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Nicotine and Vascular Dysfunction

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Abstract

Cigarette smoking is the single most important risk factor for the development of cardiovascular diseases (CVD). However, the role of nicotine, the addictive component of all tobacco products, in the development of CVD is incompletely understood. Although increased public awareness of the harms of cigarette smoking has successfully led to a decline in its prevalence, the use of electronic cigarettes (e-cig) or electronic nicotine delivery system has increased dramatically in recent years due to the perception that these products are safe. This review summarizes our current knowledge of the expression and function of the nicotinic acetylcholine receptors in the cardiovascular system and the impact of nicotine exposure on cardiovascular health, with a focus on nicotine-induced vascular dysfunction. Nicotine alters vasoreactivity through endothelium-dependent and/or endothelium-independent mechanisms, leading to clinical manifestations in both cigarette smokers and e-cig users. In addition, nicotine induces vascular remodeling through its effects on proliferation, migration, and matrix production of both vascular endothelial and vascular smooth muscle cells. The purpose of this review is to identify critical knowledge gaps regarding the effects of nicotine on the vasculature and to stimulate continued nicotine research.

Keywords

nicotine; nAChR; vascular dysfunction; endothelial cells; vascular smooth muscle cells

Introduction

Cigarette smoking is the single most important risk factor for the development of cardiovascular diseases (CVD), and smokers are 2–4 times more likely to develop CVD than non-smokers.[1] As summarized in "*The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General,*" the evidence is sufficient to infer a causal relationship between smoking and coronary heart disease, atherosclerotic aortic aneurysm, cerebrovascular disease, stroke, and all-cause mortality. Nicotine is the addictive component of all tobacco products; however, the role of nicotine in the development of CVD is incompletely understood. Although increased public awareness of the harms of cigarette

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Conflict of interests

The authors declare no conflict of interests.

smoking has successfully led to a decline in its prevalence, the use of electronic cigarettes (e-cig) or electronic nicotine delivery system has increased dramatically in recent years due to the perception that these products are safe. This review summarizes our current knowledge of the expression and function of the nicotinic acetylcholine receptors (nAChR) in the cardiovascular system and the impact of nicotine exposure on cardiovascular health, with a focus on nicotine-induced vascular dysfunction. The purpose of this review is to identify critical knowledge gaps regarding the effects of nicotine on the vasculature and to stimulate continued nicotine research.

Overview of Nicotinic Acetylcholine Receptors

The nAChR belong to the family of ligand-gated cation channels and are ubiquitously expressed in the central nervous system.[2] Mature nAChR are pentameric structures of different subunit combinations in defined stoichiometries (humans have 9 genetically distinct ligand-binding α-subunits and 7 modulatory non-α-subunits). The nAChR are divided into three major subtypes (Figure 1A): muscle-type, heteromeric and homomeric nAChR. The muscle-type nAChR consists of $(\alpha1)_2\beta1\delta\varepsilon$ (adult) or $(\alpha1)_2\beta1\delta\gamma$ (fetal) and is located at the neuromuscular junction, and this receptor is poorly responsive to nicotine. The heteromeric nAChR are composed of five subunits in various combinations of α and β subunits, and this type is predominately expressed on neuronal cells such as $(\alpha4)_2(\beta2)_3$-nAChR implicated in nicotine addiction and $(\alpha3)_2(\beta4)_3$-nAChR involved in neurotransmission in the autonomic nervous system. The homomeric nAChR include the $(\alpha7)_5$ and $(\alpha9)_5$ receptors and are expressed by not only neurons but also many non-neuronal cells, with the α7-nAChR being the most studied subtype.

Upon binding to endogenous ligand acetylcholine (ACh) or nicotine, the central pore of nAChR opens to allow the flow of cations (Na^+ and Ca^{2+} into and K^+ out of the cells, Figure 1B), resulting in membrane depolarization or activation of intracellular calcium-mediated signaling pathways if calcium permeability is sufficient. Due to its unusual homomeric subunit composition and the presence of five ligand binding sites, α7-nAChR exhibits high permeability to calcium, enough to couple the activity of this receptor to intracellular calcium signaling pathways. Nicotine's effect on the cardiovascular system is conferred through its ability to bind endogenous nAChR in place of the endogenous agonist ACh.

Overview of Nicotine on Hemodynamics

It is well-recognized and documented that nicotine in tobacco products imposes hemodynamic effects.[3] These include acute changes in heart rate (HR) and increases in myocardial contractility and blood pressure (BP).[4–7] Treatment with nicotine or a nicotinic agonist induces a brief but pronounced decrease in HR, followed by significant increases in both HR and BP.[7,8] The initial parasympathetic bradycardic response has been shown to be mediated by activation of α4β2-nAChR, whereas the subsequent sympathetic tachycardic and pressor responses are mediated by α7-nAChR.[8] In addition, inhaled nicotine equivalent to cigarette smoking induces high magnitude fluctuations of BP, irregular pulse BP and cardiac arrhythmia.[9] The α7-nAChR also participates in baroreflex regulation that maintains

BP homeostasis, as α7-nAChR knockout (KO) mice have impaired sympathetic tachycardic response to sodium nitroprusside (SNP)-induced vasodilation.[10]

In the medulla, injection of nicotine into the nucleus of the solitary tract (NTS) and area postrema elicits bradycardia and hypotension; in contrast, injection of nicotine into the rostral ventrolateral medulla (RVLM) produces dose-dependent and long-lasting increases in both systolic and diastolic BP.[11] Nicotine can activate NTS catecholamine neurons directly through α4β2-nAChR and indirectly through increased glutamate release via α7-nAChR.[12] The cardiovascular effects of central α7- and α4β2-nAChR activation have also been shown to involve the release of vasopressin.[13] On peripheral postganglionic sympathetic nerve endings including the adrenal medulla, nicotine stimulation of nAChR results in catecholamine release, more potently than ACh.[14] Because an increase in cytosolic calcium is a prerequisite for chromaffin cell exocytosis,[15] it is likely that α7, α9, and/or α9/α10 nAChR activation would trigger instructive signaling cascades contributing to catecholamine release from these cells.[14]

The effects of nicotine on long-term BP control is controversial. Although surveys of outpatient BP measurement report that smokers have either similar or slightly lower BP compared to matched nonsmokers,[16,17] studies of ambulatory BP monitoring show that long-term cigarette smoking increases average HR and BP throughout the day.[18,19] Findings from our laboratory show that chronic nicotine inhalation in mice leads to a transient increase in BP.[20] Mice exposed to nicotine (daily 12 h on/12 h off) initially exhibited elevations in both systolic and diastolic BP (weeks 1–3), which then returned to baseline following prolonged exposure (weeks 4–8), indicating development of tolerance and/or activation of compensatory mechanisms. In addition, the BP increase within the first week of nicotine exposure was associated with a lack of systolic BP dipping, which is considered a risk factor for cardiovascular diseases and end organ damage.[21,22] Importantly, our study found that 8-week nicotine inhalation exposure leads to elevation in pulmonary BP (pulmonary hypertension) with pulmonary vascular and right ventricular remodeling.[20] Interestingly, in RV samples from patients with pulmonary arterial hypertension, α7-nAChR expression was increased and acetylcholinesterase activity was reduced versus controls.[23]

Nicotine and Vascular Reactivity

Both vascular endothelial cells (EC) and vascular smooth muscle cells (VSMC) express multiple α and β subunits of nAChR,[24–28] rendering the vasculature a direct target of nicotine. In terms of vascular reactivity, nicotine exerts primarily vasoconstrictive effects through endothelium-dependent and/or endothelium-independent mechanisms (Figure 2).

Nicotine Impairs Endothelium-Dependent Vasodilation

Activation of the endothelium can elicit a multitude of pathways with the production of vasoactive substances that travel to the underlying VSMC to induce vasoconstriction or vasodilation, and these include the endothelin, nitric oxide (NO) and prostacyclin pathways.[29] Both human and animal studies have implicated nicotine's involvement in altering these pathways, hindering blood vessels' ability to dilate.

Endothelin-1 (ET-1) is a potent vasoconstrictor produced by vascular EC and plays a vital role in maintaining vascular tone. It acts on two G protein-coupled receptors (GPCR), ET_A and ET_B, located on the underlying VSMC to activate pathways leading to vasoconstriction. To maintain cardiovascular balance, some ET-1 may also bind ET_B receptors on the EC to induce vasodilatory effects via formation of prostacyclin or NO.[30] Cigarette smoking has been associated with elevated blood ET-1 levels in healthy smokers,[31] and pulmonary arteries from smokers and chronic obstructive pulmonary disease patients showed a higher expression of ET_A and ET_B.[32] Cigarette smoke exposure also induces ET-1 and ET_A/ET_B expression in experimental animals,[33–35] and a recent study showed that e-cig exposure for 4 weeks in rats resulted in increased cardiac ET-1 levels.[36] In addition, cigarette smoke extract induces ET-1 expression in cultured EC[37] and ET_A/ET_B in cultured VSMC or arterial segments.[32,38–40] The expression of ET_A/ET_B has been shown to be mediated by mitogen-activated protein kinase (MAPK) pathways and downstream transcription factors such as nuclear factor-κB.[32,38–40] In contrast, exposure to nicotine alone in culture (24 h) fails to induce the expression of either ET-1[41] or ET_A/ET_B.[38,39] However, nicotine was shown to increase ET-1 release from cultured human umbilical vein endothelial cells (HUVEC), with a maximal effect observed at 5 minutes post exposure.[42] This acute nicotine-induced ET-1 release likely leads to alteration in vasoreactivity. For example, treatment with an ET_A receptor antagonist blocked nicotine-induced increase of mean arterial BP in rats, suggesting nicotine's acute pressor effect is mediated, at least in part, by ET-1 binding of ET_A on VSMC.[43] Similarly, another study showed that intraportal nicotine infusion in rats decreased hepatic blood flow in a dose-dependent manner through ET-1 and ET_A/ET_B receptors, while pretreatment with the ganglionic nicotinic receptor blocker hexamethonium attenuated nicotine's effects.[44] In addition, long-term nicotine exposure in animals has been shown to increase ET-1 expression. Nicotine administered orally for 28 days in male rats led to increased ET-1 expression in the aorta.[45] Subcutaneous injection of nicotine (0.1 mg/kg per day) for 6 weeks in female ovariectomized rats resulted in increased plasma ET-1 levels, which can be prevented by estrogen replacement therapy, indicating the protective effects of estrogen.[46] The role of nicotine in cigarette smoke-induced overexpression of ET_A and/or ET_B *in vivo* is not clear.

Another pathway by which endothelium-dependent vasodilation occurs is through the formation of NO from L-arginine catalyzed by endothelial NO synthase (eNOS).[47] Cigarette smoking, e-cig use and nicotine administration have all been shown to reduce NO bioavailability.[48,49] Nicotine treatment leads to reduced eNOS expression in cultured carotid and uterine arteries,[50,51] and in nicotine-treated uterine arteries, the phosphorylation levels of eNOS (Ser1179) are also significantly decreased.[50] In a recent study, nicotine exposure in HUVEC was shown to reduce the expression of GTP cyclohydrolase 1 (GTPCH1), the rate-limiting enzyme for the production of tetrahydrobiopterin (BH4), an essential cofactor for eNOS.[52] Reduced bioavailability of cofactor BH4 leads to eNOS uncoupling and the generation of superoxide rather than NO.[52] Importantly, dietary supplementation of BH4 attenuated nicotine-induced endothelial dysfunction in $ApoE^{-/-}$ mice.[52] In addition, oral nicotine administration in experimental animals significantly increased plasma level or EC expression of the endogenous eNOS inhibitor, asymmetric dimethylarginine (ADMA),[53,54] and this effect was mediated by nicotine-induced downregulation of dimethylarginine

dimethylaminohydrolase (DDAH, a major hydrolase of ADMA) via activation of the α7-nAChR.[53] Finally, multiple studies suggest that nicotine-induced production of reactive oxygen species (ROS) contributes to nicotine-induced impairment of NO-mediated endothelium-dependent vasodilation.[55–57]

Prostacyclin (PGI_2) is an effective vasodilator produced by the vascular endothelium from arachidonic acid via pathways involving the enzymes cyclooxygenase and PGI_2 synthase. PGI_2 then acts on its receptors on VSMC (commonly referred to as IP receptors) to induce VSMC relaxation via the G protein (Gs) linked cAMP pathway.[58] Although cigarette smoking has been associated with decreased synthesis of PGI_2 in both humans and animal models,[59–62] the role of nicotine on the production of PGI_2 is less clear. In cultured HUVEC and bovine pulmonary artery EC, nicotine exposure at levels comparable to the plasma levels of human smokers did not affect the levels of PGI_2.[63,64] However, nicotine perfusion in human umbilical artery *in vitro* led to a decline in PGI_2 production.[65] In rabbits, 1-week nicotine infusion *in vivo* caused a significant reduction of PGI_2 in the heart.[66] In isolated and perfused rabbit hearts, however, nicotine perfusion alone did not alter PGI_2 levels in the myocardium.[67] Instead, this study showed that nicotine significantly worsened ischemia-induced decrease in PGI_2.[67] In rats, nicotine administered in drinking water for 10 days resulted in reduced plasma level of PGI_2 in a dose-dependent manner[68] and continuous subcutaneous infusion of nicotine over 7 days resulted in reduced PGI_2 production in the aorta.[69] The above studies indicate that the effects of nicotine on PGI_2 may depend on the cell/tissue types as well as *in vitro*, *ex vivo* or *in vivo* conditions. In addition, the mechanisms through which nicotine regulates PGI_2 synthesis or metabolism require further investigation.

A standard technique to examine endothelium-dependent vasodilatory response is through stimulation with ACh or methacholine. Both ACh and methacholine bind to muscarinic ACh receptors on vascular EC and induce vasodilation through endothelium-derived NO and/or prostaglandins.[70] Aortas isolated from mice exposed to cigarette smoke or e-cig for 8 months exhibited reduced vasodilatory response to methacholine; in contrast, their responses to the NO donor SNP were not affected, indicating intact NO-cGMP signaling in VSMC.[71] Importantly, human subjects who chewed nicotine gum also showed reduced vasodilation of the brachial artery in response to methacholine.[72]

Nicotine Impairs Endothelium-Independent Vasodilation

Most human and animal studies suggest that cigarette smoke, e-cig or nicotine exposure do not alter VSMC's vasodilatory response to NO as SNP-induced vasodilation is generally preserved.[71–73] When subjected to increasing doses of sublingual nitroglycerin, however, smokers exhibited significantly lower dose-response curve to nitroglycerin-induced brachial artery dilatation compared to matched non-smoking controls.[74] This study suggests that smokers may suffer reduced sensitivity to NO-induced endothelium-independent vasodilation.

Nicotine may also diminish endothelium-independent vasodilation via interaction with ATP-sensitive K^+ channels.[75] These channels are ubiquitously expressed on VSMC and upon activation, the outflow of K^+ results in hyperpolarization of the membrane and subsequent

closure of voltage gated Ca^{2+} channels, leading to decreased intracellular Ca^{2+} and VSMC relaxation. In a hamster cheek pouch arteriole reactivity study, both acute and chronic nicotine treatment resulted in significantly reduced vasodilatory response to ATP-sensitive K^+ channel activators, and this effect is likely mediated by nicotine-induced superoxide anion production as treatment with superoxide dismutase attenuated the effects of nicotine.[75]

Nicotine has also been shown to enhance VSMC's vasoconstrictive response to α1 adrenoceptor agonist. Aortas isolated from mice exposed to cigarette smoke or e-cig for 8 months exhibited enhanced response to phenylephrine, indicating increased α1-adrenergic receptor activation on VSMC.[71] In human skin vasculature, acute nicotine treatment has been shown to amplify norepinephrine (NE)-induced vasoconstriction.[76] This enhanced constrictor response is likely specific to the NE signaling pathway, as nicotine treatment in rats selectively increased bone vascular constriction to NE, but not arginine vasopressin.[77]

Nicotine Induces Neurogenic Vascular Relaxation

Nicotine has been shown to induce neurogenic vascular relaxation in multiple vascular beds.[78–80] Neurogenic relaxation of cerebral arteries is an important mechanism of maintaining adequate blood flow to the brain, serving as a protective mechanism to meet O_2 demand in an acutely stressful situation. Stimulation of nAChR located on perivascular sympathetic nerves by nicotine causes NE release from nerve terminals in cerebral arteries, which subsequently induces NO production in the neighboring cholinergic-nitrergic nerves via β_2-adrenergic receptors, leading to nitrergic dilations of cerebral arteries.[81,82] The α3β2- and α7-nAChR expressed by perivascular sympathetic nerves contribute to nicotine-induced nitrergic neurogenic vasodilation.[81,82] It is important to note, however, that chronic exposure to nicotine promotes oxidative stress and endothelial dysfunction, eventually leading to hypoperfusion of the cerebral arteries.[49,83]

Nicotine and Vascular Remodeling

In addition to altered vasoreactivity, nicotine has been shown to impact survival, proliferation, migration, as well as matrix production in both EC and VSMC, leading to vascular remodeling (Table 1 and Figure 3).

Nicotine and EC Remodeling

Nicotine at concentrations similar to those found in human plasma after smoking promotes angiogenesis in a variety of models,[84,85] and its role in diseases involving pathological angiogenesis has been reviewed in depth.[86–88] Nicotine's proangiogenic effects have been shown to be partly mediated by the α7-nAChR through vascular endothelial growth factor (VEGF), phosphatidylinositol 3-kinase (PI3K) and MAPK signaling pathways.[84] Furthermore, the α7-nAChR agonist 3-(2, 4)-dimethoxybenzylidene anabaseine (DMXB) mimics nicotine's proangiogenic effects.[84] Nicotine increases DNA synthesis and cell proliferation in EC *in vitro*.[85,89–91] Acute nicotine exposure also induces EC migration and the formation of capillary-like structures *in vitro* in a manner similar to that produced by common angiogenic factors,[91] and these effects are attenuated by α7-nAChR antagonism.[90] Furthermore, calf aortic EC displayed cytoskeletal reorganization of actin filaments and

vimentin after stimulation with nicotine, which was shown to be mediated by increased EC release of the homodimer platelet-derived growth factor (PDGF) BB.[92] In human coronary artery EC treated with proapoptotic factors, nicotine exposure reduced the number of apoptotic cells as compared to controls, indicating that nicotine has antiapoptotic activity.[93] In addition, treatment with the selective α7-nAChR agonist, PNU282987, decreased HUVEC apoptosis in response to radiation exposure.[94] Furthermore, no morphological changes consistent with cytotoxicity are observed in EC after exposure to nicotine at concentrations similar to those seen in habitual smokers.[91]

The aforementioned proangiogenic effects *in vitro* and *in vivo* were observed following acute exposures to nicotine. In a murine hindlimb ischemia model, short-term exposure to nicotine (2 weeks in drinking water starting at the time of ischemia surgery) promoted vascular sprouting consistent with the previous findings, however, prior exposure to nicotine for 16 weeks (before the surgery) abolished the effects of nicotine to increase capillary density in the ischemic hindlimb.[95] It should be noted that prior exposure to nicotine for 8 weeks did not impact the proangiogenic effect of nicotine, further indicating that angiogenic blunting is due to prolonged exposure. In addition, capillary sprouting was decreased in aortic segments isolated from mice exposed to nicotine in their drinking water for 52 weeks compared to those from vehicle treated control mice.[95] *In vitro*, chronic nicotine exposure for 2 weeks led to decreased cell migration and tube formation.[96] Interestingly, chronic nicotine exposure still resulted in decreased EC apoptosis.[96] The effects of chronic exposure to nicotine were accompanied by attenuation of nicotine-induced VEGF release.[95] Finally, the activation of α9-nAChR has been shown to be anti-proliferative in EC and opposes the action of α7-nAChR.[26]

The effects of nicotine on EC are likely dose dependent, as EC exposed to nicotine concentrations higher than those seen in habitual smokers ($>10^{-6}$ M) do not exhibit changes in proliferation and instead display increased release of lactate dehydrogenase and morphological changes consistent with cytotoxicity.[91] Similar dose dependency has also been demonstrated *in vivo* in a murine hindlimb ischemia model.[85] Taken together, the effects of nicotine on EC remodeling and angiogenesis vary depending on both the dosage and length of exposure. Thus, further studies are needed to better elucidate the chronic effects of nicotine on EC in habitual users of inhaled nicotine products.

Nicotine and VSMC Remodeling

VSMC reprogramming and dysfunction in response to external stress play important roles in the pathogenesis of vascular diseases.[97,98] Acute nicotine exposure at concentrations similar to levels in habitual smokers increases DNA synthesis, promotes proliferation, and protects against apoptosis in VSMC.[99–103] Cotinine, an active metabolite of nicotine, is an even greater inducer of DNA synthesis.[99] Nicotine's mitogenic effect on VSMC has been shown to be mediated by basic fibroblast growth factor, transforming growth factor (TGF)-β and autocrine PDGF signaling.[101,102,104] In addition, nicotine induces reorganization of cytoskeletal structures in VSMC, including changes in α-actin, vimentin, and β-tubulin.[102,105] In response to PKC activation, both nicotine and cigarette smoke extract induce actin cytoskeletal remodeling in the form of podosomes,[106] a hallmark of invasive cells.[107] The

above cytoskeletal changes are important in nicotine-induced VSMC migration, which has been shown to be at least partially mediated by the α7-nAChR;[105,106] in addition, myosin light chain kinase,[105,108] MAPK activation[109,110] and PDGF signaling[102] have also been implicated. VSMC proliferation and migration has also been shown to be facilitated by nicotine-induced hypomethylation of microRNA (miR)-200b gene promoter, which results in increased miR-200b expression.[108] The increased miR-200b leads to reduced RhoGDIA (Rho specific guanine nucleotide dissociation inhibitor A), increased Rho GTPase activity, and consequently changes in cytoskeletal protein expression involved in VSMC proliferation and migration.[108] Finally, aortic VSMC from rats exposed to nicotine for 28 days exhibited elevated expression of thrombospondin-1, TGF-β1 and plasminogen activator inhibitor-1, all of which are makers of neointima formation.[111]

It should be noted that, similar to nicotine's effects on EC, nicotine induced VSMC remodeling also exhibits dose dependency. The optimal changes are observed at nicotine concentrations similar to the plasma levels in habitual smokers, whereas higher levels ($\geq 10^{-4}$ M) result in reduced VSMC viability.[99,101]

Nicotine and Vascular Matrix Remodeling

In addition to affecting the major cell types of vessels, nicotine has been shown to elicit changes to the vascular extracellular matrix (ECM).[112–114] Aortas harvested from mice exposed to nicotine for 4 weeks via osmotic pumps demonstrated significant collagen and fibronectin accumulation coupled with increased elastin fragmentation.[112] Increases in collagen and fibronectin are indicative of fibrogenesis, and nicotine has been shown to induce fibrosis in multiple organ systems.[115] Furthermore, both cigarette smoke extract and nicotine increased primary rat cardiac fibroblast (CF) proliferation and collagen synthesis, which was inhibited by mecamylamine (nonselective nAChR antagonist), α-bungarotoxin (selective α7-nAChR antagonist) and knockdown of α7-nAChR with siRNA.[116] Similarly, *in vitro* exposure to nicotine increased production of collagen type I and III in CF isolated from neonatal rats, which was attenuated by α-bungarotoxin.[117] Another mechanism by which nicotine can impact the ECM is through increased matrix metalloproteinase (MMP) production by EC and VSMC.[112,113,118] The balance between MMP and tissue inhibitors of metalloproteinase is important for vascular integrity, and its disturbance in vascular remodeling has been extensively reviewed.[119,120] In human retinal microvascular EC, acute exposure to nicotine (100 nM) significantly increased expression of the gelatinases, MMP-2 and MMP-9, and this effect was mediated by α7-nAChR.[118] Increased expression and activity of MMP-2/9 were also observed in VSMC acutely exposed to 150 nM nicotine.[113] Similar increases in gelatinase activity were observed in aortic homogenates harvested from rats acutely and chronically exposed to nicotine at concentrations similar to those found in humans after smoking one and three cigarettes.[113] In addition to increased gene and protein expression of MMP-2/9, a recent study demonstrated that aortic segments harvested from mice chronically exposed to nicotine exhibited increased elastolytic activity accompanied by elastin thinning and fragmentation, indicative of increased susceptibility to aortic aneurysm.[114]

The mechanisms through which nicotine elicits changes in vascular matrix are not completely understood. One study investigated the involvement of an oxidized nicotinamide adenine dinucleotide (NAD^+)-dependent protein deacetylase, sirtuin-1 (SIRT1), as SIRT1 inhibition has been linked to cigarette smoking-induced arterial stiffness.[112] In both human VSMC and murine aortas, nicotine exposure reduced the protein level and activity of SIRT1. Importantly, SIRT1 overexpression in mice attenuated nicotine-induced vascular remodeling, leading to reduced accumulation of collagen and fibronectin, reduced elastin fragmentation and MMP-2 expression. This study further showed that the downregulation of SIRT1 by nicotine was due to reduced SIRT1 stability, as nicotine-induced generation of peroxynitrite ($ONOO^-$) irreversibly uncoupled zinc from SIRT1. Furthermore, SIRT1 inactivation by $ONOO^-$ activated the YAP (Yes-associated protein)-mediated abnormal ECM remodeling.[112]

One clinical manifestation of nicotine-induced matrix remodeling is arterial stiffness, which can be measured by pulse wave velocity (PWV), or the rate at which pressure waves move down the vessel. PWV has been established as a highly reliable prognostic parameter for cardiovascular morbidity and mortality in a variety of adult populations including older adults, patients with hypertension, diabetes, and end-stage renal disease. Mice exposed to nicotine via osmotic pumps for 4 weeks exhibited significantly increased PWV and stiffness in both abdominal aorta and carotid artery.[112] Long term (8-month) cigarette smoke and e-cig exposure in mice have also been shown to increase PWV.[71] Importantly, recent studies in healthy human volunteers showed that vaping of e-liquid containing nicotine, but not e-liquid without nicotine, induced significant increases in PWV and arterial stiffness.[121,122]

Conclusion and Future Directions

The impact of nicotine exposure on the cardiovascular system is complex, from its modulation of autonomic function to its direct effects on individual cell types in the vasculature. Although the initial presentations of nicotine-induced vascular dysfunction may be insidious (changes in vasoreactivity and vascular remodeling as discussed in this review), these changes contribute to the pathogenesis of serious medical conditions including atherosclerosis, abdominal aortic aneurysm, coronary artery disease and myocardial infarction.[123–125]

Nicotine has been studied for over 50 years, however, our understanding of the impact of nicotine on cardiovascular function and its associated mechanisms is far from complete. In terms of nicotine-induced vascular dysfunction, most studies have implicated the involvement of α7-nAChR; however, investigation into other nAChR that could play important roles in the vascular effects of nicotine is needed. For example, it has been shown that α1-nAChR mediates nicotine-induced atherogenic response in EC.[126] In the setting of nicotine-induced carcinogenesis, α3-containing nAChR have been shown to inhibit programmed cell death and promote cell survival, whereas α9-nAChR regulate cell detachment and migration.[127] Identification of the specific nAChR subtypes responsible for the harmful effects of nicotine could help develop targeted therapies for nicotine-associated vascular diseases.

Another important and interesting question remained to be answered is whether and how chronic nicotine exposure alters the expression and/or activity of nAChR in the cardiovascular system. Chronic nicotine exposure has been shown to result in numerous neuroadaptations, including the upregulation of particular nAChR subtypes associated with long-term desensitization of the receptors.[128,129] In addition, inactivation of nAChR by ROS[130] associated with cigarette smoke or nicotine exposure could lead to upregulation of nAChR as well. Upregulation of ligand binding to nAChRs is observed in the brains of both smokers and animals chronically exposed to nicotine, with functional upregulation of α4β2 and α7 subtypes of nAChR.[131] In a recent study, inhalation of e-cig vapor for six months in mice was shown to increase α7-nAChR expression in brain regions involved in nicotine addiction.[132] Future research is needed to understand changes in nAChR in the cardiovascular system in smokers and e-cig users and their impact on cardiovascular function.

The e-cig epidemic, especially among young adults and youth, has become a significant public health issue. This review focused specifically on nicotine's effect on the cardiovascular system; however, e-cig contain additional constituents including humectants (e.g. propylene glycol and vegetable glycerine) and flavorings. While most e-cig additives are "generally recognized as safe" for oral ingestion by the Food and Drug Administration, the safety of direct inhalation of these chemicals is not fully understood. For example, cinnamaldehyde, a compontent of cinnamon flavorings, has been shown to impair respiratory innate immune cell function through alterations of proinflammatory cytokines and the prodcution of ROS.[133,134] In addition, carbonyl compounds (formaldehyde, acetaldehyde and acrolein), free radicals and various metals have been detected in e-cig emissions as the result of thermal decomposition of e-cig liquid and the heating of the metal coils in the device.[135–137] These harmful chemicals cause oxidative stress and inflammation and may produce additive and synergistic effects with nicotine on the vasculature.[138] Finally, newer generation of e-cig devices such as JUUL uses proprietary nicotine salts rather than alkalinized nicotine, producing more efficient nicotine delivery and achieving plasma-nicotine levels as high as or higher than traditional cigarettes.[139] The long-term health consequences of e-cig inhalation on the cardiovascular system are still largely unknown and warrant further investigation.

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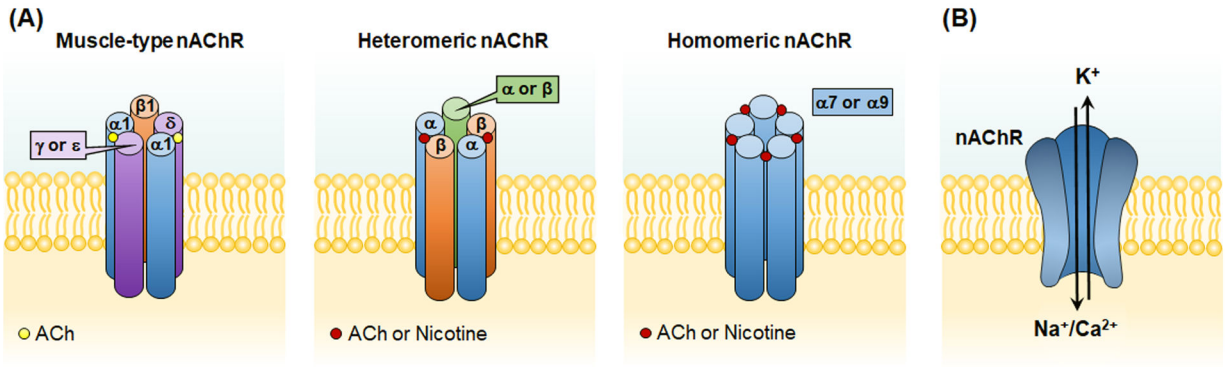

Figure 1. Nicotinic Acetylcholine Receptors (nAChR).

(A) The nAChR are divided into three major subtypes: muscle-type, heteromeric and homomeric nAChR. The muscle-type nAChR consists of $(\alpha 1)_2\beta 1\delta\varepsilon$ (adult) or $(\alpha 1)_2\beta 1\delta\gamma$ (fetal) and is located at the neuromuscular junction, and this receptor is poorly responsive to nicotine. The heteromeric nAChR are composed of five subunits in various combinations of α and β subunits, and the homomeric nAChR are composed of five α subunits (α7 or α9). Ligands (ACh or Nicotine) bind to the α subunits at the subunit interface. (B) The nAChR are ligand-gated cation channels. Upon binding to endogenous ligand ACh or nicotine, the central pore of nAChR opens to allow the flow of cations (Na^+ and Ca^{2+} into and K^+ out of the cells). ACh, acetylcholine.

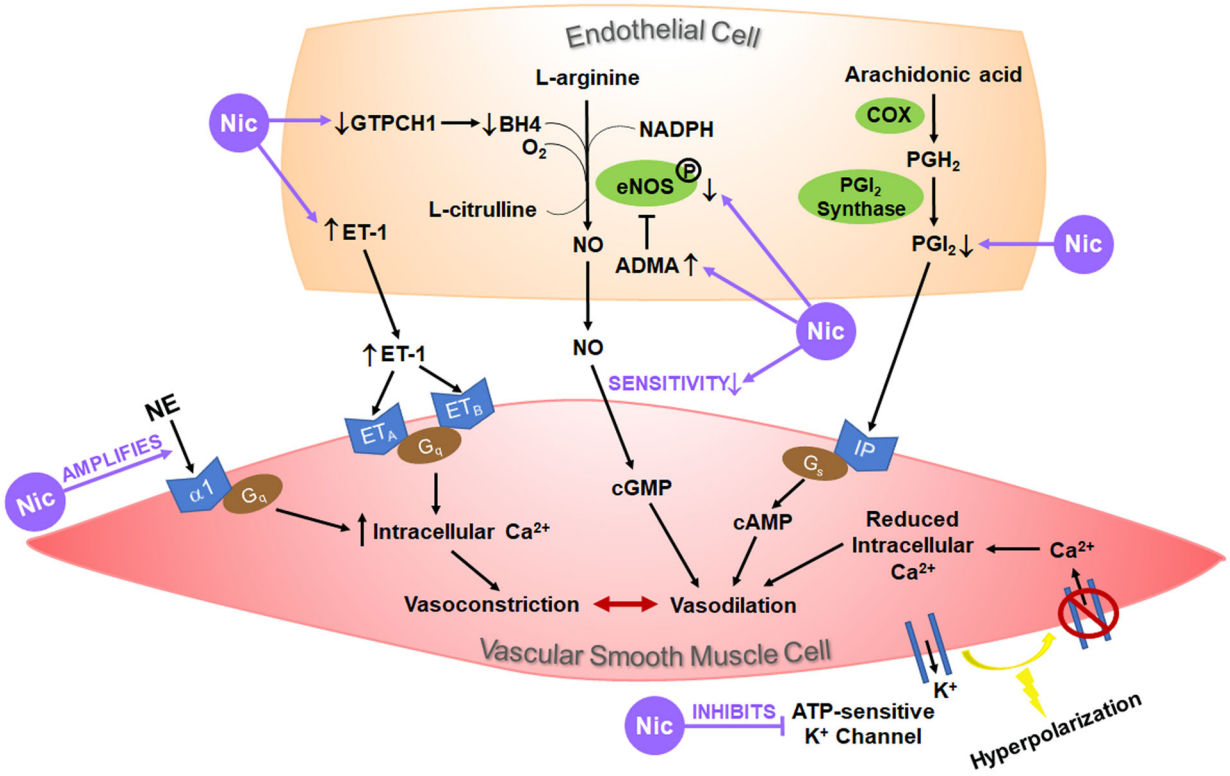

Figure 2. Nicotine alters vascular reactivity through endothelium-dependent and endothelium-independent mechanisms.

Activation of the endothelium elicits a multitude of pathways with the production of vasoactive substances that travel to the underlying vascular smooth muscle cells (VSMC) to induce vasoconstriction or vasodilation. Nicotine (Nic) has been shown to upregulate the production or release of the vasoconstrictor endothelin-1 (ET-1) and inhibit endothelial production of the vasodilators nitric oxide (NO) and prostacyclin (PGI_2). In VSMC, nicotine promotes VSMC contraction by amplifying its response to norepinephrine (NE), by upregulating ET-1 receptor (ET_A and/or ET_B) expression, and/or by inhibiting ATP-sensitive K^+ channels. Up- and down-regulation by nicotine are indicated by ↑ and ↓, respectively. ADMA, asymmetric dimethylarginine (the endogenous eNOS inhibitor); BH4, tetrahydrobiopterin (an essential cofactor for eNOS); COX, cyclooxygenase; eNOS, endothelial nitric oxide synthase; GTPCH1, GTP cyclohydrolase 1 (the rate-limiting enzyme for BH4 production); PGH_2, prostaglandin H_2.

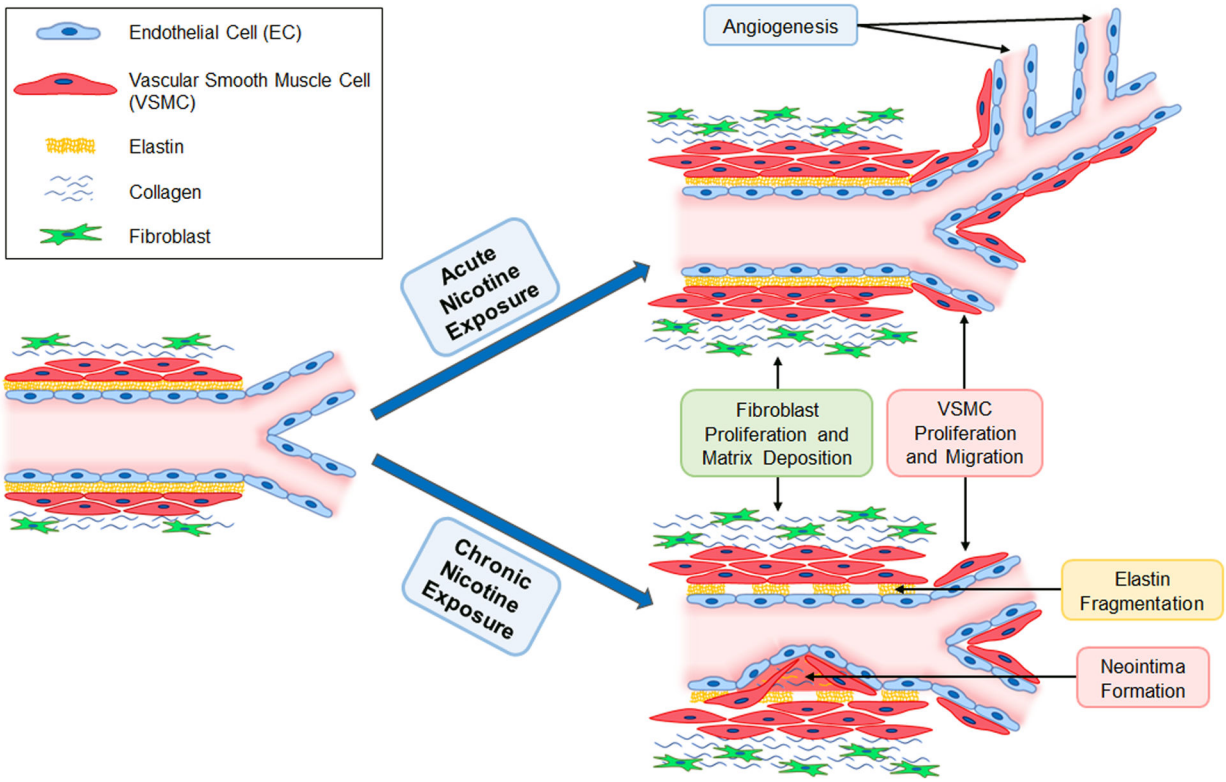

Figure 3. Nicotine and Vascular Remodeling.

Acute nicotine exposure at concentrations similar to those found in human smokers promotes angiogenesis, whereas chronic exposure to nicotine blunts its proangiogenic response. Both acute and chronic nicotine exposure lead to fibroblast proliferation, extracellular matrix deposition, and vascular smooth muscle cell (VSMC) proliferation and migration. In addition, chronic nicotine exposure is associated with elastin fragmentation and neointima formation.

Table 1.

Summary of Nicotine's Effects on Vascular Remodeling.

Vascular Component	Nicotine Exposure		Nicotine's Effects
EC	Acute	*in vitro* (≤ 96 h)	Increased DNA synthesis[89] and cell proliferation;[85,89,91] increased PDGF BB release;[92] increased VEGF * and activation of VEGF receptor 2;[84] inhibition of apoptosis;[85,93] cytoskeletal reorganization;[92] increased cell migration and tube formation *[84,85,90,91,95]
		in vivo (≤ 3 weeks)	Increased vascular growth/capillary density *[84,85]
	Chronic	*in vitro* (> 96 h)	Decreased cell migration and tube formation;[95,96] inhibition of apoptosis[96]
		in vivo (> 3 weeks)	Blunting of nicotine's acute angiogenic effect[95]
VSMC	Acute	*in vitro* (≤96 h)	Increased DNA synthesis *[99–104] and cell proliferation; *[99,101,108] increased PDGF release;[102] inhibition of apoptosis; *[100] cytoskeletal reorganization and podosome structure alterations; *[102,105,106] increased cell migration *[105,106,108,109]
		in vivo (≤ 3 weeks)	None reported
	Chronic	*in vitro* (> 96 h)	None reported
		in vivo (> 3 weeks)	Increased median thickness of the thoracic arteries;[108] morphological changes and neointima formation;[111] increased mitoses[111]
ECM	Acute	*in vitro* (≤ 96 h)	Increased collagen production;[112,116] increased MMP-2/9[113,118]
		in vivo (≤ 3 weeks)	Increased gelatinase activity[113]
	Chronic	*in vitro* (> 96 h)	Increased collagen production *[117]
		in vivo (> 3 weeks)	Increased MMP-2/9; *[112–114,118] increased gelatinase activity;[113] increased elastolytic activity;[114] collagen and fibronectin accumulation;[112] elastin thinning and fragmentation[112,114]

All observations summarized here were at nicotine concentrations $\leq 10^{-6}$ M.

* Effect has been shown to be mediated, at least in part, by α7-nAChR.