensity: 30 – 45 min.</td>
<td>↑NRF2, ↓MDA, ↓HMOX1</td>
</tr>
<tr>
<td>Ma et al. (2013)</td>
<td>Male Sprague-Dawley rats, 4-6 weeks old.</td>
<td>Cigarette smoke exposition in a Plexiglass smoking box (0.25m²). 15 cigarette/day, 2 h each day for 45 days.</td>
<td>Running performed after cigarette smoking protocol.</td>
<td>8 circles/day for 15 days on the ring shaped 300 cm long runway.</td>
<td>↑Airway hyperreactivity ↑ERDOS in bronchoalveolar lavage. ↓8 isoprostane in lung parenchyma. ↓GPx expression. Inhibits reduction of CuZnSOD. ↓Expression of IL-10. ↓Expression of MCP1.</td>
</tr>
<tr>
<td>Hassel et al. (2014)</td>
<td>Female A/JolaHsd mice, 9 weeks old.</td>
<td>Mainstream cigarette smoking. 6 hr/day, 5 days/week, 14 weeks, 100 – 200 mg/m³.</td>
<td>Running performed after cigarette smoking protocol.</td>
<td>Interval training 1 hr/day, 5 days/week, 4 weeks after exposure to tobacco; intervals of 4 min of 25° inclination at 85 – 90% of FC max, alternating with 2 min to 50 – 60 % inclination.</td>
<td>↓SOD ↓GPx ↓CAT ↓MDA ↓CuZnSOD ↓Expression of MCP1.</td>
</tr>
<tr>
<td>Kuru et al. (2014)</td>
<td>Sprague-Dawley rat, weight 200-250 g.</td>
<td>Secondary stream, 2 cigarette intervals of 30 min, 6 days/week for 4 weeks. Intrapertitoneal Nicotine 0.1 mg/kg/day.</td>
<td>Swimming performed concurrently with nicotine treatment protocol.</td>
<td>60 min/day, 5 time per week for 4 weeks. At the end of the protocol, induction of acute stress by electrical shocks. Anxiety test at the beginning and end.</td>
<td>↑MDA ↓SOD ↓Histological damage score ↓Intestinal edema, alveolar degeneration, hemorrhage.</td>
</tr>
</tbody>
</table>

CO: Carbon monoxide, SOD: Superoxide dismutase, CAT: Catalase, SOD-1: Superoxide dismutase 1, ADP: Adenosine diphosphate, MMP: Metalloproteinase, IGF-1: Insulin-like growth factor 1, CACT: Carnitine acyl-carnitine translocase, CPTII: Carnitine palmitoyltransferase II, GLUT4: Glucose transporter type 4, HIF-1: Hypoxia-inducible factor 1, NMDA: N-methyl D-aspartate, ROS: Reactive oxygen species, NRP2: Nuclear transcriptional factor (erythroid-derived 2)-like 2, HMOX1: Heme-oxygenase1, IL: Interleukin, MCP-1: Chemoattractant monocyte-1 protein, GSH: Glutathione, NFκB: Nuclear factor kappab, 6, 8, 12, 17, tumor necrosis factor α (8-isoprostane), which are significantly increased.

Discussion

Effects of ET on oxidative stress

The studies showed that ET seems to be effective in normalizing the physiological REDOX state in experimental smoking. Menegali et al showed in C57BL/6 mice that 8 weeks of swimming exercise was effective in preventing the smoking-induced O2 overproduction in lung tissue. However, no effects on lipid peroxidation and carbonyl compounds were observed. Toledo et al, observed in C57BL/6 mice exposed to mainstream tobacco smoke that 24 weeks of treadmill training (50% maximal velocity) was effective in reducing reactive oxygen species (ROS) and 8-isoprostane synthesis in bronchoalveolar lavage and lung parenchyma respectively. Similar results were observed by Kuru et al who revealed that ET reversed the increase of MDA levels in lung parenchyma of smoking animals. Additionally, Nesi et al,
demonstrated that ET performed before the onset of smoking was effective in decreasing the lipid peroxidation and carbonyl compounds in the lung, compared with non-pre trained animals. In vascular beds, Mayhan et al demonstrated that 4 weeks of moderate treadmill exercise was effective in preventing the O₂ overproduction in pial arteries of rats chronically treated with nicotine (2mg/kg, 4 Weeks). In relation to the antioxidant mechanisms, some studies have shown that physical training promotes the expression and activity of antioxidant enzymes in the pulmonary parenchyma of smoking rats. The main changes occurred in enzymes such as: SOD, catalase (CAT) and glutathione peroxidase (GPx). However, other studies showed only discrete effects induced by ET on SOD expression in lung parenchyma of both nicotinized and smoking animals. Interestingly, Nesi et al showed that the activity of SOD and GPX is higher and CAT is lower in the lung parenchyma of trained mice after smoking protocol compared with sedentary animals. On the other hands, studies performed in animals treated chronically with nicotine showed that ET increased the expression of SOD, CAT, GPX in lung parenchyma and cerebral microvasculature. The REDOX imbalance induced by cigarette smoke promotes the muscular proteolysis in the skeletal muscle, which could be attenuated by ET. Recent studies have demonstrated that aerobic training prevents the muscle proteolysis by a downregulation of the ubiquitin proteasome system and metalloproteinases 2 and 9 activities in skeletal muscle of rats exposed to cigarette smoke.

Effect of ET on inflammatory response

The studies showed that ET decreases the macrophages and neutrophils infiltration in the lung tissue of animals exposed to cigarette smoke. Additionally, prolonged training protocols also demonstrated to prevent the decrease in IL-10 expression (anti-inflammatory cytokine) and increase of MCP-1 in lung tissue. Interestingly, Ma et al. demonstrated that 8 weeks of ET reversed the overexpression of the specific pulmonary marker of inflammatory response FIZZ1/RELMα in rats previously exposed to cigarette smoke (45 days).

On the other hands, ET has also proven to reverse the increment of intercellular adhesion molecule-1 (ICAM-1), vascular cytoadhesion molecule-1 (VCAM-1) on T cells induced by cigarette smoke, which indicates that ET could promote immunomodulatory mechanisms on a systemic level. The figure 1 shows a scheme regarding the preventive effect of exercise training on oxidative stress and inflammatory response in the cardiopulmonary system of animals exposed to cigarette smoke.

Effects of ET on respiratory system

The studies revealed that aerobic ET is effective in preventing the rupture of interalveolar septa and emphysema onset in animals exposed to cigarette smoke as well as to nicotine treated rats. However, contradictory results were observed in relation to the changes on functional variables. Toledo y cols revealed that the histological changes were not associated with changes in airway resistance and thoracopulmonary elastance, while Ma y cols demonstrated that ET attenuated the increase in airway hyperreactivity induced by cigarette smoking. Interestingly, Cilen et al. stated that smoking combined with extreme inactivity was associated with lower lung compliance and lower total lung capacity compared with active rats.

Effects of ET on cardiovascular system

Some studies showed contradictory results regarding to the effects of ET on ventricular function in animals exposed to cigarette smoke. Hassel et al. observed that high intensity interval training (HIT) restored the right systolic ventricular function in female mice exposed to cigarette smoke (14 weeks). Similar results were observed by Bowen et al. who demonstrated that HIT augments the left and right ventricular function in female mice exposed to cigarette smoke. By the contrast, the study of Reis Junior et al revealed that the ET augmented the myocardial hypertrophy and promoted myocardial dysfunction in male rats.
In relation to vascular physiology, it has been demonstrated that ET improves the endothelial function in both nicotine and cigarette smoke exposed rats. Specifically, Bowen et al observed that ET increased the eNOS activation in the aorta of mice exposed to cigarette smoke, which could explain the ameliorative effects of HIT on endothelial dysfunction secondary to smoking. Interestingly, de Sá et al. observed that 2 weeks of ET was effective in preventing the increase of heart rate and systolic blood pressure after a single dose of cigarette smoke. The figure 2 shows a summary of the biological effect of exercise training on respiratory and cardiovascular system of animals exposed to cigarette smoke.

**Figure 2.** Biological effects of exercise training in respiratory and cardiovascular system of animals exposed to cigarette smoke.

Finally, according to the evidence it is possible to conclude that the ET performed before, concurrently or after smoking can blunt or even reverse the oxidative stress and inflammation in cardiovascular and respiratory system of animals exposed to cigarette smoke. This allow to expand the role of ET in the setting of treatment of smoking cessation, inasmuch as this could be important to support its use as an integral non-pharmacological strategy, with positive effects in both nicotine withdrawal and cardiopulmonary function.

Future studies should be performed in order to elucidate the applicability of these results in clinical setting.

**References**


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