EDITORIAL COMMENT

The Janus Face of Nicotinic Angiogenesis*

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In 1559, Jean Nicot, a French ambassador in Lisbon, sailed to Portugal to negotiate the marriage of Princess Marguerite de Valois to King Sebastian of Portugal. When he returned, he brought tobacco plants which had an immediate success, and was called nicotine: the term later came to refer only to the active ingredient of the plant, which was identified as an alkaloid. Nicotine is a major component of the particulate phase of cigarette smoke, and it is also the contributing agent of tobacco dependency. Its metabolites are highly carcinogenic (1) as shown by several prospective studies. Today, the tobacco epidemic kills more than 4 million people around the world annually and projected estimates are dim: 10 million deaths a year worldwide by the year 2015. Besides cancer, tobacco smoking strongly predisposes the individual to clinical atherosclerotic syndromes. Smoking impairs endothelium-dependent vasodilation, increases leukocyte count and inflammatory markers, enhances the local recruitment of leukocytes, and worsens lipid profile (2).

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It appears that everything went wrong with Nicot’s decision. However, not tobacco smoking but nicotine itself has the potential to be a valuable pharmaceutical agent: it specifically binds to the cholinergic site on cationic ion channels receptors (nAChR) in many tissues, including the endothelium. This action has been shown to confer some protection against Parkinson’s disease, Alzheimer’s disease, ulcerative colitis, and sleep apnea (3). Surprisingly, some novel and positive effects of nicotine paradoxically involve the cardiovascular system. It has been shown that nicotine stimulates endothelial-cell proliferation via nAChR (4) and increases expression of endothelial nitric-oxide synthase (5). In 2001, Heeschen et al. (6) found that nicotine reduces apoptosis and increases proliferation of endothelial cells; expands capillary networks; and enhances the angiogenic response to inflammation, ischemia, atherosclerosis, and neoplasia. They also demonstrated that these proangiogenic effects are mediated by non-neuronal nAChR (6) and subsequently showed that the cholinergic angiogenic pathways are dependent on vascular endothelial growth factor (VEGF) and the phosphatidylinositol 3-kinase and mitogen-activated protein kinase pathways (7). This evidence suggested that nicotine may even have healing properties in the cardiovascular system revealing possible therapeutic implications. In this issue of the Journal, a new important paper by Heeschen et al. (8) demonstrates that endothelial progenitor cells (EPCs) participate in nicotine-mediated angiogenesis. Endothelial progenitor cells are marrow-derived cells involved in post-natal vasculogenesis and maintenance of endothelial homeostasis. Reduction of the EPC pool is associated with atherosclerotic diseases (9), and the amount of EPCs in peripheral blood reflects cardiovascular health and predicts future events (10,11). The authors show that systemic nicotine administration stimulates angiogenesis after femoral artery ligation with concomitant increase in plasma levels of VEGF and c-kit ligand, which sustained bone marrow mobilization of CD34+ Flk-1+ EPCs. Using parabiotic mouse pairs, they show that EPC incorporation into the nascent vasculature is potently enhanced in nicotine-treated animals versus controls. The parabiosis model represents an ideal assay to track the fate of EPCs in vivo, because it explores entirely endogenous processes and avoids biases of bone marrow transplantation. This study convincingly demonstrates that ischemia-induced angiogenesis stimulated by nicotine is mediated by EPC mobilization and recruitment; it also provides mechanistic insights showing that in vitro exposure to nicotine stimulates EPC growth and recruitment; it also provides mechanistic insights showing that in vitro exposure to nicotine stimulates EPC growth and recruitment.

However, there remain unanswered questions about the effects of nicotine on EPCs that will need further consideration. First, the authors show that systemic nicotine administration in stimulating ischemic angiogenesis. Nonetheless, local nicotine itself promoted angiogenesis without reaching the systemic circulation. It is conceivable that nicotine locally induces angiogenic factors, which, in turn, stimulate vessel growth by activation of resident endothelial cells; alternatively, the recruitment of circulating EPCs cannot be excluded. Unfortunately, we do not know whether EPC mobilization takes place also after local nicotine injection.

Second, an important observation is that nicotine did not stimulate EPC mobilization in the absence of acute ischemia. One logical explanation is that tissue nAChR undergoes hypoxic up-regulation during ischemia, and its subsequent activation by nicotine promotes the release of one or more mobilizing agents, such as VEGF or stem-cell-derived factor-1, both of which are regulated by hypoxia-sensing systems. Indeed, the authors have previously demonstrated that nicotine induces the expression of VEGF (7). Therefore, we should note that, to stimulate angiogenesis, the nicotinic pathway will necessitate the presence of acute ischemia, possibly limiting its therapeutic effects on chronic stable atherosclerotic diseases.

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Third, surprisingly, in vitro nicotine stimulated EPC growth at a $10^{-7}$ to $10^{-6}$ molar concentration, which is very close to the concentrations at which nicotine induces cytotoxicity ($10^{-6}$ mol), whereas inhibition of hematopoiesis has been shown with higher concentrations ($10^{-5}$ to $10^{-4}$ mol) (13).

Notwithstanding these limitations, the findings reported by Heeschen et al. (8) represent an important preliminary proposal to stimulate vasculogenesis in a clinical setting of ischemia. A practical consequence of this has been shown: nicotine was able to accelerate wound healing in control and genetically diabetic mice (14). From a clinical point of view, the use of nicotine can be hypothesized in those conditions associated with decreased number of EPCs. A case for this is diabetes mellitus, which is characterized by a decreased number and function of EPCs (9,15).

Another potentially beneficial effect of nicotine is its ability to induce VEGF expression: this may be relevant because it has been suggested that progressive down-regulation of VEGF is a pivotal event in the development of diabetic cardiomyopathy (16).

Obviously, the therapeutic translation of nicotine use in the clinical setting raises relevant questions. The major tobacco-related diseases (cancer, atherosclerosis, and macular degeneration) have a proangiogenic stage, which might be mediated by nicotine through EPC mobilization and recruitment. Indeed, EPCs may be involved also in harmful angiogenesis, such as in cancer growth (17), plaque neovascularization (18), and proliferative retinopathy (19). However, besides special conditions in which smoking may increase EPCs (20,21), we must recognize that chronic smokers themselves have a profound EPC impairment and reduction, and that smoking cessation increases EPCs independently from the use of nicotine patches (22,23). Therefore, we are compelled to keep the effects of nicotine totally distinct from those of tobacco smoking. Nonetheless, with nicotine and EPCs, we are facing an angiogenic paradox. Let us imagine designing a trial to test a systemically administered nAChR agonist for diabetic ischemic foot ulcers; necessarily, we will be puzzled by the potential harmful effects of improper cholinergic angiogenesis on atherosclerotic plaque growth and retinal neovascularization in those patients. Therefore, local nicotine administration may be preferred to avoid side effects at distant sites. Another possible limitation to nicotine use applied to the complex human phenotype: the PI-3K/Akt pathway, critical for both EPC mobilization and cholinergic angiogenesis (7,24), is dysfunctional in many conditions of increased cardiovascular risk, including diabetes (25). Furthermore, if nicotinic angiogenesis requires EPCs, the severe impairment of the endogenous EPC pool in diabetes and other conditions may limit significantly the actual therapeutic potentialities of nicotinic agonists in the clinical setting. Finally, we have recently shown alterations in hypoxia-sensing systems that not only prevent EPC mobilization in diabetes (26) but they may also inhibit nicotinic angiogenesis.

In conclusion, we are learning more about extraordinary favorable actions of nicotine, but further efforts are needed to unravel the implications of nicotinic angiogenesis in relation to EPC biology, before its clinical use. Where? (systemic vs. local), when? (patient selection), and how much? (the minimal efficacious dose) remain open questions.

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