Update on the Pharmacokinetics and Redox Properties of Protein-Bound Uremic Toxins

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ABSTRACT: Protein-bound uremic toxins, such as indoxyl sulfate, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid, *p*-cresyl sulfate, hippuric acid, and indoleacetic acid, have been the subjects of extensive investigations. In this review, we summarized the recent works providing the new insight on the pharmacokinetics and redox properties of these uremic toxins. They have a common characteristic of being difficult to remove by conventional dialysis because they all bind tightly to serum albumin. They are transported via organic anion transporters to various tissues, and accumulate not only in the kidney but also in other tissues including vascular endothelial cells, smooth muscle cells, osteoblasts, and the central nervous system. Accumulated uremic toxins alter nonrenal drug clearance. Intracellular accumulated uremic toxins have been linked to the induction of oxidative stress and the stimulation of proinflammatory cytokines through the production of reactive oxygen species, which play a role in the progression of chronic kidney disease and the development of complications. Unfortunately, despite the massive amount of information on the undesirable effects of uremic toxins, methods for improving the detoxification of these toxins appear to be lacking. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:3682–3695, 2011

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INTRODUCTION

A wide variety of substances that are excreted by the kidney under normal conditions are retained in the body when renal function is impaired. These retained solutes, which are involved in the development and manifestation of the uremic syndrome, are referred to as uremic toxins. The European Uremic Toxin Work Group (EUTox) classified 90 retention solutes into three groups according to molecular weight and serum protein binding characteristics: 45 small water-soluble compounds (molecular weight <500 Da) with no known protein binding properties, 25 molecules that bind to proteins (most of these protein-bound solutes have a molecular weight <500 Da, although two are mid-sized molecules), and 22 mid-sized molecules.[1,2]

Among these uremic toxins, organic anions, such as indoxyl sulfate (IS), 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF), *p*-cresyl sulfate (PCS), indoleacetic acid (IA), and hippuric acid (HA) (Fig. 1) are low-molecular-weight compounds. However, they should be considered as high-molecular-weight substances in general circulation as they bind strongly to plasma protein, mostly albumin (molecular weight: 66 kDa). Therefore, this group of toxins is difficult to be removed with conventional hemodialysis even though their molecular sizes should be small enough to pass through the dialysis membrane. It has been proposed that these organic anions cause the uremic syndrome, including the deterioration of renal function

Abbreviations used: CKD, chronic kidney disease; CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid; CYP, cytochrome P450; HA, hippuric acid; HSA, human serum albumin; IA, indoleacetic acid; IS, indoxyl sulfate; OAT, organic anion transporter; PCS, *p*-cresyl sulfate.

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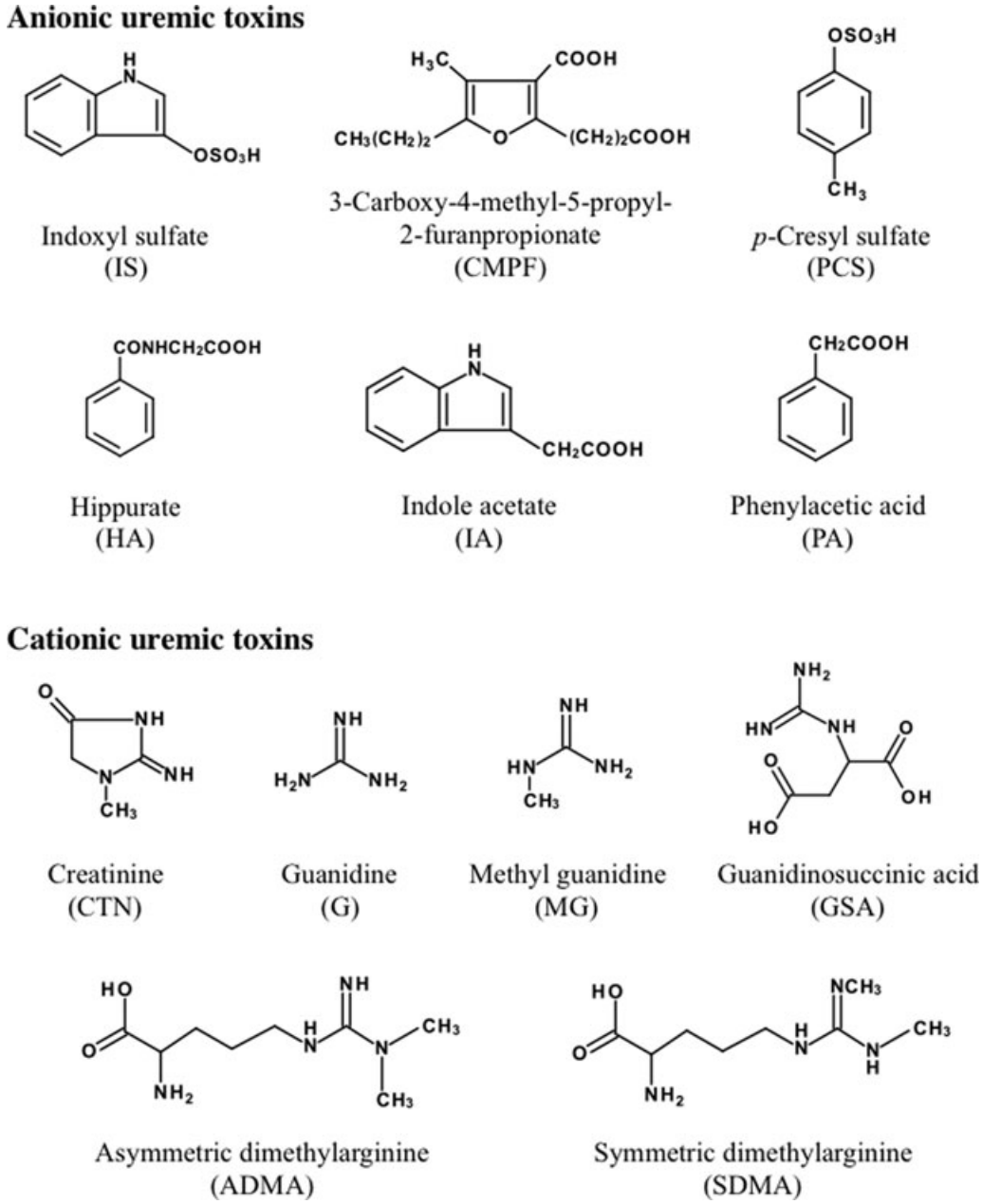

Figure 1. Chemical structures of anionic and cationic uremic toxins.

in chronic kidney disease (CKD)[3–6] and the onset of complications, such as vascular lesions,[7–9] bone disorders,[10,11] and the central nervous system (CNS) dysfunction[12–15] of CKD. In those tissues, organic anion transporters (OATs) mediate the cellular transport of uremic toxins, and uremic toxins that accumulate intracellularly stimulate the production of proinflammatory cytokines through the production of reactive oxygen species (ROS), which play a pathogenic role in CKD.[16] In addition to the organic anions, several cationic guanidino compounds have also been demonstrated to show a proinflammatory impact.[17]

In order to develop effective treatment strategies for overcoming the difficult clinical problems caused by uremic toxins, it is important to develop new insights related to the pharmacokinetics, including cellular transport, albumin binding and their effect on nonrenal drug clearance, and the redox properties of these compounds (Table 1).

PHARMACOKINETICS OF UREMIC TOXINS

Tissue Distribution of Uremic Toxins via Tranporters

Indoxyl Sulfate

The serum level of IS is known to be markedly elevated in the serum of patients with CKD (the serum concentration 100 μM–1 mM in the case of CKD