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REVIEW ARTICLE

Smoking and Endothelial Dysfunction: An Integrated - Medical and Molecular Review

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ABSTRACT

Cigarette smoke is a complex mixture of about 7,000 different toxic substances, many of which are generated during the burning of the tobacco leaf, some in the gas phase and others in the particulate matter. The gas phase represents approximately 60% of the smoke from the burning of tobacco, 99% of this phase is composed of nitrogen, oxygen, carbon dioxide, carbon monoxide, hydrogen, argon, and methane. Atherosclerosis associated with smoking is not necessarily an effect of nicotine, but probably the joint action of the various constituents of cigarette smoke. ROS from the gas phase of tobacco contributes to the onset and progression of atherosclerosis. Bupropion and varenicline are used for smoking cessation despite the side effects; however, we are still far from effective treatment to assist the definitive discontinuation of the habit of smoking. This review discusses the main mechanisms associated with vascular damage from the smoking.

Key-words – Smoking cessation, nicotine, smoke, blood pressure, hypertension, cigarettes, endothelium, endothelial dysfunction

Introduction

The casual act of lighting a cigarette and sucking the smoke has its origin lost in time. It is practically impossible to determine how and when someone first had the idea of burning dried tobacco leaves and sucking up their smoke. Long before Europeans arrived in America, smoking was a daily part of the native Americans' daily lives, and its function was much more related to their religious beliefs than to the pure and simple pleasure of tobacco consumption.

In Europe, it was Jean Nicot, the French ambassador to the Portuguese court, who introduced and disseminated tobacco. Nicot's initiative later caused the botanist De La Champ to baptize tobacco, scientifically, as herbanicotiana, giving the name of the ambassador to all kinds of plants to which tobacco belongs.

In adult non-smokers, there is a greater risk of cardiovascular disease caused by smoking, in proportion to the time of exposure to smoke, and the risk of myocardial infarction is 30% higher than in nonexposed non-smokers [1]. Smoking is responsible for approximately 45% of deaths in men younger than 65 years old and more than 20% of all deaths due to coronary disease in men over 65 years old. In addition, male smokers between 45 and 54 years old are almost three times more likely to die from myocardial infarction than non-smokers from the same age group[2].

The percentage of smokers of other tobacco products (cigars, pipes, cigarillos, Indian cigarettes, and hookah) is low: 0.8% on average[3-8]. Thus, we will concentrate our attention on cigarettes in this update. There are two ways to inhale cigarette smoke: (1) when the smoker sucks by absorbing toxic substances (primary stream) through the mouth; and (2) when smoke is released freely from the burning tip of the cigarette or other tobacco derivatives into ambient air endangers the health of non-smokers (second-hand)[9].

Cigarette smoke is a complex mixture of about 7,000 different toxic substances, many of which are generated during the burning of the tobacco leaf, some in the gas phase and others in the particulate matter[10]. The gas phase represents approximately 60% of the smoke from the burning of tobacco, 99% of this phase is composed of nitrogen, oxygen, carbon dioxide, carbon monoxide, hydrogen, argon, and methane. The remaining 1% is represented by 43 other components. The aromatized hydrocarbons present in tobacco smoke considered carcinogenic contain four to six condensed rings, the main representative of which is benzopyrene. Other toxic components less studied are nitrosamines, radioactive substances, polonium 210 and carbon 14, DDT pesticides, benzene, heavy metals (lead and cadmium), nickel, hydrogen cyanide, ammonia, and formaldehyde[10-13].

According to a report from the World Health Organization, smoking was ranked second as a leading cause of premature death and disability worldwide[14]. This is because tobacco smoke generates reactive oxygen species (ROS) that cross the alveolar epithelium to reach blood circulation and promote cytotoxic lesions in the different tissue targets. Interaction among cigarette smoke components, the endothelium, and the vascular wall is demonstrated by vascular morphological changes, such as those observed experimentally in cultures of endothelial cells and isolated organs, characterized by endothelial disruption, endothelial cell desquamation, apoptosis, cell repair, and cell proliferation[15] a key process in maintaining vascular integrity[16,17].

Structural and Functional Changes of the Vascular Wall

Experimental evidence in humans and animals shows that smoking promotes functional changes (endothelial dysfunction (ED)) and structural changes in the wall of conductance arteries (large arteries), muscular arteries (medium arteries), and resistance arteries (microcirculation). These alterations include changes in compliance and stiffness of the vascular wall[18,19] with a significant reduction of the elastic properties of the vascular wall probably mediated by stimulation of the sympathetic nervous system, responsible for the effects on blood pressure, pulse pressure, and pulse wave profile amplification in the aorta with increased central systolic pressure[20-23]. Contributing factors to this manifestation are endothelium dysfunction (ED), vascular remodeling by increasing the thickness of the intima and media layers of medium-sized arteries and microvascular beds, and reduction of lumen/wall thickness ratio[24].

Coronary Vascular Reactivity

Changes in coronary vascular tone take place 5 minutes after the consumption of a cigarette and are characterized by a 7% decrease in flow speed and increased coronary resistance by 21%, regardless of changes in heart rate and blood pressure. Coronary vasoconstriction induced by smoking is mediated by alpha-adrenergic stimulation, which causes immediate proximal and distal constriction of these arteries and an increase of tonus in resistance vessels[25]. This effect is

attributed to the action of nicotine, which promotes local (norepinephrine) and systemic (epinephrine) release of catecholamines. There is also a reduction of prostacyclin levels (PGI) since nicotine decreases its synthesis in the endothelium of the coronary arteries without affecting TXA2[26-28].

Microcirculation Responses

Evaluation of the vasodilatory microcirculation response, by infusing nicotine into fragments of human skin properly prepared for this purpose, has demonstrated an accentuation of the vasoconstriction induced by norepinephrine[29]. Experimental studies of arteriolar circulation in oral mucous of hamsters show a change of endothelium-dependent vasodilation during nicotine infusion, which is prevented by infusion of superoxide dismutase (SOD), suggesting that the formation of oxygen-free radicals contributes to decreasing the endothelium-dependent vascular response in the microcirculation[29].

Gaseous Tobacco Smoke

The main ROS present in the gaseous phase of tobacco smoke is superoxide anions, hydrogen peroxide, hydroxyl, peroxynitrite, and free radicals of organic compounds, which are highly reactive substances. Due to their short half-life, they are readily inactivated by antioxidants, such as catalase, GSH, and SOD, both cellular (SOD1 CuZnSOD cytoplasmic and SOD MgSOD mitochondrial), and extracellular (SOD3 CuZnSOD), also known as extracellular- The mechanism by which nicotine induces pathological angiogenesis involves the endothelial cholinergic pathway. It is known that the endothelial cell, which has acetylcholine receptors (Ach), synthesizes ACh from acetyl-coenzyme A and choline via acetyltransferase from choline (ChAT). Choline reuptake is essential for ACh synthesis. The presence of a transporter with a high affinity for choline has been demonstrated in endothelial cells and vascular smooth muscle SOD[30].

Cardiovascular and Atherosclerosis - Mechanisms

Atherosclerosis associated with smoking is not necessarily an effect of nicotine, but probably the joint action of the various constituents of cigarette smoke. ROS from the gas phase of tobacco contribute to the onset and progression of atherosclerosis.

Exposure of endothelial cells to tobacco smoke, which contains oxygen-free radicals, inactivates NO, which is converted into peroxynitrite promotes protein nitrosylation, reduced activity of endothelial NO synthase (eNOS), increased expression of uncoupled eNOS, activation of NADPH oxidase (higher endogenous source of ROS), and increased oxidative stress. As a consequence of reduced NO bioavailability and increased oxidative stress, stimulation of the tumor necrosis factor NF-κB and immediate increase in the expression of adhesion molecules (ICAM, VCAM, etc.), selectin (E-selectin, P-selectin), an inflammatory cytokine, recruiting platelets, macrophages, and lymphocytes, as well as activation and endothelial cell dysfunction and subsequent loss endothelial cells by apoptosis or necrosis, occurs. The reduction of NO-derived endothelial cells promotes the contraction of vascular smooth muscle cells (VSMC) of the medium layer of the vascular wall (vasoconstriction)[16,31,32].

Smoking has an adverse effect on lipid metabolism, especially in heavy smokers (>25 cigarettes per day), such as increasing VLDL-cholesterol and triglycerides levels and decreasing HDL-cholesterol (HDL mainly -2) and apolipoprotein A levels, actions that promote increased Changes in lipid profile can be reversed after one year of smoking cessation[33,34]. Oxidation studies in vitro by incubation of LDL cholesterol with nicotine and/or cotinine and monitoring of lipid peroxidation markers confirmed the hypothesis that smokers' LDL is highly susceptible to oxidation[35,36] particle oxidized LDL cholesterol, with greater atherogenic potential[33,36,37,38].

Hypercoagulability and Thrombogenicity and mechanisms

Smoking causes a hypercoagulability state by (1) increased circulating levels of procoagulant factors; (2) reduction of anticlotting factors; (3) increased blood viscosity; (4) increment in circulating levels of fibrinogen; (5) increase in plasma levels of von Willebrand factor; and (6) the activation of factor VII and coagulation cascade and tissue factor derived macrophages. Furthermore, there is a decrease due to reduced fibrinolysis inhibitor of the expression of tissue factor, decreased tissue plasminogen activator, and increase of tissue plasminogen activator inhibitor that is positively correlated with the number of cigarettes smoked per day [Clinical and Therapeutic Aspectsyugar[.

The relevance of cardiovascular involvement in active or passive smokers is based on robust epidemiological data. It should be added that tar smoking, even after declining between 1980 and 2010, has been gaining market share

again among adolescents. From the pharmacological point of view, it is well known the means used by cigarette manufacturers to cause and maintain addiction: lower concentrations of nicotine in cigarettes leads to a progressive need for a greater number of cigarettes for the consumer to gain initial pleasure (tolerance mechanism). The Association of these findings creates a high risk of atherothrombosis[32].

Smoking Cessation – Bupropion and Varenicline

Bupropion, previously used as an antidepressant, has been employed for the same purpose, with a therapeutic success of 30%[27]. This drug can trigger convulsions in smokers with a history of epilepsy and in those cases, it is contraindicated. Few small studies exist on the two therapies used simultaneously, and the results point to no more than 50% smoking cessation in 6 months[36,39].

Varenicline, a partial and selective agonist of the nAChR alpha4 beta2 (α4β2-nAChR) which involves enforcement mechanisms and dependence associated with nicotine, is a new drug developed specifically for smoking cessation. This drug partially stimulates nicotinic acetylcholine receptors alpha4 beta2 (4β2-nAChR), promotes the release of dopamine in the brain center of the clearing, and blocks the action of nicotine on these receptors[40]. For this dual mechanism, varenicline showed greater efficacy on the urgent need to smoke (crack) on withdrawal symptoms (depression, irritable accounting, frustration, anger, anxiety, and difficulty concentrating) and the effects of reward, satisfaction, and reinforcement associated with smoking.

However, more studies are needed to confirm the efficacy of this new therapeutic method[36]. Therefore, we are still far from effective treatment to assist the definitive discontinuation of the habit of smoking.

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