The Gut: The Forgotten Organ in Uremia?

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Introduction

When the glomerular filtration rate decreases, the concentration of retained solutes [1] depends on the interference between removal, which in most cases is decreased, and a variable degree of generation [2] (fig. 1). A substantial part of this generation process is regulated in the intestine. In spite of its importance, this option is rarely taken into account in reviews of uremic toxicity and/or in the development of therapies.

Pathophysiological Elements

Uremic solute generation per se is ruled by several mechanisms (fig. 1): endogenous production by often endocrine processes without interference of intestinal absorption as is the case for most peptides; for the purines uric acid or xanthine, intestinal absorption plays a role only after excessive intake of nutrients containing large amounts of nucleotides as precursors (i.e. organ meat, sweetbread); intake of exogenous toxins via the gastrointestinal tract as food components which remain entirely or partially unaffected by digestion (e.g. advanced glycation end products, AGEs); intake of exogenous products via the gastrointestinal tract, digestion in the intestine and uptake of the digested end product followed by further metabolic modification in the body; if the absorbed compound is not further modified by metabolism and since it is conceivable that the digested end product is a

Key Words
Gut · Uremia · Uremic retention solutes · p-Cresol

Abstract

Part of the uremic retention solutes are generated in the intestine, but this option is rarely discussed in the literature. In this publication, we describe consecutively the role of the intestine in generating uremic retention solutes, the pathophysiological importance of the generated solutes and therapeutic options that are inspired by this knowledge. Apart from its role as a route via which uremic toxins or their precursors enter the body, the intestine also acts as an active player by presenting more precursors for fermentation due to disturbances in assimilation caused by uremia, followed by alterations in further processing related to changes in the composition of the fermenting flora. Many of the toxins generated or introduced into the body via the intestine (advanced glycation end products, indoles, phenols) play an active role in vascular damage. Intestinal therapeutic interventions that could help decrease solute concentration are restriction of dietary intake, however at the expense of increasing the risk of malnutrition, rerouting of intestinal metabolism by administration of prebiotics or probiotics and/or the administration of active sorbents such as AST-120 (Kremezin®).
nutrient (e.g. amino acids), it is generally not noxious as such; it becomes only a toxin upon further modification (e.g. some of the guanidine compounds); intake of exogenous products via the gastrointestinal tract, digestion in the intestine followed by metabolic transformation by the intestinal enzymes or bacteria into toxins, only then uptake of this product and often further metabolic modification in the body (e.g. phenols and indoles).

Sources of these uremic toxins might not only be pure nutrients, but also food preservatives (benzoic acid generating phenols) [3], flavor correctors (pennyroyal oil generating p-cresol) [4], environmental toxins (toluene generating phenol) [5], alternative therapeutic agents or psychedelic drugs (menthofuran generating p-cresol) [6].

In addition, the concentration of uremic solutes in the gut may also be influenced by excretion into the intestine, e.g. by the gall bladder. A further contributing factor is a shift in the composition of the intestinal flora due to the uremic condition, favoring overgrowth of bacteria producing toxic compounds (fig. 2) [7]. Metabolism of peptides and proteins by anaerobic germs (putrefaction) generates phenols and indoles [8]. When those microbes are killed, a decrease in fecal and urinary excretion of phenolic and aromatic substances ensues [9]. In addition, changes in assimilation (digestion plus absorption) of proteins make more substrate available for fermentation [10, 11], as illustrated by the higher daily urinary p-cresol excretion in subjects with a glomerular filtration rate of <30 ml/min compared to those with ≥60 ml/min [11]. This results in a higher generation rate in chronic kidney disease than in normal subjects, even if the patients with renal failure are neither catabolic nor anabolic.

Some compounds might be neither metabolized nor absorbed, so that they ultimately leave the intestinal tract unmodified; this is the case with resistant starches, cellulose or gums. Such compounds can of course have no direct biological or toxic impact, but they can still affect toxicity indirectly by modifying the constitution or function of the intestinal flora (see section below on therapeutic options).

**Examples of Intestinally Generated Uremic Toxins**

**Advanced Glycation End Products**

AGEs are typically retained in older subjects, diabetics and patients with kidney failure. In diabetes, a large part of the generation of AGEs is attributed to the glycation of proteins, peptides and amino acids due to excess glucose.
Other sources are posttranslational modifications due to microinflammation and oxidation which play a role in diabetics, uremics as well as in the elderly.

The third major source of AGEs are food products which have been processed by heating [12]. Several studies have demonstrated that nutritional ingestion of AGEs increases their concentration, both in nondiabetics [13] and in diabetics [13, 14].

More importantly, those studies also showed that nutritional AGEs conveyed some of the deleterious pathophysiological effects of these compounds such as inflammation [12] or endothelial dysfunction [13].

**Phenols**

Intestinal fermentation of the amino acids phenylalanine and tyrosine generates p-cresol, phenol [15] and very likely also phenylacetic acid as well as other phenols.

For a long time it has been thought that after its generation p-cresol was absorbed as such by the intestine and then distributed over the body, since upon analysis the molecule was found in serum of subjects with normal and disturbed renal function [16]. Only recently has it become clear that after its absorption, p-cresol is conjugated in the intestinal wall to p-cresylsulfate as well as to p-cresylglucuronide, while what remains of p-cresol after transfer into the portal vein is modified further on to p-cresylglucuronate in the liver, leaving very little or no remnant p-cresol present in the body (fig. 3). Although no similar data about conjugation of other phenols is available, it is conceivable that some of these (e.g. phenol itself) may be conjugated as well.

The reason why p-cresol was considered for a long time as a major phenolic compound in the body is attributable to an artifact created by the preparation of the samples for analysis. Until a few years ago, virtually all determination methods used deproteinization by acidification as a first step, causing hydrolysis of the p-cresol conjugates. Deproteinization without acidification left p-cresylsulfate intact, with virtually no detectable p-cresol [17].

**Indoles**

Similar to phenol, indole is generated by the bacterial flora, now with tryptophan as the mother compound. The main indole detected in uremics is indoxylsulfate, but this sulfated conjugate resists acidic hydrolysis, in contrast to p-cresylsulfate.

The phenolic and indolic conjugates are not necessarily generated by the same metabolic process, as suggested by the diverging metabolic behavior of the two compounds under identical clinical conditions [18].
**Biological Impact**

Although it is not the intention to present an in-depth review of the biological impact of the discussed compounds, a brief summary of their potential toxicity will allow the reader to realize that influencing concentration, e.g. by changing intestinal generation or absorption, might have clinical benefits.

*Advanced Glycation End Products*

AGEs have been associated with inflammation, oxidation, leukocyte stimulation and endothelial dysfunction [12, 13, 19]. Many early in vitro studies showing those effects have, however, been performed with artificially prepared AGEs [20] of which it was uncertain whether they were structurally related to the compounds retained in uremia. More recently, also the proinflammatory impact of AGEs present in dialysis patients has been demonstrated [19].

Up to now only a limited number of studies has addressed the relation between AGE concentration and outcome. One study paradoxically found the best outcomes in the group with the highest AGE concentration, possibly pointing to an overriding effect of nutritional status which at the same time improves survival and supplies extra AGEs [21]. Other studies demonstrated a direct correlation between mortality and concentration of low-molecular-weight AGEs [22] and skin autofluorescence, a presumed indicator of skin AGE content [23].
Phenols

*p*-Cresylsulfate has a proinflammatory impact on monocytes and lymphocytes [24]. To the best of our knowledge, this is the only study as of today demonstrating a biological impact for this compound.

Several observational studies show a relationship between *p*-cresol and overall mortality [25], cardiovascular disease [26], infectious complications [27] and uremic symptoms [28]. As all these data were obtained with analytical methodology applying acidification, it is conceivable that those findings on *p*-cresol can be extrapolated to the real main retention product, *p*-cresylsulfate. Interven- tional trials showing a positive impact of decreasing concentration of phenols are not available.

In contrast to *p*-cresylsulfate, the mother compound *p*-cresol is a strong inhibitor of leukocyte response [24, 29]. Although it is unlikely that *p*-cresol exerts this effect on the immune cells throughout the body, because of the absence of direct contact, such an immunosuppressive effect might be at play in the gut-associated lymphoid tissue, which is very likely in more direct contact with the intestinal content, and an important element in shaping the immune response within the rest of the body [8].

Indoles

A host of in vitro and in vivo animal studies point to indoxylsulfate as causing inflammation [30], endothelial dysfunction [31] and disturbances of bone metabolism [32]. In addition, it has repeatedly been associated with loss of residual renal function [33], by itself a factor with strong impact on outcome [34]. Inhibition of intestinal absorption of indoxylsulfate by the sorbent AST-120 (Kremezin®) has been associated with a postponement of the start of dialysis [35] and, if applied before the start of dialysis, with better outcomes once dialysis was undertaken [36]. Although controlled, these studies have been performed in small populations so that they need confirmation.

In summary, the set of uremic toxins selected for this discussion are all characterized by in vivo and/or in vitro toxicity to the cardiovascular system, one of the main clinical problems haunting the uremic population today [37]. Evidence is not solid enough, however, to allow firm recommendations about the necessity of their removal.

Therapeutic Possibilities

Therapeutic modalities (table 1) implicating intestinal factors should especially be considered in view of the difficult removal of the relevant compounds even with the most efficient dialysis therapies [38, 39].

Type of Therapy

Restriction of the dietary intake of AGES results in a decrease in concentration [14]. If this intervention results in less dietary protein intake, it may however result in malnutrition. Also intestinal generation of phenols and indoles is dependent on dietary protein intake [40, 41]. Since proteins are almost the only source of these molecules, the threat of malnutrition, if one intervenes via dietary protein restriction, is even more likely here.

Therefore, it seems more appealing to change generation via other strategies. A first option aims at modifying

<table>
<thead>
<tr>
<th>Method</th>
<th>Target molecule</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Diet</td>
<td>AGEs, phenol, indoles</td>
<td>decrease concentration</td>
</tr>
<tr>
<td>Prebiotics</td>
<td>Urea, phenol, indoles</td>
<td>decrease concentration</td>
</tr>
<tr>
<td>Gum arabic fiber</td>
<td><em>p</em>-cresol</td>
<td>decrease concentration</td>
</tr>
<tr>
<td>Oligofructose-enriched inulin</td>
<td><em>p</em>-cresol</td>
<td>decrease concentration</td>
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<tr>
<td>Lactulose</td>
<td>Phenol</td>
<td>decrease concentration</td>
</tr>
<tr>
<td>Resistant starch</td>
<td>Urea</td>
<td>decrease concentration</td>
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<tr>
<td>Probiotics</td>
<td>Urea, <em>p</em>-cresol</td>
<td>decrease concentration</td>
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<tr>
<td><em>Lactobacillus</em></td>
<td><em>p</em>-cresol</td>
<td>decrease concentration</td>
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<td><em>Bifidobacterium</em></td>
<td><em>p</em>-cresol, phenols indoles</td>
<td>decrease concentration</td>
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<tr>
<td>Lactic acid bacteria</td>
<td><em>p</em>-cresol</td>
<td>decrease concentration</td>
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<tr>
<td>AST-120</td>
<td><em>p</em>-cresol, indoles</td>
<td>survival; preservation of renal function</td>
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the intestinal flora to refrain generation of toxins, either by prebiotics [42–45], which are nondigestible compounds beneficially modifying the composition and/or function of the intestinal flora, or by probiotics, which are bacteria administered as food components or supplements providing specific benefits themselves [7, 43, 44, 46–48].

Finally, oral sorbents may be administered to bind solutes and prevent their intestinal absorption. To the best of our knowledge, AST-120 (Kremezin®) is the only therapeutic sorbent of the solutes under discussion, with an impact on outcome parameters shown in a number of studies [35, 36]. Especially the absorptive capacity of AST-120 on indoxylsulfate has been emphasized, although also p-cresol is absorbed [49].

**Target Molecules**

Several studies aim at reducing urea alone [42, 47, 48]. In as far as urea per se is a relatively inert uremic solute, strategies aimed only at urea removal [47, 48] are less appealing than therapies reducing total nitrogen load, including urea [42]; the latter approach supposedly affects toxicity more globally and less selectively.

Several approaches directly reduce p-cresol [7, 43, 44], phenol [7, 45] and/or indoxylsulfate [7].

**Outcomes**

All studies with probiotics and prebiotics evaluate the impact on solute concentration in serum or on their fecal or urinary excretion, which should be considered only as surrogate endpoints. All studies mentioned above show a decrease in concentration [7, 42–48]. The studies with AST-120 obviously affect the concentration of indoxyl-sulfate and p-cresol [49, 50] but show in a few publications also an impact on the timing of the start of dialysis [35] and on survival [36] as hard(er) endpoints; however, data are not convincing enough to allow definite conclusions.

**Hemodialysis versus Peritoneal Dialysis**

While removal of p-cresol and indoxylsulfate is markedly higher with hemodialysis than with peritoneal dialysis [18, 51, 52], serum concentration in peritoneal dialysis patients is paradoxically low [51–53]. These discrepancies cannot be explained by differences in protein intake so that other causes should be considered; some of these may be related to the intestine: intestinal blood losses, laxative use, digestive transit or intake of binding agents such as phosphate binders or potassium-binding resins [51]. These data suggest that uremic toxin supplementation may differ based on intestinal factors, even if no direct intervention via diet, probiotics or prebiotics has taken place.

**Conclusions**

The intestine is a major source of uremic toxin generation and/or uptake. Some of the toxins involved (AGEs, phenols, indoles) have a substantial biological impact. Many of these effects are related to vascular damage. Administration of prebiotics and probiotics as well as of sorbents (AST-120) decreases their concentration. Studies showing that such a decrease has a positive impact on outcome are, however, scarce and need confirmation.

### References


