Uloga proinflammatory dejstava nikotina na moždanu cirkulaciju kod šloga

Role of proinflammatory effects of nicotine on the brain microvasculature in stroke

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APSTRAKT

Pušenje cigareta je naširoko priznato kao jedan od glavnih faktor rizika za moždani udar na koji je moguće uticati. Dokazi ukazuju na to da nikotin negativno utiče na cerebralni protok krvi i krvno-moždanu barijeru. Skorašnje studije ukazuju da pušenje, a naročito nikotin, ima izražen proinflammatory efekat, izazivajući hroničnu inflamciju microvasculature mozga. Ovo je praćeno povećanom leukocitnom infiltracijom u mozgu tokom ishemije / re-perfuzije. Veličina moždanog infarkta je usko povezana sa dozom izlaganja nikotinu, u smislu da veće doze nikotina izazivaju teža oštećenja mozga. I dok su štetne posledice pušenja po zdravlje dobro poznate osnovni mehanizmi toksičnosti nisu u potpunosti razjašnjeni.

Ključne reči: šlog; pušenje duvana; nikotin, cirkulacija.

ABSTRACT

Cigarette smoking is widely recognized as a major modifiable risk factor for stroke. Evidence suggests that nicotine adversely affects cerebral blood flow and the blood-brain barrier. Some recent findings have indicated that cigarette smoking, particularly nicotine, has a profound proinflammatory effect, causing a chronic inflammatory state of brain microvasculature. This was accompanied by enhanced leukocyte infiltration into brain during ischemia/reperfusion. The brain infarct size was closely associated with the exposed dose of nicotine, pinpointing that increased levels of nicotine directly aggravate brain injury. While the harmful effects of smoking on public health have been well demonstrated the underlying mechanisms of toxicity are not completely understood.

Key words: stroke; cigarette smoking; nicotine; circulation.

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A stroke or "brain attack" occurs when a blood clot blocks an artery or a blood vessel breaks, interrupting blood flow to an area of the brain. When either of these things happen, brain cells begin to die and brain damage occurs. Two million brain cells die every minute during stroke, increasing risk of permanent brain damage, disability or death. Stroke is the third leading cause of death and the primary cause of long-term disability in the United States, killing over 133,000 people each year, and a leading cause of serious, long-term adult disability. There are an estimated 7,000,000 stroke survivors in the U.S. over age 20. Approximately 795,000 strokes will occur this year, one occurring every 40 seconds, and taking a life approximately every four minutes. About 87 percent of all strokes are ischemic. Hemorrhagic strokes account for thirteen percent of all strokes, yet are responsible for more than thirty percent of all stroke deaths. The estimated direct and indirect cost of stroke in the United States in 2010 is \$73.7 billion.^{1,2}

There are two types of risk factors for stroke: controllable and uncontrollable. Controllable risk factors generally fall into two categories: lifestyle risk factors or medical risk factors. Lifestyle risk factors can often be changed, while medical risk factors can usually be treated. Controllable risk factors are: high blood pressure, atrial fibrillation, high cholesterol, diabetes, atherosclerosis, circulation problems, tobacco use and smoking, alcohol use, physical inactivity, obesity. Uncontrollable risk factors are age, gender, race, family history, previous stroke or TIA, fibromuscular dysplasia, patent foramen ovale.

Cigarette smoking is widely recognized as a major modifiable risk factor for stroke. An estimated 43.8 million people, or 19.0% of all adults (aged 18 years or older), in the United States smoke cigarettes. Cigarette smoking is more common among men (21.6%) than women (16.5%). Cigarette smoking is the leading cause of preventable death in the United States, accounting for more than 440,000 deaths, or one of every five deaths, in the United States each year.³⁻⁷ Smoking causes about a two-fold increase in the risk of stroke occurrence. There is a dose-response relationship between cigarette consumption and stroke risk, whereas smoking cessation leads to a prompt stroke risk reduction. The risk of stroke increased as the number of cigarettes smoked increased. The relative risk of stroke in heavy smokers (>40 cigarettes per day) was twice that of light smokers (fewer than ten cigarettes per day). Lapsed smokers developed stroke at the same level as nonsmokers soon after stopping. Stroke risk decreased significantly by two years and was at the level of nonsmokers by five years after cessation of cigarette smoking.

A substantial body of evidence suggests that nicotine adversely affects cerebral blood flow and the blood-brain barrier and is a risk factor for stroke. Chronic exposure to tobacco or nicotine, a major active component of cigarettes, can cause regional cerebral blood flow (rCBF) following nasal nicotine administration to overnight abstinent tobacco smokers in relationship to the known brain distribution of nicotinic cholinergic receptors (nAChRs). Domino EF et al, in their study have been shown that the brain areas with a large number of nAChRs, such as the thalamus, showed an significant increase in CBF after nicotine nasal spray treatment given in doses of 1-2.5 mg administered to overnight abstinent tobacco smokers. Other areas that have few nAChRs, such as the cerebellum, also showed an increase in relative CBF.⁸ Some recent findings have indicated that cigarette smoking, particularly nicotine, has a profound proinflammatory effect, causing a chronic inflammatory state of brain microvasculature. Shayna T et al, proposed in their analysis that isolated brain microvessels after nicotine exposure shown higher expression of inflammatory mediators, cytokines (IL-1 β , TNF- α , and IL-18), chemokines (CCL2 and CX3CL1), and adhesion molecules (ICAM-1, VCAM-1, and P-selectins), and this was accompanied by enhanced leukocyte infiltration into brain during ischemia/reperfusion.⁹ In addition, some recent findings have indicated that cigarette smoking, and particularly nicotine, has a profound proinflammatory effect, causing a chronic inflammatory state with increased levels of circulating leukocytes, C-reactive protein, and fibrinogen, as well as enhanced leukocyte rolling and adhesion in the cerebral microcirculation and chemoattractant activity for neutrophil migration.^{10,11,12}

Nicotine have been also shown proinflammatory effects at several different target sites including the vascular interface, leukocytes, and respiratory and intestinal epithelia. At these targets, nicotine alters expression of proinflammatory mediators, directly or indirectly aggravating the outcome of inflammation.

Nicotine shown ability to activate Human umbilical vein endothelial cells (HUVEC) as evidenced by induction of ICAM and VCAM expression in vitro. The biological effects of these adhesion molecules are demonstrated by a marked increase in mononuclear leukocyte (MNL) adhesion to HUVEC. MNL adhesion and subsequent migration into the intima, if occurring in vivo, may be a vital step in the pathogenesis of atherosclerotic cardiovascular disease associated with nicotine exposure.¹³ Sikora L et al in their study demonstrated that nicotine significantly enhanced rolling and adhesion of leukocytes within lung microvessels comprising arterioles and postcapillary venules in a dose-dependent manner, but failed to

induce leukocyte emigration. Nicotine-induced rolling and adhesion was significantly higher in venules than in arterioles.¹⁴ Some studies have indicated that nicotine regulates leukocyte rolling and adhesion mediated by P-selectin and CD18 and reactive oxygen radical-dependent mechanisms in cerebral microvessels of the mouse.¹²

Smokers are also reported to be at increased risk for thrombosis. Platelet activation is frequently observed in smokers in response to increased levels of platelet activating factor, Von Willebrand factor, catecholamines, and thromboxane. This phenomenon has been confirmed *in vitro*¹⁵ and *in vivo*.¹⁶ All these factors pose a serious threat at the level of brain microvasculature where vascular tone regulatory mechanisms are absent. Elevated C-reactive protein (CRP) levels caused by cigarette smoking, can also promote endothelial dysfunction by lowering the production of nitric oxide (NO) and diminishing its bioactivity.¹⁷

Besides affecting the brain endothelium under resting conditions, nicotine also affected the development of brain ischemic/reperfusion (I/R) injury. Nicotine enhanced infarct size and worsened neurological status. Furthermore, the brain infarct size was closely associated with the exposed dose of nicotine, pinpointing that increased levels of nicotine directly aggravate brain injury.⁹ The potential reason for the enhanced ischemic injury may be that prior nicotine treatment induces a low inflammatory response, which can be a solid substrate for a profound response to ischemic injury at the brain blood barrier (BBB) and in brain parenchyma. Recently published study results indicated a significant downregulation in expression anti-inflammatory cytokines IL-10 or IL-1ra.⁹ Taking into consideration that IL-10 and IL-1ra act as neuroprotective mediators (prevent apoptotic events and glutamate excitotoxicity), particularly after brain I/R injury, the imbalance in pro- and anti-inflammatory mediators generated by nicotine may affect the susceptibility of neurons and glial cells to injury, and this could play a role in expanding infarct size in nicotine-treated animals. Alterations in the BBB proinflammatory phenotype even before ischemic onset, as well as the profound effect during the reperfusion injury, may facilitate potential stroke onset and enhance the final ischemic outcome. Therefore, the actions of nicotine could be defined as "breaking the system of defense" at the level of BBB and brain tissue, which in turn affects neuronal viability and worsens the outcome. Nicotine has been implicated in BBB changes leading to brain edema formation. It is known that nicotine alters the Na⁺, K⁺, 2Cl cotransporter 1 (NKCC1) on the abluminal surface of the BBB during *in vitro* hypoxia/aglycemia conditions, affecting the development of both

cytotoxic and vasogenic brain edema.^{18,19,20} The exacerbation of brain edema may contribute to worsening of stroke outcome by nicotine, particularly to the neurological deficit and high mortality rate.

In summary, while the harmful effects of smoking on public health have been well demonstrated the underlying mechanisms of toxicity are not fully understood. At the cerebrovascular level and specifically at the BBB cigarette smoking can severely impair endothelial physiology by directly affecting endothelial tight junctions and the ionic homeostasis across the endothelium. The exposure to highly reactive oxygen species generated by cigarette combustion can cause oxidative damage and trigger a strong inflammatory cascade that can lead to the onset and/or facilitate the progression of many CNS disorders. Nicotine exerts marked effects on the expression of inflammatory mediators at the level of the microvasculature also changing the brain endothelium to a proinflammatory phenotype. This phenotype change may affect stroke occurrence and enhance ischemia-induced brain injury in a dose-dependent manner. Both men and women can reduce their risk of cardiovascular disease through smoke-free living. The state of health begins to improve immediately after quitting as the risk of brain attack reduces considerably already during the first 1-2 years. According to the WHO, one year after quitting the risk of cerebrovascular disease decreases by 50 percent, and within 15 years the relative risk of dying from cerebrovascular disease for an ex-smoker approaches that of a long-time smoker. According to several studies five years after quitting, the former smoker has no higher risk of stroke than the non-smoker.²¹

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