Chronic nicotine exposure and acute kidney injury: new concepts and experimental evidence

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Although the pathological role of smoking in the development of cardiovascular diseases, cancer [1] or chronic obstructive pulmonary diseases has been widely accepted, its impact on kidney function has only recently been recognized, as reviewed in [2, 3]. Epidemiological studies concluded that smoking is an important remediable risk factor for development of proteinuria [4, 5], progression of diabetic nephropathy [6], evolution of chronic kidney disease (CKD) to end-stage renal disease [7–9] and graft failure in renal transplant patients [2, 10]. At this moment in time, there is a lack of prospective studies evaluating the role of nicotine abuse as a renal risk factor in patients with primary hypertension or primary renal disease [3]. In spite of the clinical and experimental data, the mechanisms responsible for the reported effects have not yet been fully identified. Although some attention has been paid up till now to the role of smoking in CKD, chronic nicotine-mediated exacerbation of acute kidney injury (AKI) may be an underestimated entity, probably masked by other frequently occurring risk factors such as hypertension, diabetes or obesity. Due to the fact that the current therapeutic array of AKI only consists of supportive care and treatment of the underlying causes and considering the growing evidence on the importance of AKI as a precursor to CKD, the issue of smoking as a risk factor for AKI may warrant more attention.

In an interesting paper published in the present issue of Nephrology Dialysis Transplantation [11], Arany et al. investigated in detail the influence of chronic nicotine exposure on the exacerbation of ischaemia-reperfusion-induced oxidative stress and AKI in an in vivo and in vitro mouse model. Based on their previous work [12–15], the authors illustrated nicely that chronic nicotine exposure increased the ischaemia-reperfusion-induced AKI-dependent renal expression of p66shc. The adaptor protein p66shc is a newly recognized mediator of mitochondrial dysfunction, controlling cellular responses to oxidative stress.

The activation of p66shc by oxidative stress is accomplished by the phosphorylation at its Ser36 residue, which facilitates its translocation to the mitochondrial intermembrane space and a H2O2-dependent binding to cytochrome c. The oxidation of cytochrome c results in an excessive generation of reactive oxygen species (ROSs), depolarization of the mitochondria and apoptotic or necrotic death of renal cells through inhibition of the prosurvival epidermal growth factor receptor/ras/MEK/ERK pathway [13, 14]. This paper thus unveils a novel mechanism by which nicotine abuse may be involved in the development of AKI. It broadens our knowledge of the previously described pathways [12–15] and may help us to elucidate the exact link between nicotine and the occurrence of acute/CKD.

In previous studies, several potential mediators of smoking-induced renal damage have been discussed, which can be subdivided into non-haemodynamic and haemodynamic mechanisms [3, 16]. Besides the smoking-induced activation of the renin–angiotensin system which is one of the multiple complex and heterogeneous mechanisms, Arany et al. focused in detail on the oxidative stress-dependent Ser36 phosphorylation of p66shc through generation of ROSs, mitochondrial depolarization and consequent injury in cultured proximal tubule cells [11]. This process can be compared with the effects of indoxyl sulphate (IS), a uraemic retention product believed to be involved in the progression of chronic damage, on the p53 pathway [17]. IS is synthesized in the liver from indole, which is generated from tryptophan in dietary proteins by the intestinal flora. As a uraemic toxin, it accumulates in serum and the renal tubules when renal function deteriorates. IS stimulates the expression and phosphorylation of p53 through ROS production [18]. Activation of nuclear factor-kappa B (NF-kB) and ROS production in proximal tubular cells are responsible for a reduced renal expression of Klotho in CKD [19], which in turn results in fastened senescence of tubular cells and renal damage. The involvement of IS in renal

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It has to be mentioned that the reported smoking-induced renal damage mechanisms are influenced by several factors. First of all, cigarette smoke is composed of multiple chemicals in the form of particles or gases with a hydrophilic, lipophilic and amphiphilic nature, which could be responsible for the nephrotoxic effect [3, 21]. In the study of Arany et al. [11], mice received either nicotine bitartrate (Sigma-Aldrich, St Louis, MO) in a 2% saccharine solution at 200 µg/mL concentration or a 2% saccharine solution as their drinking source for 4 weeks. Although the authors argue that this method resulted in comparable plasma nicotine concentrations as those found in chronic smokers [22], nicotine is only one component of the heterogeneous cigarette smoke and one might wonder whether similar results would be obtained after cigarette smoke exposure.

The dose and the length of nicotine exposure may partly explain the contradictory beneficial findings of nicotine in previously published papers. Lower plasma cotinine levels may result in different effects and signals. In contrast to the adverse events of chronic nicotine, several studies reported anti-inflammatory effects of nicotinic acetylcholine receptor agonists in ulcerative colitis, sepsis, hypersensitivity pneumonia, experimental type 1 diabetes and even in renal ischaemic-reperfusion injury [23–25]. In an experimental mouse model of lipopolysaccharide (LPS)-induced septic AKI, administration of nicotinic agonists significantly abrogated renal leukocyte infiltration and attenuated kidney injury. More specifically, the LPS-and tumour necrosis factor-alpha-induced inflammatory chemokine production by human renal proximal tubular epithelial cells, human renal glomerular endothelial cells and human mesangial cells was attenuated by nicotinic agonists and suppressed both ATP-dependent and ATP-independent proteasome activity [17]. Long-term oral nicotine administration showed a preserved kidney function, a reduced proteinuria, a reduced renal inflammation and protected progression of renal structural damage in Munich Wistar Frömter rats with proteinuria. However, these renoprotective effects may be limited to the specific animal models in which they are described [23].

Renal susceptibility genes or polymorphisms may also influence the nephrotoxic effect of smoking in different individuals [3]. Nicotine is a weak base with a pKₐ of 8.0 [22], which is primarily filtered by the glomeruli and both secreted and reabsorbed at the tubular level. The renal clearance rate is pH-dependent, being low under conditions of urinary alkalinity with a large reabsorption fraction and being high under conditions of urinary acidity with a minimal reabsorption due to ion trapping [26]. In contrast to nicotine, the clearance of cotinine (pKₐ = 4.7) is much less sensitive to pH [27]. As illustrated in a study of 139 pairs of twins, the net secretory/reabsorptive renal clearance rates of nicotine and cotinine are interrelated, but are also influenced by a different combination of (non-additive) genetic and environmental factors. The genetic component of the variation in reabsorption clearance of nicotine may be determined by the corresponding genetic variety in reabsorptive transporters [28]. Nicotine is a substrate of the human organic cation transporter OCT2/SLC22A2, which is expressed in the basolateral membranes of renal proximal tubule cells. Besides nicotine, OCT2 governs the entry of many circulating toxins into the tubular epithelium [29]. Genetic variation and kidney-specific expression of this renal uptake transporter, which is regulated by DNA methylation, could explain genetic variance in the renal clearance of nicotine [30]. Moreover, as genetic polymorphisms of this transporter are associated with altered drug pharmacokinetics, further research should focus on drug–nicotine interactions in the development and treatment of AKI [31]. In a similar way as the co-administration of an inhibitor of organic anion transporter (probenecid) to reduce the renal toxicity of the antiviral agent cidofovir [32], selective inhibitors of OCT2 (e.g. proton pump inhibitors) may hold therapeutic potential in protection against Ch-NIC-induced nephrotoxicity [33].

In conclusion, the paper by Arany et al. provides us with new insights into the pathways of chronic nicotine-mediated AKI and could have important clinical consequences if the observations in the mouse model can be confirmed in humans. The acute effects of smoking on renal haemodynamics and urinary albumin excretion may differ, depending on smoking habits and underlying pathology. Due to the probable huge socioeconomic consequences, there is a call for (epidemiological) studies, investigating the relationship between AKI and the active or passive exposure to tobacco smoke. Moreover, novel studies should focus on the underlying pathophysiology of smoking-related increment in protein excretion via damage to the glomerular filter or the tubular albumin degradation pathway. This may give nephrologists an opportunity to develop a more targeted approach in the treatment of AKI.

**CONFLICT OF INTEREST STATEMENT**

None declared.


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