Nicotine and the kidney: Mr. Hyde, and perhaps some Dr. Jekyll

Milos N. Budisavljevic and David W. Ploth
Medical University of South Carolina, Charleston, South Carolina

literature regarding the effects of smoking on the kidney is rather abundant. However, data assessing the singular effects of nicotine on the kidney are sparse. There are more than 100 substances in tobacco, and nicotine is not a direct cause of most of the tobacco-related diseases (2). Nicotine is, however, highly addictive and as such is, in large part, responsible for the ill effects of smoking. This commentary will focus only on the effects of nicotine on the kidney.

Nicotine administered intravenously (iv) at 2 μg/kg/min over 10 min results in the exposure equivalent of smoking one cigarette and will result in a nicotine plasma level of 15–20 ng/ml. These and other data suggest a volume of distribution for nicotine equal to or greater than total body water. Although nicotine is absorbed with high efficiency across oral and respiratory membranes, the bioavailability of orally administered nicotine is only 20–45% (11).

One of the earliest reported and still best characterized actions of nicotine is the direct stimulation of release of antidiuretic hormone (ADH), resulting in increased urinary osmolality and decreased free water clearance (3).

Studies of the hemodynamic effects of nicotine on kidney function reveal a more complex picture. Early experiments in dogs demonstrated that either iv (1–3 mg) or intrarenal arterial infusion (0.5 μg·min⁻¹·kg⁻¹ over 15 min) of nicotine increased the glomerular filtration rate (GFR), urine volume, and sodium excretion without having a significant effect on fractional excretion of sodium, renal blood flow (RBF), or systemic arterial blood pressure (BP). These effects were attributed to nicotine-induced catecholamine release (3, 20). Higher doses (24–36 μg·min⁻¹·kg⁻¹) resulted in increased systemic arterial pressure (9).

In rats, 100 μg/kg of iv nicotine or chronic exposure to oral nicotine resulted in increased arterial BP, decreased GFR, and no change in RBF (22). A lower dose of 2 μg·min⁻¹·kg⁻¹ over 30 min or 2 mg·kg⁻¹·day⁻¹ for 7 days had no effect on BP or GFR measured by inulin clearance (19).

In humans, exposure to 4 mg of nicotine gum (~2 mg would be absorbed) by nonsmokers significantly increased (8 ± 1 mmHg) mean arterial pressure (MAP), whereas estimated renal plasma flow (ERPF) and GFR decreased by 15 ± 4 and 14 ± 4%, respectively. In habitual smokers, the same nicotine exposure increased MAP similarly but ERPF and GFR remained unchanged. The mostly absent renal effects in smokers were ascribed to a dramatic 87% increase in urinary cGMP. Nicotine had not changed urine volume or sodium excretion in either group (5). Similar effects of 6 mg of nicotine gum on BP and GFR were observed by Ritz et al. (21).

Prenatal exposure to nicotine, at least in rats, does not seem to affect body weight, kidney weight, total number of nephrons, or glomerular size when assessed later in life. However, prenatal exposure to nicotine resulted in increased BP 14 wk after birth in some but not all wild rat strains and early after birth in spontaneously hypertensive rats (4).

As alluded to above, the acute effects of nicotine, leading to hemodynamic changes, are mediated through activation of the sympathetic nervous system. On the other hand, chronic exposure to nicotine, mediated through nicotinic receptor activation in nonneuronal tissues, may be associated with structural modifications of kidney architecture involving vascularization, extracellular matrix, and inflammation.

The kidney is a highly vascularized organ, and the effects of nicotine on the endothelium are, therefore, of particular interest. Endothelial cells express nicotinic acetylcholine receptors (nAChR) (13). However, the effects of nicotine on the function of the arterial endothelium have been and continue to be controversial. Various reports suggest no change, increases, or even decreases in endothelium-dependent relaxing factors in response to nicotine (6, 16). Of major importance is the recent report that nicotine stimulates angiogenesis and that this activity is mediated through activation of the α7nAChR. Nicotine-induced angiogenesis appeared to be, at least in part, independent of vascular endothelial growth factor (VEGF), indicating two distinct but interdependent pathways of angiogenesis (7).

In 2002 Markowitz (15) described features of idiopathic nodular glomerulosclerosis as a distinct clinicopathological entity linked to hypertension and smoking. These novel observations suggested that “mesangial nodules appeared to contain increased endothelial-lined vascular spaces, suggesting a potential mechanism for neovascularization” (15). In contrast, mesangial nodules in diabetic glomerulosclerosis are avascular, displacing vascular channels to the periphery of the nodules. Immunohistochemical staining failed to demonstrate altered expression of VEGF in these nodules, and a potential role of other endothelial growth factors has been suggested. It seems possible, if not likely, that nicotine might be such an angiogenic factor responsible for nodular neovascularization (17).

In an issue of the *American Journal of Physiology-Renal Physiology*, Agarwal et al. (1) argue that long-term oral treatment with nicotine preserves renal function and reduces inflammation in a rat model of progressive kidney disease. Nicotine had no effects on body and kidney weight, systolic BP, and urine output. The level of nicotine exposure measured by plasma cotinine level was equivalent to that of a heavy to very heavy smoker consuming 20–40 cigarettes/day. Despite some weaknesses, the present study has three major strengths. The drug was administered in multiple doses, the study was of significantly long duration, and kidney function was measured. Given the alleged harmful effect of nicotine on the kidney in a model of diabetic renal disease (although, in all fairness, it appears that the diabetic mice in this study were exposed to significantly higher nicotine doses than controls) (10), how can we interpret the value of the current study?

Predictably, variable effects obtained with the same drug may be the result of differences in doses or dosing schedules,
routes or duration of administration, age, gender, species, disease models, or stage of the disease within a particular model. Inhibition of particular intracellular pathways or angiogenesis stimulation in one model, or even the stage of disease within the same model, may produce different outcomes. For example, too little glomerular VEGF may cause thrombotic microangiopathy, while excess VEGF may lead to glomerular basement membrane thickening, accumulation of mesangial matrix, and inflammatory infiltrates (18). It is possible that the proangiogenic activity of nicotine may have other effects in different forms of glomerular injury. In addition to angiogenesis, nicotine increases expression of matrix metalloproteinases (6) and decreases inflammation (also through activation of \( \alpha_7 \)nAChR) (24) and in such a way may potentially ameliorate some forms of glomerulosclerosis.

The anti-inflammatory effects of nicotine resemble those of the so-called “cholinergic anti-inflammatory pathway” mediated through vagal nerve stimulation (23). These vagal nerve effects appear to be abolished in animals lacking \( \alpha_7 \)nAChR. At this point, it is difficult to assess how much the chronic effects of nicotine differ and/or depend on intact cholinergic neuronal supply and to what extent structural changes would occur in a transplanted denervated organ. Although information is incomplete, in rat models of ischemia-reperfusion injury intraperitoneal treatment with nicotine appeared to exert a renoprotective effect in vagotomized animals, and oral administration of nicotine attenuated pulmonary allograft rejection (8, 25).

We are a long way, if ever, from suggesting nicotine as a potential agent to slow the progression of kidney disease. However, nicotine may teach us how to achieve this goal and find less toxic and more efficacious agents that protect the kidney. Given the scarcity of effective medications, and recent concerns regarding combinations of antiangiotensin agents (12, 13), we cannot afford to disregard any approach that may appear promising.

AUTHOR CONTRIBUTIONS

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REFERENCES