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Nicotine: the link between cigarette smoking and the progression of renal injury?

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Jaimes, Edgar A., Run-Xia Tian, and Leopoldo Raij. Nicotine: the link between cigarette smoking and the progression of renal injury? Am J Physiol Heart Circ Physiol 292: H76–H82, 2007. First published August 18, 2006; doi:10.1152/ajpheart.00693.2006.—Cigarette smoke (CS) is the most important source of preventable morbidity and mortality in the United States. Recent clinical studies have suggested that, in addition to being a major cardiovascular risk factor, CS promotes the progression of kidney disease. The mechanisms by which CS promotes the progression of chronic kidney disease have not been elucidated. Here we demonstrate for the first time that human mesangial cells (MCs) are endowed with the nicotinic ACh receptors (nAChRs) α4, α5, α7, β2, β3, and β4. Studies performed in other cell types have shown that these nAChRs are ionotropic receptors that function as agonist-regulated Ca2+ channels. Nicotine induced MC proliferation in a dose-dependent manner. At 10−7 M, a concentration found in the plasma of active smokers, nicotine induced MC proliferation (control, 1,328 ± 50 vs. nicotine, 2,761 ± 90 counts/minute (cpm); *P < 0.05) and increased the synthesis of fibronectin (50%), a critical matrix component involved in the progression of chronic kidney disease. We and others have shown that, in response to PKC activation, MC synthesize reactive oxygen species (ROS) via NADPH oxidase. In the current studies we demonstrate that PKC inhibition as well as diphenylethenedionium and apocynin, two inhibitors of NADPH oxidase, prevented the effects of nicotine on MC proliferation and fibronectin production, hence establishing ROS as second messengers of nicotine. Furthermore, nicotine increased the production of ROS as assessed by 2,7′-dichlorofluorescein diacetate fluorescence (control, 184.4 ± 26 vs. nicotine, 281.5 ± 26 arbitrary fluorescence units (AFU); *n = 5 experiments, P < 0.05). These studies unveil previously unrecognized mechanisms that induce nicotine, a component of CS, as an agent that may accelerate and promote the progression of kidney disease.

glomerular mesangium; extracellular matrix; cell proliferation; reactive oxygen species

Cigarette smoking has been identified as the most important source of preventable morbidity and mortality in the United States (4, 27). In addition to being a risk factor for atherosclerosis and cancer, recent epidemiologic studies suggest that cigarette smoking increases the risk for progressive chronic kidney disease and accelerates the rate of progression of renal failure among patients with diabetes (31, 41, 45) and hypertension (3, 16, 28, 37). Clinical studies have indicated a correlation of smoking and the development of proteinuria in patients with polycystic kidney disease (5), as well a deterioration of renal function in patients with lupus nephritis (51), polycystic kidney disease, and glomerulonephritis (32, 46).

The mechanisms by which cigarette smoking accelerates the progression of chronic kidney disease have not been well studied. Studies from the laboratory of Jaimes and colleagues (17, 36) have demonstrated that stable compounds present in cigarette smoke produce endothelial dysfunction by increasing the vascular production of reactive oxygen species (ROS). Recent studies utilizing ambulatory blood pressure measurements have documented that cigarette smoking is associated with transitory increases in blood pressure (25, 29, 35) that have been attributed to direct stimulation of postganglionic sympathetic nerve endings (9) and related to nicotine since they are not observed with nicotine-free cigarettes (1). Nicotine administration leads to transitory elevations in blood pressure accompanied by a decrease in glomerular filtration rate and effective renal plasma flow in nonsmokers (12). In subjects with IgA nephropathy, a glomerular disease that characteristically affects the mesangium, nicotine administration is associated with increased urinary albumin excretion and reductions in glomerular filtration rate (38, 39).

Recent experimental studies (14) have demonstrated that nicotine is a potent stimulus for angiogenesis both in vivo and in vitro via activation of specific nicotinic ACh receptors (nAChRs). These nAChRs are ionotropic receptors that function as agonist-regulated Ca2+ channels and that are expressed by neuronal as well nonneuronal cells, including endothelial and vascular smooth muscle cells (14, 15). Whether nAChRs are expressed in glomerular cells is, however, not known. ROS are important mediators for the growth-related responses of a variety of cytokines and growth factors including ANG II (18), PDGF (47), and transforming growth factor-β (TGF-β) (22, 30). Nicotine has been shown to stimulate the production of ROS in lung and colon epithelial cells (10, 53). Whether ROS mediate the growth-promoting effects of nicotine in mesangial cells is, however, not known.1

The studies reported herein were designed to 1) determine whether mesangial cells possess nAChRs and 2) determine

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whether nicotine through activation of these receptors promotes mesangial cell proliferation and extracellular matrix production via ROS.

**METHODS**

**Mesangial cell culture.** Human mesangial cells were purchased from Cell Systems (Kirkland, WA), grown in CSC-Complete media (Cell Systems) supplemented with 10% fetal calf serum (Cell Systems). Cells were passed by trypsinization when confluent and used between the third and ninth passages.

**Cell proliferation.** [3H]thymidine incorporation was used as an index of cell proliferation as described (18). Briefly, cells were fasted for 72 h in maintenance media (Cell Systems) and stimulated for 24 h with nicotine (10⁻¹⁰ M to 10⁻⁷ M) or PDGF (10 ng/ml). Four hours before being harvested, cells were pulsed with [³H]thymidine (1 μCi/ml). At the end of this incubation period, cells were washed three times with PBS; protein was precipitated with 1 ml TCA 10% for 5 min and solubilized in 1 ml 0.5 N NaOH-0.1% SDS. Duplicate aliquots (0.5 ml) were removed and counted in a liquid scintillation counter and results expressed as counts per minute (cpm) per million cells.

**Western blot analysis.** Western blot analysis was performed as previously described (20, 21). Cells were fasted for 72 h in maintenance media (Cell Systems) and stimulated for 24 h with nicotine (10⁻⁷). Cell homogenates were washed once with PBS and resuspended in 300 μl homogenization buffer [containing (in mM) 50 Tris·HCl (pH 7.6), 100 NaCl, 2 EDTA, 2 EGTA, 1 DTT, and 1 PMSF and 1% Triton X-100] and incubated on ice for 30 min. Thereafter, lysates were centrifuged for 30 min at 10,000 g at 4°C. Supernatants were collected and the protein content was determined by Bio-Rad. Thirty micrograms of protein were separated by SDS-PAGE (6% acrylamide gel) and transferred to a nitrocellulose membrane. Blots were incubated overnight with one of the following antibodies: mouse anti-α₂-nAChR MAbs (Sigma-Aldrich), anti-α₃-nAChR MAbs (Santa Cruz Biotechnology), anti-α₄-nAChR MAbs (Sigma-Aldrich), anti-α₅-nAChR MAbs (Sigma-Aldrich), anti-α₇-nAChR MAbs (Sigma-Aldrich), anti-β₂-nAChR MAbs (Santa Cruz Biotechnology), anti-β₃-nAChR MAbs (Santa Cruz Biotechnology), anti-β₄-nAChR MAbs (Santa Cruz Biotechnology), polyclonal anti-fibronectin antibody (Santa-Aldrich), and polyclonal anti-actin antibody (Santa Cruz Biotechnology). After being washed, the blots were incubated with goat anti-rabbit antibody (Santa Cruz Biotechnology) for 1 h, and the signal was detected by luminol chemiluminescence.

**mRNA isolation and real-time quantitative RT-PCR.** Fibronectin mRNA expression was determined by real-time PCR. Total RNA was isolated by utilizing the RNeasy Mini Kit (Qiagen, Valencia, CA). A 5-μg aliquot of total RNA was used for cDNA synthesis using the Superscript preamplification system (Life Technologies). Primers and probes for fibronectin were designed using Primer Express software (50) and resulted in a proliferative response that was ~50% of that obtained with the potent mitogen PDGF: control, 932 ± 55; nicotine, 1,319 ± 82 (P < 0.05 vs. control); and PDGF, 1,836 ± 160 cpm (n = 3 experiments in duplicate; P < 0.05 vs. control, and P < 0.05 vs. nicotine).

To determine the role of nAChR signaling on the pro-proliferative effects of nicotine, we treated human mesangial cells with nicotine (10⁻⁷ M) with and without the nonspecific nAChR blocker hexamethonium (10⁻⁴ M) (15) or the muscarinic receptor blocker atropine (10⁻⁷ M) (14, 15). As shown in Fig. 3, the nAChR blocker hexamethonium but not the muscarinic receptor blocker blocker atropine prevented the effects of nic-
Nicotinic receptor blockers atropine (10^{-6} M) and dihydroβ-erythroidine (10^{-6} M) prevented the increases in mesangial cell proliferation in response to nicotine, demonstrating that NADPH oxidase-derived ROS are important intracellular signals responsible for nicotine-induced mesangial cell proliferation (Fig. 6). To assess the effects of these inhibitors under basal conditions, human mesangial cells were treated with DPI or apocynin for 24 h, and cell proliferation was assessed by [3H]thymidine incorporation. Treatment with DPI but not with apocynin reduced [3H]thymidine incorporation in unstimulated cells: control, 397 ± 136; DPI, 206 ± 108 (P < 0.05 vs. control); and apocynin 492 ± 172 cpm/million cells (n = 3 experiments). Pretreatment with the cell-permeable superoxide scavenger Tiron (5 mM) (21) prevented the effects of nicotine on mesangial cell proliferation, further suggesting a role for ROS on the growth-promoting effects of nicotine.

Superoxide anion produced as a result of increased NADPH oxidase activity rapidly dismutates to H_{2}O_{2} spontaneously or via superoxide dismutase. As shown in Fig. 6, catalase (800 U/ml) (18), an enzyme that decomposes H_{2}O_{2}, inhibited nicotine-stimulated mesangial cell proliferation, suggesting that H_{2}O_{2} is the main ROS responsible for nicotine-stimulated mesangial cell proliferation. Treatment of unstimulated cells with catalase did not result in significant reductions in mesangial cell proliferation, suggesting that these effects are mediated via nAChR activation. To determine whether in addition to increasing mesangial cell proliferation, nicotine increases extracellular matrix expression, we measured fibronectin protein expression in human glomerular mesangial cells exposed to nicotine (10^{-7} M). As shown in Fig. 5, nicotine induced a significant increase in fibronectin protein expression. To determine whether transcriptional mechanisms were involved, we measured fibronectin gene expression by real-time RT-PCR in human glomerular mesangial cells exposed to nicotine (10^{-7} M) with and without the nicotine receptor blocker hexamethonium (10^{-4} M). Nicotine induced a fivefold increase in fibronectin mRNA expression: control ΔCr, 11.37 ± 2.04 vs. nicotine ΔCr, 8.75 ± 1.25; n = 6 experiments, P < 0.05 that was prevented by the nicotine receptor blocker hexamethonium: ΔCr, 12.19 ± 2.23, n = 3 experiments, P = not significant (NS) vs. control.

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**ROS mediate nicotine-induced mesangial cell proliferation and fibronectin production.** We and others have demonstrated that ROS play a major role as intracellular mediators of growth-related responses to growth factors and cytokines, such as ANG II, PDGF, and TGF-β. To investigate whether NADPH oxidase-derived ROS participate in the growth-promoting effects of nicotine, human mesangial cells were exposed to DPI, a compound that by tightly binding to flavoproteins is an effective inhibitor of flavin-containing oxidases, such as NADPH oxidase (10^{-5} M) (18) or apocynin, a specific NADPH oxidase inhibitor (10^{-4} M) (17) before nicotine. Treatment with DPI or apocynin prevented the increases in mesangial cell proliferation in response to nicotine, demonstrating that NADPH oxidase-derived ROS are important intracellular signals responsible for nicotine-induced mesangial cell proliferation (Fig. 6). To assess the effects of these inhibitors under basal conditions, human mesangial cells were treated with DPI or apocynin for 24 h, and cell proliferation was assessed by [3H]thymidine incorporation. Treatment with DPI but not with apocynin reduced [3H]thymidine incorporation in unstimulated cells: control, 397 ± 136; DPI, 206 ± 108 (P < 0.05 vs. control); and apocynin 492 ± 172 cpm/million cells (n = 3 experiments). Pretreatment with the cell-permeable superoxide scavenger Tiron (5 mM) (21) prevented the effects of nicotine on mesangial cell proliferation, further suggesting a role for ROS on the growth-promoting effects of nicotine.

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Fig. 5. Nicotine increases fibronectin production in human mesangial cells. The effects of nicotine fibronectin production by mesangial cells are prevented by the NADPH oxidase inhibitors diphenyleneiodonium (DPI; $10^{-5}$ M), apocynin ($10^{-4}$ M), and catalase (800 U/ml). A: representative Western blot analysis for fibronectin and actin that was used to control for unequal loading: control (lane 1), nicotine (lane 2), nicotine + DPI (lane 3), nicotine + apocynin (lane 4), and nicotine + catalase (lane 5). B: densitometry data analysis performed after reprobing the blot with an α-actin antibody. Results are expressed as means ± SE; $n = 3$–6 experiments in duplicate. *$P < 0.05$ vs. control. OD, optical density.

Fig. 6. Nicotine-induced mesangial cell proliferation is prevented by the NADPH oxidases inhibitors DPI and apocynin as well as by catalase and Tiron. Results are expressed as means ± SE, $n = 3$ experiments in duplicate. *$P < 0.05$ vs. control; #$P < 0.05$ vs. control.

Fig. 7. Nicotine increases reactive oxygen species production as assessed by flow cytometric analysis. Human mesangial cells were stimulated with nicotine ($10^{-7}$ M), stained with 2',7'-dichlorofluorescin diacetate and analyzed by flow cytometry. Reactive oxygen species are expressed as a histogram of fluorescence. Dotted line histogram represents unstimulated mesangial cells; solid line histogram represents nicotine-stimulated cells.
MAPKs activation has been shown to participate in growth-related responses to growth factors and cytokines including ANG II (18), TGF-β (13), and PDGF (6). To determine the role of MAPK-1 on the growth-promoting effects of nicotine, we stimulated mesangial cells with nicotine (10⁻⁷ M) with and without the ERK1/2 inhibitor PD-98059 (10⁻⁶ M) or the p38 MAPK inhibitor SB-202190 (10⁻⁶ M) (48). ERK1/2, but not p38 MAPK, inhibition prevented the effects of nicotine on mesangial cell proliferation (Fig. 8), suggesting a critical role for ERK1/2 on the growth-promoting effects of nicotine in mesangial cells. Furthermore, ERK1/2 inhibition also prevented the effects of nicotine on fibronectin production in mesangial cells (Fig. 9).

**DISCUSSION**

In these studies we have identified, to the best of our knowledge for the first time, the presence of functionally active nAChRs in human mesangial cells and demonstrated that nicotine, at concentrations similar to those found in the plasma of smokers (50), promotes mesangial cell proliferation and upregulates critical molecules involved in extracellular matrix production.

Recent epidemiologic studies demonstrated that cigarette smoking increases the risk for progressive chronic kidney disease and has been shown to accelerate the rate of progression of renal failure among patients with diabetes (31, 41, 45) and hypertension (3, 16, 28, 37). The role of smoking in primary renal diseases is less known, but clinical studies have indicated a correlation with the development of proteinuria in patients with polycystic kidney disease (5) and deterioration of renal function in patients with various nephritides, including lupus nephritis (51) and IgA nephropathy, a glomerular disease that predominantly affects the glomerular mesangium (32, 46).

The mechanisms by which cigarette smoking is a risk factor for progressive chronic kidney disease have not been established. Clinical and experimental evidence suggests that smoking has significant systemic and renal hemodynamic effects. Studies utilizing ambulatory blood pressure measurements have shown that cigarette smoking is associated with significant, albeit transitory, increases in blood pressure in subjects with normotension (29), a prior history of hypertension (25), diabetes (35), and primary glomerular disease (33, 38). Recent population-based, cross-sectional studies have demonstrated that the risk in developing hypertension is higher among smokers, especially for men >60 yr old (11). The transitory increases in blood pressure observed in smokers have been attributed, at least in part, to direct stimulation of postganglionic sympathetic nerve endings, leading to an increase of plasma concentrations of norepinephrine and epinephrine (9). It has been postulated that these effects are related to nicotine since they are not observed with nicotine-free cigarettes (1). Moreover, in subjects with IgA nephropathy, nicotine administration is associated with increased urinary albumin excretion and reductions in glomerular filtration rate compared with healthy volunteers (38, 39).

Nicotine is a major component of tobacco and responsible in large part for the psychoactive and addictive effects of cigarette smoking via its action in the central nervous system (34). In addition, recent studies have demonstrated that nicotine also has significant biological effects outside of the central nervous system. In the vasculature, nicotine has been shown to stimulate angiogenesis and promote atherosclerosis (14). The effects...
of nicotine in the vasculature appear to be mediated by non-neuronal nAChRs. These nAChRs are ionotropic receptors that function as agonist-regulated Ca\(^{2+}\) channels and that are expressed by neuronal as well nonneuronal cells, including endothelial and vascular smooth muscle cells (8, 15, 24, 26, 52). We have now identified the presence of functionally active nAChRs in human mesangial cells, suggesting that nicotine may have important biological actions in the glomerulus. The nAChRs have a pentameric structure consisting of five nAChR subunits organized around a central channel and can be either homo- or hetero-oligomeric (7). The expression of the \(\alpha7\) subunit results in the formation of nAChRs that can be blocked by nanomolar concentrations of \(\alpha\)-bungarotoxin because of the high affinity of the \(\alpha7\) subunit for this compound (23). Our results suggest that human mesangial cells express hetero-oligomeric nAChRs containing the \(\alpha7\) subunit, given the inhibitory effects with nanomolar concentrations of \(\alpha\)-bungarotoxin, and also containing the subunits \(\alpha4\) and \(\beta2\), given the inhibitory effects of \(\alpha\)-lobeline and dihydro-\(\beta\)-erythroidine.

In addition to inducing vascular smooth muscle cell proliferation, nicotine has also been shown to increase extracellular matrix deposition by several cell types. Nicotine increases fibronectin production in lung fibroblasts in vivo and in vitro (40), and in dermal fibroblasts, nicotine, acting via the \(\alpha3\) nAChR, significantly increases the expression of type I collagen, elastin, and matrix metalloproteinase-1 (2). Here we demonstrate that nicotine is a powerful stimulus for mesangial cell proliferation and fibronectin production, therefore providing a potential mechanism for the deleterious effects of cigarette smoking on the progression of chronic kidney disease, particularly since our experiments were performed in human mesangial cells and utilized concentrations of nicotine similar to those found in active smokers (50).

We have previously demonstrated that ROS mediate mesangial cell proliferation and hypertrophy in response to ANG II (18). In the current studies, apocynin and DPI, two inhibitors of NADPH oxidase, prevented the effects of nicotine on mesangial cell proliferation and fibronectin production, suggesting that NADPH oxidase-derived ROS mediate the growth-related effects of nicotine in human mesangial cells. Moreover, our flow cytometry assays demonstrate that nicotine increases the production of ROS via NADPH oxidase. In recent studies (17), we have also demonstrated that stable compounds, such as acrolein, present in cigarette smoke increase the endothelial production of ROS via NADPH oxidase activation.

We and others have shown that PKC activation is involved in NADPH oxidase activation in several cell types, including mesangial cells and vascular smooth muscle cells (18, 44). In our current studies, PKC inhibition inhibited mesangial cell proliferation and fibronectin production in response to nicotine, suggesting that PKC activation is required for the growth-promoting effects of nicotine, probably by participating in the activation of NADPH oxidase.

ROS, including \(O_2^-\), have been shown to promote activation of MAPKs (42, 49), a process that is associated with growth-related responses (6, 18). ERK1 and ERK2, the best studied MAPKs, are involved in cellular growth and differentiation in response to a variety of stimuli, including ANG II (18), PDGF (6), and TGF-\(\beta\) (13). In our studies, specific ERK1/2 inhibition with PD-98059 prevented mesangial cell proliferation and fibronectin production in response to nicotine, suggesting that ERK1 and ERK2 activation is required for the growth-promoting effects of nicotine. In contrast, p38 MAPK inhibition did not significantly inhibit the growth-promoting effects of nicotine, suggesting that p38 MAPK does not play a significant role on these effects.

In summary, our past (17) and, particularly, present studies unveil novel mechanisms by which cigarette smoke may accelerate and promote the progression of chronic kidney disease.

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