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Review

Nicotine signaling and progression of chronic kidney disease in smokers

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ABSTRACT

The deleterious health effects of cigarette smoking are far reaching, and it remains the most important modifiable risk factor for improving overall morbidity and mortality. In addition to being a risk factor for cancer, cardiovascular disease and lung disease, there is strong evidence, both from human and animal studies, demonstrating a role for cigarette smoking in the progression of chronic kidney disease (CKD). Clinical studies have shown a strong correlation between cigarette smoking and worsening CKD in patients with diabetes, hypertension, polycystic kidney disease, and post kidney transplant. Nicotine, in addition to its role in the addictive properties of cigarette smoking, has other biological effects via activation of non-neuronal nicotinic acetylcholine receptors (nAChRs). Several nAChR subunits are expressed in the normal kidney and blockade of the α7-nAChR subunit ameliorates the effects of nicotine in animal models of CKD. Nicotine increases the severity of renal injury in animal models including acute kidney injury, diabetes, acute nephritis and subtotal nephrectomy. The renal effects of nicotine are also linked to increased generation of reactive oxygen species and activation of pro-fibrotic pathways. In humans, nicotine induces transitory increases in blood pressure accompanied by reductions in glomerular filtration rate and effective renal plasma flow. In summary, clinical and experimental evidence indicate that nicotine is at least in part responsible for the deleterious effects of cigarette smoking in the progression of CKD. The mechanisms involved are the subject of active investigation and may result in novel strategies to ameliorate the effects of cigarette smoking in CKD.

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1. Introduction

There are over a billion cigarette smokers worldwide, with over one third of the population above 15 years of age being smokers [1]. Cigarette smoking is the single most important modifiable risk

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factor for adverse health outcomes and has been identified as the most important source of preventable morbidity and mortality in the United States [2,3]. Cigarette smoking associated diseases are responsible for one in every five deaths in the developed world, and are the most common cause for premature death in the adult population [1]. Cigarette smoking associated diseases are also responsible for 6–15% of the healthcare costs in the developed world [1]. Cigarette smoking is a major risk factor for different types of cancer, atherosclerotic vascular disease, including coronary artery disease and stroke, obstructive lung disease, cataracts and macular degeneration, osteoporosis and peptic ulcer disease [1,4]. Moreover, accumulating clinical evidence indicates that cigarette smoking is also a risk factor in the progression of chronic kidney disease (CKD) of different etiologies including diabetes and hypertension [5–10]. Cigarette smoking has also been associated with worsening of renal function after renal transplantation [11–17]. CKD is a major public health problem worldwide, although particularly serious in the United States [18]. Despite improvements in the therapy of major risk factors, such as diabetes and hypertension, the incidence and prevalence of CKD continues to increase with the number of prevalent patients with ESRD surpassing 550,000 in 2009 [18]. Although it is now well established that tobacco smoking accelerates the progression of CKD, the mechanisms involved have not been identified.

Mainstream cigarette smoke contains over 4000 compounds, including reactive oxygen species, stable reactive aldehydes and ketones and carbon monoxide among others [19]. Amid the numerous compounds present in tobacco smoke, nicotine is one of the biologically active and stable compounds present in large concentrations in tobacco that can be acquired through active and passive smoking. In addition to being responsible for the addictive properties of tobacco smoking, nicotine has a variety of biological effects that may play an important role in the pathogenesis of different conditions including renal disease.

This review focuses on the biologic effects of nicotine, with special emphasis on the effects in the kidney, and summarizes the clinical evidence and experimental evidence implicating cigarette smoking and nicotine exposure as major risk factors in the progression of chronic kidney disease.

2. Biologic effects of nicotine

Nicotine mediates its effects via the activation of muscle and neuronal nicotinic acetylcholine receptors (nAChRs) [20]. The nAChRs are a family of transmembrane ligand-gated ion-channels consisting of five subunits that result from the combinatorial assembly of different nAChR subunits [20]. The muscle nAChRs consist of five subunits: α1 and four non-α subunits (β1, δ, ε, γ) and have binding capacity in the micromolar range [21]. The neuronal nAChRs are ~50-fold more sensitive to nicotine than the muscle nAChRs with binding capacity in the nanomolar range, and can be homopentamers or heteropentamers. Ten subunits, which can form neuronal nAChRs, have been identified, of which seven are α-like subunits (α2–α7, α9–α10) and three are non-α subunits (β2–β4). Receptor pentamers can be constructed from various combinations of α and β subunits [20]. The diversity of nAChRs subunits is a major determinant of the specialized properties and functions of the mature receptors. In the central nervous system the high affinity nicotine-binding receptor consists of at least α4 and β2 nAChR subunits [22,23]. In the brain, the various nAChR subunit combinations differ in their distribution, pharmacological and kinetic properties [24]. The two main types of nAChRs in the brain are the α7 homo-oligomer, characterized by a fast activation, low affinity (binding affinity K_i 400–1500 nM) and a high Ca^{2+} permeability [25–27]; and the α4β2 hetero-oligomer, which is typified by a high affinity (binding affinity K_i 0.6–1.0 nM) and slow desensitization [24,28]. The nAChRs are also expressed in non-neuronal cells including bronchial epithelial cells, endothelial cells, vascular smooth muscle cells and human mesangial cells as we have previously demonstrated (Table 1) [29–34]. In contrast to the central and peripheral nervous systems where the distribution and composition of the nAChRs has been extensively studied, the distribution, composition and binding properties of these receptors in the kidney are not well known.

In addition to its well-recognized role as mediator of the addictive effects of tobacco smoking, nicotine has a variety of other biological effects that may play an important role in the pathogenesis and progression of a variety of pathologic conditions. In the vasculature, nicotine promotes atherosclerosis, angiogenesis and lesion growth in mouse models of lung cancer [35]. In these studies nicotine at a concentration of 10 nM induced the formation of capillary-like structures in cultured endothelial cells and induced endothelial cell proliferation at concentrations between 1 and 10 nM. In vivo the administration of nicotine in the drinking water at a concentration of 100 μg/mL resulted in levels of nicotine similar to those found in the plasma of smokers and increased atherosclerotic plaque in Apo-E deficient mice, tumor size in mice after subcutaneous injection of Lewis lung cancer and neovascularization after limb ischemia. The angiogenic effects of nicotine are inhibited by specific blockade of the α7-nAChR suggesting an important role of this receptor in these effects [33]. In these studies the angiogenic effects of nicotine were found to be partially dependent on vascular endothelial growth factor (VEGF), and completely dependent on the phosphatidylinositol 3-kinase, mitogen activated protein kinase pathways and NF-κB activation [33]. Moreover in recent studies we have demonstrated that the administration of nicotine (100 μg/mL in the drinking water) exacerbated the formation of atherosclerotic plaque in Apo E deficient mice but not in mice Apo E deficient and lacking CD36, an important mediator of oxidized LDL (oxLDL) uptake and contributor

Table 1
Distribution of specific nAChR subunits in different tissues detected by mRNA or protein expression.

nAChR subunit	Tissue distribution in non-neuronal tissues
α2	Vascular smooth muscle
α3	Lymphoid tissue, keratinocytes, bronchial epithelial cells, endothelial cells, vascular smooth muscle, astrocytes
α4	Muscle, lymphoid tissue, alveolar macrophages, alveolar epithelial cells, neuroepithelial bodies, vascular smooth muscle, astrocytes, mesangial cells
α5	Muscle, bronchial epithelial cells, endothelial cells, vascular smooth muscle
α7	Muscle, lymphoid tissue, macrophages, keratinocytes, bronchial epithelial cells, neuroepithelial bodies, endothelial cells, astrocytes, mesangial cells
α9	Keratinocytes
α10	Endothelial cells, vascular smooth muscle
β2	Muscle, lymphoid tissue, alveolar macrophages, keratinocytes, neuroepithelial bodies, endothelial cells, mesangial cells
β3	Astrocytes, mesangial cells
β4	Muscle, lymphoid tissue, endothelial cells, astrocytes, mesangial cells