Nicotine and Vascular Dysfunction: A Comprehensive Review

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Introduction

- Cigarette smoking is the single most important risk factor for the development of cardiovascular diseases (CVD).
- Although increased public awareness of the harms of cigarette smoking has successfully led to its decline, the use of electronic cigarettes (e-cig) has increased significantly in recent years due to the perception that these products are safe.
- Nicotine is the addictive component of all tobacco products; however, the role of nicotine in the development of CVD is incompletely understood.
- Here, we summarizes our current knowledge of the expression and function of the nicotinic acetylcholine receptors (nAChR) and the impact of nicotine exposure on cardiovascular health, with a focus on nicotine-induced vascular dysfunction and remodeling.

Receptors and Hemodynamics

- Nicotine's effect on the cardiovascular system is conferred through its ability to bind endogenous nAChR in place of the endogenous agonist ACh.
- In terms of nicotine-induced vascular dysfunction, most studies have implicated the involvement of α7-nAChR, which exhibits high permeability to calcium.
- Treatment with nicotine or a nicotinic agonist induces a brief but pronounced decrease in HR, followed by significant increases in HR and BP.
- 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.

Nicotine Induces Vasoconstriction

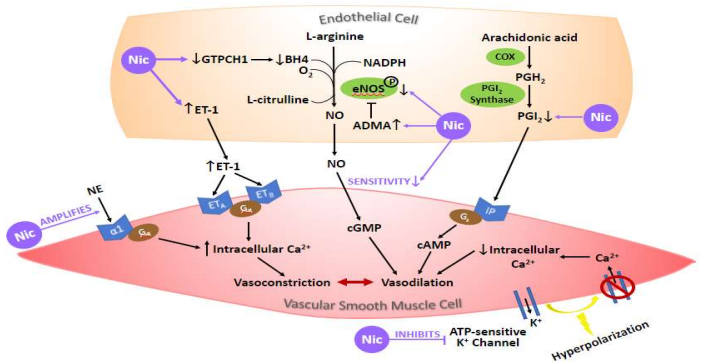

Figure 1. Nicotine induces endothelium-dependent and endothelium-independent vasoconstriction. ADMA, asymmetric dimethylarginine; BH4, tetrahydrobiopterin; COX, cyclooxygenase; ET-1, endothelin-1; eNOS, endothelial nitric oxide synthase; GTPCH1, GTP cyclohydrolase 1; NE, norepinephrine; Nic, nicotine; NO, nitric oxide; PGH_2, Prostaglandin H_2; PGI_2, prostacyclin.

Nicotine and Vascular Remodeling

Vascular Component	Nicotine Exposure	Effects
Endothelial Cells	Acute (in vitro: ≤48 h; murine in vivo: ≤ 3 weeks)	Induces DNA synthesis
		Increases cell proliferation
		Increases PDGF BB release
		Increases expression and release of VEGF* and activation of VEGF Receptor 2
		Induces cytoskeletal reorganization
		Increases cell migration*, tube Formation*, and sprouting
		Decreases apoptosis
	Chronic (in vitro: ≥ 2 weeks; murine in vivo: ≥16 weeks)	Decreases cell migration, tube formation, and sprouting
		Downregulates α7-nAChR mRNA expression
		Decreases apoptosis
Vascular Smooth Muscle Cells	Acute (in vitro: ≤96 h)	Induces DNA synthesis*
		Increases cell proliferation
		Increases PDGF release
		Induces cytoskeletal reorganization*, alters podosome structure*
		Increases cell migration*
		Decreases apoptosis*
	Chronic (in vivo: ≥ 4 weeks)	Induces morphological changes
		Increased mitoses
Extracellular Matrix	Acute (in vitro: ≤48 h, in vivo: less than 2 h)	Increased activity of MMP-2/9
		Increased gelatinase activity
	Chronic (in vivo ≥ 2 weeks)	Increased activity of MMP-2/9
		Increased gelatinase activity
		Increased collagen and fibronectin accumulation
		Elastin thinning and fragmentation
		Increased elastolytic activity

Table 1. Summary of Nicotine's Effect on Vascular Remodeling. MMP, matrix metalloproteinase. All observations summarized here were at nicotine concentrations ≤10^{-6} M. *Effect has been shown to be mediated, at least in part, by α7-nAChR.

Conclusions

- In terms of vascular reactivity, nicotine exerts primarily vasoconstrictive effects through endothelium-dependent and/or endothelium-independent mechanisms.
- Nicotine has been shown to impact survival, proliferation, migration, as well as matrix production in both EC and VSMC, leading to vascular remodeling.
- Identification of the specific nAChR subtypes responsible for the harmful effects of nicotine could help develop targeted therapies for nicotine-associated vascular diseases.
- With the increasing popularity of e-cig, especially among young adults and youth, more studies are needed to investigate the long-term health effects of e-cig inhalation on the cardiovascular system.

Ongoing Research

1) Andrew Zhen Li (David Lefer's lab): Thoracic aortas of air- and nicotine- exposed mice

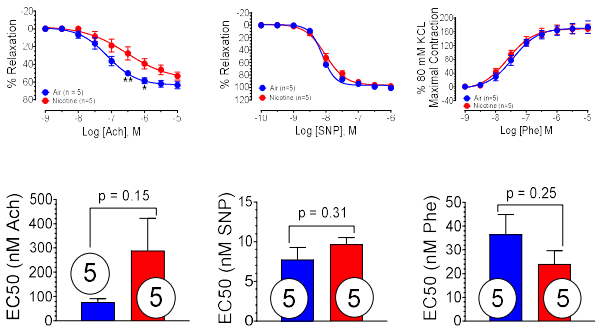

Figure 2. Effects of Chronic Nicotine Inhalation on Vascular Reactivity. Ach, acetylcholine; Phe, phenylephrine; SNP, sodium nitroprusside;

2) LSUHSC Department of Physiology is currently focusing on how nicotine alters eNOS/NO pathway as this pathway has shown to be a key player in nicotine's effects on vasculature.