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Review

Emerging Roles of Aryl Hydrocarbon Receptors in the Altered Clearance of Drugs during Chronic Kidney Disease

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Abstract: Chronic kidney disease (CKD) is a major public health problem, since 300,000,000 people in the world display a glomerular filtration rate (GFR) below 60 mL/min/1.73m². Patients with CKD have high rates of complications and comorbidities. Thus, they require the prescription of numerous medications, making the management of patients very complex. The prescription of numerous drugs associated with an altered renal- and non-renal clearance makes dose adjustment challenging in these patients, with frequent drug-related adverse events. However, the mechanisms involved in this abnormal drug clearance during CKD are not still well identified. We propose here that the transcription factor, aryl hydrocarbon receptor, which is the cellular receptor for indolic uremic toxins, could worsen the metabolism and the excretion of drugs in CKD patients.

Keywords: AhR; uremic toxins; drug clearance

Key Contribution: Patients with chronic kidney disease require the prescription of numerous medications. The alteration of renal- and non-renal clearance makes dose adjustment challenging in these patients, with frequent drug-related adverse events. We propose here that the transcription factor, an aryl hydrocarbon receptor, which is the cellular receptor for indolic uremic toxins, could worsen the metabolism and the excretion of drugs in CKD patients. Thus, the modulation of aryl hydrocarbon receptor (AhR) activity could be proposed as a possible and future potential target to modulate drug clearance in patients.

1. Chronic Kidney Disease

Chronic kidney disease (CKD) incidence has increased in recent years, and the global prevalence is estimated to be 8% to 16% [1,2]. The global prevalence of CKD is about 200 million people [3]. In the end of 2009, in the United Kingdom, the average prevalence was 794 per million population [4]. In India, the average age-adjusted incidence rate between the years 2002 to 2005, was of 229 per million population [5]. In the United States, approximately 20 million people have CKD, and the estimated cost for their care (CKD and CKD-related comorbidities) is \$26,000 per patient [6]. This high prevalence of CKD makes it a broad public health problem. CKD is characterized by kidney damage, including structural or functional impairments maintained for at least 3 months. CKD is mainly defined as an increase in the urinary excretion of albumin and a decrease in glomerular filtration rate (GFR) [7]. Considering the estimated levels of GFR, CKD is classified into five stages. Individuals with normal renal function are included in stage 1 and have a GFR equal to or greater than 90 mL/min/1.73 m². A persistent GFR below 60 mL/min/1.73 m² (stage 3) indicates a moderate loss

of kidney function. In stage 5, GFR is lower than 15 mL/min/1.73m², due to the kidney failure; these patients require chronic dialysis treatment or kidney transplantation (National Kidney Foundation, <https://www.kidney.org>, 2002).

Cardiovascular disease (CVD) is the main cause of death in patients with CKD. The cardiovascular mortality rate is 10 to 30 times higher than in the general population [8,9]. Kidney function impairment is associated with left ventricular hypertrophy [10], increased arterial stiffness and calcification [11–13], arterial thrombosis [14] and hemostatic disorders [15], and endothelial injury and dysfunction [16–19]. Traditional risk factors, such as diabetes, hypertension, dyslipidemia, and tobacco use are not enough to explain this high mortality in CKD patients [9,20]. Thus, specific risk factors associated with CKD were proposed to play a major role in cardiovascular mortality, such as uremic toxins [21].

Since patients with CKD have high rates of complications and comorbidities, there is a relevant impact on medication administration. Specific and related complications of CKD increase the need for drug intake, so the dose adequacy is difficult to identify and drug side effects are more frequent [22–24]. All of the kinds of drugs used for CKD treatment and CKD-related diseases are listed in Table 1. Concomitant intake of assorted drugs can affect the efficacy of drug therapy due to drug–drug interactions. Drugs' efficacy can also be affected by interindividual variations, such as genetic polymorphisms, epigenetic influences, microbiota, sex, age and disease states [25–29]. Understanding factors that can modify the metabolism of drugs is essential to improve the accuracy of prescriptions for patients. Furthermore, it is well known that renal impairments modify drug disposition and clearance in patients with CKD. Indeed, subjects exhibiting a smaller kidney size, a low number of functioning nephrons, and a decreased renal blood flow have a reduced capacity to eliminate substrates. To avoid toxicity, adverse effects, and poor outcomes, methods have been developed to estimate the real required dose of a drug. For example, the “Dettli method” considers the kidney elimination rate and the patient creatinine level. It assumes that the renal excretion reduces linearly in relation to this marker of renal function, whereas the non-renal clearance remains unchangeable [30,31]. For a long time, it was assumed unnecessary to adjust the dosage of drugs that are mainly metabolized and eliminated by the liver. However, during CKD, even drugs with a non-renal elimination require dosage adjustments to individualize therapy [32,33]. This is presumably a result of changes in drug pharmacokinetics, including the expression and activity of drug-metabolizing enzymes (DME) and drug transporters.

Table 1. List of the drugs used for the treatment of chronic kidney disease (CKD) and CKD-related diseases.

Cardiovascular Drugs	Metabolism
β-receptor blockers	insulin
calcium channel blockers	antidiabetics (sulfonylureas, biguanides/metformin, thiazolidinediones, insulin)
antianginals	thyroid hormones
angiotensin-converting-enzyme inhibitors	diphosphonate
angiotensin receptor blockers	vasopressin analogues
Alpha blockers	calcium
thiazide diuretics	allopurinol
loop diuretics	phosphate chelators
heparin	
Warfarin	
direct oral anticoagulant	
antiplatelet drugs	
3-hydroxy-3-methylglutaryl-CoA reductase reductase inhibitors	

Table 1. Cont.

Cardiovascular Drugs	Metabolism
Digestive System	For Infections and Infestations
antacids proton pump inhibitors (PPIs) H2-receptor antagonists Laxatives	antibiotics Anti-tuberculous drugs antivirals
Central Nervous System	For the Immune System
hypnotics anesthetics antidepressants (including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) anticonvulsants/antiepileptics benzodiazepines antihistamines	vaccines immunoglobulins immunosuppressants monoclonal antibodies corticosteroids
Pain Killers	
Paracetamol Tramadol pioids	

2. Drug Metabolism

Normally, the human body is capable of metabolizing and clear xenobiotics. Whether xenobiotics primarily belong to dietary compounds including plant and fungal-derived metabolites, they now include environmental pollutants and drugs. Most xenobiotics undergo two main phases, I and II, during their process of transformation, before their elimination from the body [34,35]. The first phase consists mainly of reactions of oxidation, reduction, hydrolysis, and hydration. It consists of the addition of a functional group ($-\text{OH}$, $-\text{COOH}$, $-\text{SH}$, $-\text{O}-$, or NH_2), and it plays an important role in controlling the drug's biological activity. Reactions in phase I are mainly led by the cytochrome P450 (CYP) superfamily of microsomal enzymes. These DME are expressed abundantly in the liver, gastrointestinal tract, kidney, and lung [36]. CYPs, especially CYP1A1/2 and CYP1B1, possess many binding sites, so they can metabolize several substrates with different structures. Besides drugs, CYPs can also interact with dietary compounds, such as caffeine, theophylline, mushrooms, naringin, and furanocoumarins, which are components found in grapefruit juice. CYPs can also interact with endogenous substrates like cholesterol, steroids, and bile acid. For example, the widely-consumed caffeine and theophylline undergo a complex metabolism, in which they are mainly transformed by CYP1A2 and to a lesser extent by CYP3A4 and CYP2E1 [37,38]. CYP2C9 is also involved in caffeine 7-N-demethylation and in the oxidation of steroids, such as progesterone and testosterone, as well as all-trans-retinoic acid [39]. Grapefruit juice at 25% inhibits the activities of CYP3A4, CYP2D6, and CYP2C9, and one of its compounds, bergamottin, inhibits the activities of CYP1A2, CYP2C9, CYP2C19, and CYP2D6 [40]. In the classic pathway of bile acid synthesis, cholesterol is converted to 7 α -hydroxycholesterol parCYP7A1. Drug–drug interactions can also induce or inhibit CYP activity, influencing the metabolism as well as the toxicity and efficacy of one or both drugs [41]. In phase II, drugs and their metabolites are subjected to conjugative reactions, such as glucuronidation, methylation, sulfation, and acetylation ($-\text{OH}$, $-\text{NH}_2$, $-\text{CH}_3$, $-\text{SO}_3\text{H}$, or $-\text{CH}_3\text{CO}$). The aim of this phase is to convert phase I substrates and their potentially toxic derivatives into molecules that are less hydrophobic and that have an increased molecular weight. This results in the production of metabolites that are more easily excreted through the urine or the bile [41]. However, occasionally, this step produces biological active intermediates, resulting in an increased activity or toxicity [40,42]. Phase I and II enzymes play an important role preparing xenobiotics for the third phase: their elimination through the action of cellular transporters [43].

Transporters play a major role in drug pharmacokinetics, since they regulate not only the elimination but also the absorption and distribution of xenobiotics. The solute carrier (SLC) and ATP-binding cassette (ABC) are the most studied transporter superfamilies [44,45]. They have a major role in homeostasis by regulating transport between body fluid compartments. For this reason, these transporters are most expressed in epithelial barriers, including the liver, intestine, kidney, and the blood–brain barrier. Those families of transporters are mainly known for their relevance in drug disposal, but they also mediate the transport of endogenous substrates. It is also known that the two superfamilies share several substrates, which makes it difficult to determine a drug pathway. For example, SLC22A2, besides being the transporter of metformin, is also a prostaglandin transporter; statin is a substrate for SLC22A8 (OAT3) and ABCG2 (BCRP), and can also interact with other transporters from the SLCO family. In the kidneys, OAT1–4 exhibits similar endogenous substrates, such as cyclic nucleotides (cAMP, cGMP), folate, prostaglandin E2, and α -ketoglutarate, as well as antiviral, antibiotics, and diuretics, but no steroidal anti-inflammatory drugs [45–47]. The complexity of unraveling the interactions between substrates, DME, transporters, and other metabolic pathways makes it crucial to study these factors, in order to improve drug treatment in patients with CKD.

3. Alterations of Drug Metabolism during Chronic Kidney Disease

It is now established that the pharmacokinetic disposition of drugs in patients with CKD is altered. Renal failure alters the *milieu interieur* homeostasis, with an accumulation of uremic toxins altering the renal and non-renal clearance of drugs. This makes dose adjustment challenging in these patients, with frequent drug-related adverse events. However, the knowledge of the cellular and molecular mechanisms involved is not still clearly identified. In the following section, we will expose the knowledge of the changes in DME, as well as a transporter expression and activities during CKD in animal models and patients. Then we will propose possible pathways to partly explain drug impairment during CKD.

3.1. What Do We Learn from Patients and Animals Models of Chronic Kidney Disease?

Studies in humans are not so clear, due to the complexity of evaluating a drug pathway and each factor capable of interacting and modifying the drug metabolism. Diabetic patients with different degrees of renal impairments were treated with repaglinide, an antidiabetic agent metabolized by the enzyme CYP3A4, or by conjugation with glucuronic acid and excreted via the bile [48]. Patients with severe renal dysfunction showed a different elimination rate and a need for drug dosing adjustments [49]. Reboxetine, a selective norepinephrine reuptake inhibitor, was administered to patients with different severity degrees of the renal disease. An increase in renal dysfunction severity was associated with increased exposure and a reduced renal clearance of reboxetine [50]. In another study, it was shown that uremia can modify the disposition of drugs undergoing a high metabolism in the liver by alterations in kidney and liver function, as well as plasma protein concentrations [51]. Patients with more severe kidney impairment needed lower doses of warfarin, a vitamin K antagonist [52]. Although the new, nonvitamin K antagonist oral anticoagulants (NOACs) seem to be beneficial in patients with renal dysfunction [53], vitamin K antagonists remain highly prescribed oral anticoagulants in this population. In another study, fexofenadine was used as a probe of drug clearance by the intestinal and liver transporters P-gp and OATP. It was shown a decreased clearance of fexofenadine with no observed alterations in CYP3A function in patients with end-stage renal disease [54]. On the other hand, using the erythromycin breath test to evaluate the hepatic activity of CYP3A4, this enzyme function was found to be reduced in patients with CKD [55].

The erythromycin breath test illustrates the difficulties to extrapolate results obtained with a given drug after its administration in terms of enzymatic and transporter activities. Indeed, it is a standard test used to evaluate the extent of CYP3A4 activity. After injection, erythromycin (labeled with carbon-14), is converted to C-14 formaldehyde par CYP3A4, then to C-14 CO₂, which is excreted

by the lungs. The amount of C-14 CO₂ exhaled by patients is thought to reflect CYP3A4 activity. However, in fact, this test was lately shown to be also related to the activities of both an uptake organic anion transporter and the efflux hepatic P-gp transporter, responsible for the uptake and exit of erythromycin and metabolites by the hepatocytes [56]. These misinterpretations point to the need to identify all the molecular partners encountered by a given drug, to understand truly what happens after it enters the body. In this way, in vitro work could be useful.

In nephrectomized rats, only DME and efflux transporters have been studied. Phase I enzymes display altered expression. Reduced expression and activity of CYP1A1 and CYP3A2 (rat ortholog of the human gene CYP3A4) was found in the intestine [57], as well as a reduced protein expression and activity of CYP3A1, CYP3A2, and CYP2C11 in the liver [58–61]. Liver and intestinal protein levels of CYP1A2 increased in 5/6 nephrectomized Sprague–Dawley rats by 55% and 168%, respectively [62]. Phase II enzymes have also been shown to be affected during CKD. Reduced expression and activity of the acetyltransferases Nat1 and Nat2 was found in liver from rats with CKD [63]. CKD also induced changes in efflux transporters. Intestinal expression and activity of P-glycoprotein (P-gp; ABCB1) and MRP2 (ABCC2) were found to be decreased in rats after nephrectomy [64]. In the liver, contradictory results were found: P-gp was increased, with no change on MRP2 expression [65], while another team has shown no effect on P-gp expression and an increased MRP2 protein level [66].

3.2. Proposed Factors Involved in Drug Metabolism Impairments in Chronic Kidney Disease

General processes specific to CKD, such as a reduction in renal excretion, moderate acidosis, and decreased protein serum level play an important role in drug disposition and clearance. However, all molecular mechanisms involved are still not well elucidated. What are the changes in expression or activities of the endogenous molecular partners involved, and which mediators are responsible for these changes? Uremic toxins that accumulate during CKD are putative factors. Since some of uremic toxins are activators of the transcription factor, aryl hydrocarbon receptor (AhR), we propose here that AhR could participate in pharmacokinetic modifications found in patients with CKD.

3.2.1. Uremic Toxins

CKD induces the accumulation, in blood and tissues, of numerous solutes. Those with a negative impact on biological functions are called uremic toxins. To date, at least 185 substances have been identified and classified according to their physico-chemical characteristics and their behavior during dialysis: (a) toxins of low molecular weight (<500 Da) and soluble in water, which are well purified; (b) medium-sized toxins (≥500 Da) that are less well purified; and (c) toxins bound to proteins. These last ones, due to their fixation to proteins, are poorly eliminated by conventional dialysis techniques [67–71] (<http://www.uremic-toxins.org/>). Uremic toxins are involved in the progression of kidney disease and in the increased mortality in this population [72–75].

In the world of uremic toxins, those derived from tryptophan, an essential amino acid supplied by the diet, are of prime importance because of their associations with CKD complications and mortality [76–86]. Tryptophan can be metabolized through the indolic pathway by the action of intestinal bacteria. The produced indoles join the liver, to be hydroxylated by the hepatic cytochrome CYP2E1, and then indoxyl is metabolized into indoxyl sulfate (IS) by the sulfotransferase SULT1A1, into indoxyl-beta-D-glucuronide (IG) in the liver, and into indole-3-acetic acid (IAA) in the intestine and tissues [78]. Tryptophan that is not used in protein synthesis is mostly metabolized in the kynurenine pathways by tryptophan-2,3 dioxygenase (TDO) or indolamine-2,3 dioxygenase (IDO) to produce the first metabolite of this pathway, kynurenine, which is then transformed to 3-hydroxyanthranilic acid, 3-hydroxykynurenine, kynurenic acid, anthranilic acid, and quinolinic acid [78,87]. Their levels are increased during CKD; among these toxins, IS, IAA, kynurenic acid, and quinolinic acid are protein-bound.

In vitro studies suggest that uremic serum and toxins are able to impair all phases of drug metabolism: first, the cellular uptake; second, the enzymatic metabolism by phase I and phase II enzymes; and third, the extrusion from the cells.

Reyes et al. show that uremic toxins and human uremic serum reduced the hepatic uptake transport of different drugs, such as losartan, eprosartan and propranolol [88]. Quinolinic acid or indole-3-acetic acid alone inhibits the uptake of eprosartan. The uptake of losartan into rat and human primary hepatocytes was decreased in the presence of serum from hemodialyzed patients [88]. By using HEK293 cells transfected with plasmid encoding for OATP1B1, OATP1B3, or OATP2B1, the authors show that IAA partly inhibits transport by OATP1B1, whereas indoxyl sulfate and 3-carboxy-4-methyl-5-propyl-2-furanpropionate (CMPF) inhibit transport by OATP1B3 and OATP2B1 [88–90]. In rat hepatocytes, IS and CMPF can directly inhibit the uptake of erythromycin by rat organic anion transporter polypeptides 2 (rOatp2) and human OATP-C transporters [91]. In addition, four uremic toxins, including IS, IAA, and kynurenic acid, directly inhibit transport by OATP1B1 and OATP1B3 in a concentration-dependent manner [90–92]. OATP1B1/B3 are considered as the major hepatic OATPs involved in the uptake of numerous drugs, including mainly cholesterol-lowering drugs (statins, Ezetimibe glucuronide), endothelin receptor antagonists (Bosentan, Ambrisentan), antibiotics (Rifampin), anticancer drugs (Methotrexate, Docetaxel, Atrasentan), antidiabetic drugs (Répaglinide), and antiviral drugs (Grazoprevir, Paritaprevir, Voxilaprev) (Mcfeely). In addition, kynurenine has also been shown to be transported into the cell by LAT1, which is highly expressed in glial, neural, renal, and endothelial cells of the blood–brain barrier, where it handles L-DOPA and Melphalan [93]. Together, these data highlight the fact that uremic toxins could compete in this way with drugs to be transported into the cells.

When rat hepatocytes were incubated with human uremic serum, reduced mRNA expression of *CYP1A2*, *2C11*, *2D1/D2*, *3A2*, and *4A1/A3* was found, as well as lower activity of *CYP3A* and *CYP1A* [94]. In another work, normal rat hepatocytes incubated with uremic serum showed decreased mRNA and protein expression of *CYP2C6*, *2C11*, *3A1*, and *3A2*, and decreased *N*-demethylation of erythromycin [95]. IS induces the mRNA expression and activity of *CYP1A2* [96], but partly inhibits *CYP3A4* metabolism [89] in primary rat hepatocytes, *UTG1A1/4* activities in human liver microsomes, and mRNA expression of *CYP1A7* in primary human hepatocytes [97]. In addition, a pool of uremic toxins shows a more pronounced effect on *CYP* and *UTG* activities than when they are used individually, suggesting that they are able to heighten each other's effects. Indole produced by the microbiota from dietary tryptophan is hydroxylated by *CP2E1*, and could be a competitor for drugs metabolized by this cytochrome, such as anesthetics, acetaminophen, and some antiepileptic drugs.

MRP4 (*ABCC4*) and *BCRP* (*ABCG2*)-mediated efflux were inhibited by uremic toxins, including IS and IAA in a concentration-dependent manner, and these inhibitions could occur at concentrations found in patients [98,99]. In addition, kynurenic acid has been identified as a novel substrate for *MRP4* and *BCRP*, and is able to inhibit *BCRP*-mediated transport. In accordance with these last findings, the authors found that in mice invalidated for *Mrp4* or *Bcrp*, plasma levels of kynurenic acid were increased [98]. IS decreased the expression of *ABCG1* in macrophages [100], and it directly suppressed the renal expression of *SLCO4C1* [101]. Since IS, IAA, kynurenine, and CMPF are transported by *OAT1* and *OAT3* in the kidneys, they are also capable of limiting the excretion of other substrates by directly competition [102,103]. In their work to understand changes in bile acid pool, Weigand et al. show that kynurenic acid inhibits the activity of the bile salt efflux pump, whereas the uremic toxins p-cresyl glucuronide and hippuric acid increase the activities of multidrug resistance associated proteins [99].

AST-120 is an absorbent oral charcoal, used as treatment for patients with CKD in Japan, Korea, and the Philippines. It binds metabolites with molecular weights less than 1000, reducing their absorption through the intestinal barrier [104,105] and slowing the progression of CKD. However, in patients with moderate to severe CKD, Schulman et al. could not demonstrate a slowdown in the progression of renal disease [106]. The compliance of patients to the high number of pills and the absorption of drugs with AST-120 could partly explain the absence of benefits observed in this

trial [106,107]. Nevertheless, it has been shown that AST-120 reduces the uptake of two uremic toxins: IS and p-cresol sulfate (PCS). In the kidneys, the use of AST-120 in CKD rats prevented the down regulation of OAT1 transporter [108], which is also responsible for the excretion of this uremic toxin. AST-120 also recovered SLCO4C1 expression in the kidneys, while decreased plasma levels of IS were observed [101]. Studies have also shown that changes on drug metabolism can be improved after hemodialysis or kidney transplantation [109,110]. Although the use of AST-120 remains still controversial, all of these studies are largely in favor of a role of circulating factors on drug metabolism.

Besides being able to affect drug metabolism acting on biotransformation and elimination phases, uremic toxins can also change a drug's pharmacokinetics through binding to proteins. It is known that CKD affects the protein binding of several drugs [111,112]. Free, unbound fractions of the drug are usually increased during CKD due to hypoalbuminemia, a common consequence of nephrotic syndrome and malnutrition. Furthermore, uremia leads to the carbamylation of albumin, altering its binding affinity to drugs. It has been shown that uremic toxins with a high-affinity binding to albumin (IS, CMPF, IAA, and PCS) directly compete for these binding-sites with other substrates [113,114]. This competition leads to impaired distribution and an increased accumulation of the drug. This corroborates the importance of circulating molecules, such as uremic toxins, in pharmacokinetic impairments found in patients with CKD, as well as the need to improve their removal from patients. In this way, a very interesting work was recently developed by Li et al. [115]. Natural products of two plants (*Salvia miltiorrhiza* and *Carthamus tinctorius*) constituting the phytoproduct Danhong injection, used in Chinese phytomedicine, are known to bind proteins strongly. Ingeniously, the authors used the Danhong injection as a competitor of protein-bound uremic toxins, in order to increase the free fraction of these toxins and to improve their removal during a dialysis session. The results obtained are better than those observed with other treatments, such as AST-120. Indeed, the elimination is increased by 272% for PCS and by 136% for IS [115]. In addition, one could think that this natural treatment may display fewer side effects than AST-120.

3.2.2. Aryl Hydrocarbon Receptor

AhR could participate in the altered clearance of drugs in patients with CKD. Besides directly disturbing enzymes, transporters, and the binding to albumin, another way for tryptophan-derived uremic toxins to modify drug metabolism is through the activation of transcription factors (Figure 1). Indeed, most of the metabolites produced during the breakdown of tryptophan by the indolic and kynurenine pathways (IS, IAA, IG, kynurenine, and kynurenic acid) are ligands of the aryl hydrocarbon receptor (AhR) [83,116–118]; kynurenine and kynurenic acid were recently identified as such [87]. In line with the presence of high concentrations of numerous AhR ligands in patients with CKD, AhR activation is also observed in these patients. By using a reporter gene-based cell bioassay (Callux assay), one study demonstrates that the serum of 20 hemodialyzed patients can increase by three-fold the expression of a reporter gene under the control of AhR [81]. We find same results with the serum of 116 patients with CKD [119]. In addition, by gene expression profiling from blood, we show that mRNA levels of two markers of AhR activation, CYP1A1 and AhR repressor (AHRR), are increased in 20 patients with CKD [119]. The level of AhR activation is correlated with IS levels in patients with CKD, and with kynurenine levels in non-CKD patients with post-vascular injury thrombosis [120]. In animal models of CKD (5/6 nephrectomy), AhR activation occurs as well. The mRNA level of AhRR, a specific AhR target, is increased in the kidney of CKD rats (Nakayama). Similarly, in mice with CKD, we found the induction of Cyp1a1 mRNA, a specific target of AhR, in the aorta and heart, induction which does not happen in AhR^{-/-} CKD mice. After serial indoxyl sulfate injections, we observed the expression of Cyp1a1 mRNA in the aorta and heart in WT mice, but not in AhR^{-/-} mice. These works suggest that overactivation of AhR occurs during CKD.

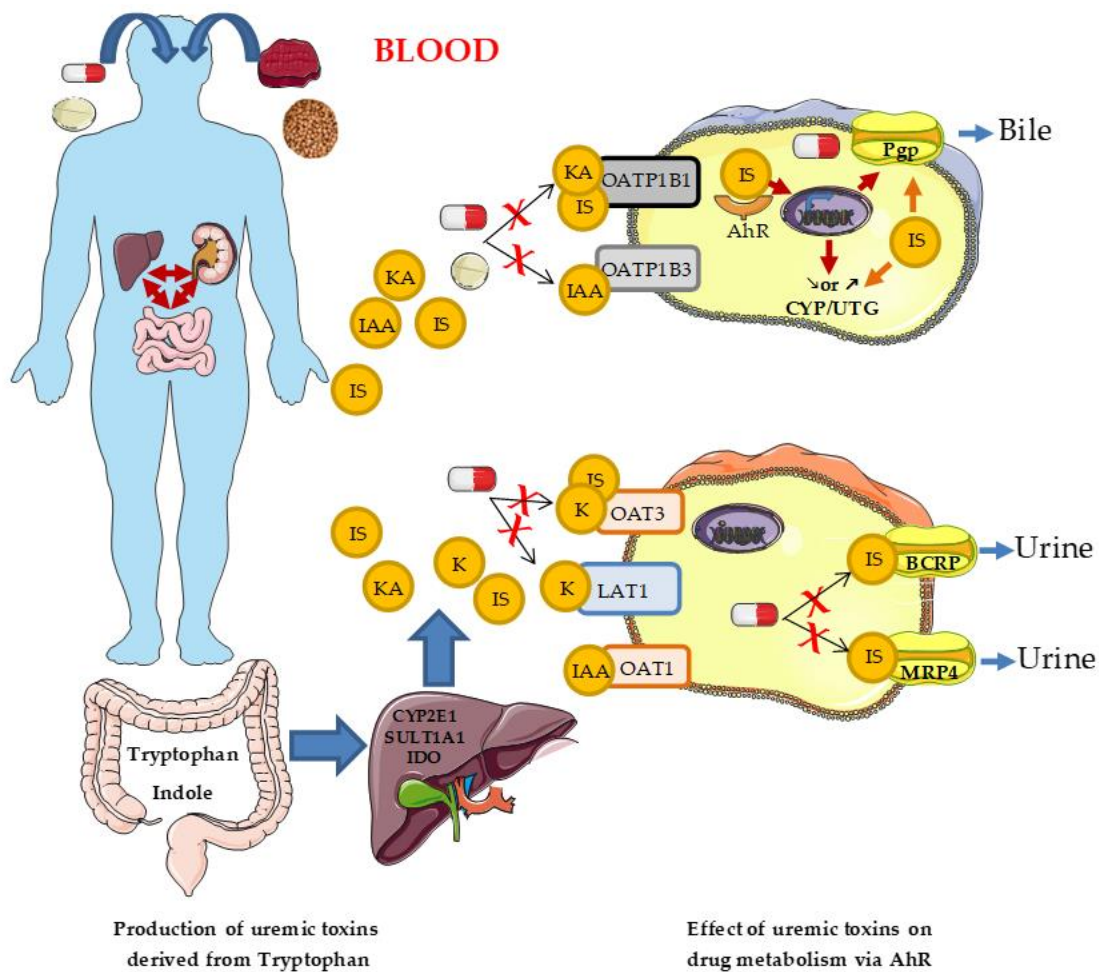


Figure 1. The effect of uremic toxins derived from tryptophan on drug metabolism via aryl hydrocarbon receptor (AhR). Indoxyl sulfate (IS), kynurenine (K), kynurenic acid (KA), and indole-3-acetic acid (IAA), produced from dietary tryptophan, are ligands of the transcription factor AhR. AhR, upon activation by these uremic toxins, can modulate the expression of genes involved in the metabolism and in the efflux of drugs. In addition, these toxins can inhibit directly these enzymes and these transporters.

One of the biological roles of AhR is to respond to xenobiotic exposure, in order to orchestrate the detoxification of its ligands [120,121]. This transcription factor is sequestered in a complex in the cytoplasm. Ligand binding to AhR induces its translocation to the nucleus [121,122] and dimerization with the aryl hydrocarbon receptor nuclear translocator (ARNT) [123]. Then, AHR/ARNT binds to a consensus DNA sequence (5'-GCGTG-3') called xenobiotic responsive element (XRE) [124]. The binding to the promoter of target genes leads to their transcription. However, little is known about the importance of AhR on the regulation of DME and drug transporters. We performed a research in PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>) to identify, among the unambiguous target genes modulated by AhR, those that are involved in drug metabolism. Four of them—cytochrome 1A2 (CYP1A2), CYP2S1, aldehyde dehydrogenase 1A1 (ALDH1A1), and ALDH3A1—belong to phase I enzymes. Among phase II DME, seven are targeted by AhR: NAD(P)H quinone dehydrogenase 1 [Nqo1], UDP-glucuronosyltransferase 1A1 [UGT1A1], UGT1A3, UGT1A4, UGT1A7, UGT1A10, and glutathione S-transferase A1 [GSTA1] [35,125–133]. Four drug transporters—multidrug resistance-associated protein 4 (MRP4, *ABCC4*), breast cancer resistance protein (BCRP; *ABCG2*), P-glycoprotein (MDR1, P-gp, *ABCB1*), and L-type amino acid transporter 1 (LAT1)—were also shown to be regulated by AhR [134–137].

CYP1A2, whose activity is monitored by its probes—caffeine and theophylline—is among the major CYPs in the liver, and accounts for about 13% of the total CYP proteins in this organ [138,139]. In regard to the top 200 drugs, CYP1A2 is involved significantly with at least 13 of them, and in a minor way with 110 others. Sindhu et al. demonstrated that CYP1A2 protein levels are increased by 55% and 168% in the liver and kidneys of 5/6 nephrectomized rats, respectively [46]. In the contrary, in the model of CKD induced by adenine, CYP1A2 activity is not significantly affected [140]. CYP2S1 was recently discovered, and it is expressed in the skin and the small intestines. This enzyme is involved in all-transretinoic acid metabolism into the skin [141,142]. There is no information about its expression in patients with CKD. CYP1A1 and CYP1B1, which belong to the classical AhR targets, do not seem to act mainly on drugs, but rather on polycyclic aromatic hydrocarbon (PAH) metabolism [143]. Nqo1 catalyzes the transformation of the highly toxic and prooxidant quinones into hydroquinones; these are less toxic and more easily excreted by the organism. Drugs like mitomycinC, β -lapachone, and benzoquinone ansamycins are activated by Nqo1 [144]. However, in another way, the increased activity of this enzyme induces resistance to 4-hydroperoxycyclophosphamide, a drug used in cancer treatment. ALDH1A1 is an important biomarker for cancer cells and cancer stem cells, and together with ALDH3A1 confers resistance to oxazaphosphorines, which include cyclophosphamide in various tumor types [145,146]. Among the superfamily of UGT enzymes, UGT1 is strongly engaged in the metabolism of drugs used to treat epilepsy (UGT1A4) [147,148], schizophrenia (UGT1A3 and UGT1A4) [149], hypertension (UGT1A1, UGT1A3, UGT1A7, and UGT1A9) [150–152], and hypercholesterolemia (UGT1A1 and UGT1A3) [153–156]. Furthermore, UGT1A9 is responsible for the metabolism of propofol (70%) into propofol glucuronide [157]. In small-cell lung cancer cells treated by doxorubicin, GSTA1 transfection has also been shown to render these cells more resistant to doxorubicin-induced apoptosis [158].

About the drug transporters, MRP4, BCRP, and P-gp are increased upon AhR activation. They belong to the ABC-binding cassette transporters, which extrude from the cell a wide variety of chemical exogenous compounds, in order to fulfill detoxification functions and protect the organism against their toxic effects [159–161]. For example, several toxic compounds from plants are extruded from cells by these multidrug transporters. The alkaloid colchicine (from *Colchicum autumnale*) binds tubulin and inhibits the polymerization dynamics of microtubules. The taxane paclitaxel (from *Taxus baccata*) stabilizes microtubules by binding to polymeric tubulin. The resulting effect of these two molecules is to stop cell mitosis. Pheophorbide a, found in algae and plants, induces phototoxicity. Thus, these multidrug transporters were and are highly precious to preserve the hunter-gatherers that we were in the past. While these transporters are used to extrude mainly chemical compounds derived from plants, their very wide specificity lead them to handle drugs, and to be considered now as the main players of the multidrug resistance process (MDR) [148,162]. Extruding drugs from cells decreases their intestinal absorption, their intracellular concentration, and thus their cellular effect. Mutsaers et al. demonstrated that uremic toxins decreased some drug transporter activities [92], and could in this way counteract increased expression under AhR activation. In addition, we have found that cardiac and kidney transplant recipients with CKD needed higher doses of cyclosporine, a P-gp substrate, to obtain the cyclosporine target blood level. These in vivo results are in accord with our findings showing that IS increases P-gp activity in an AhR-dependant way in hepatocytes [137]. Among the transporter systems expressed at the blood–brain barrier (BBB), those responsible for the transport of large amino acids (large neutral amino acid transporter 1 (LAT1)) are highly expressed. These transporters could compromise drug delivery to the brain [163]. LAT1 is expressed in both the luminal and abluminal membrane of the capillary endothelial cells at the BBB, with expression levels approximately 100-fold greater than in other tissues (e.g., placenta, retina, gut). There is some evidence that supports the involvement of the LAT system on the pharmacokinetics of several drugs and hormones, such as l-DOPA, the antitumoral drug Melphalan, and in to a lesser extent thyroxine and triiodothyronine [164]. In vitro studies with the brain capillary endothelium [165–169], renal epithelial cells [170], intestinal

epithelial cell lines [171], and plasmacytoma cells have demonstrated clearly that the uptake of l-DOPA and Melphalan takes place by L-type amino acid transporters (LAT1 and LAT2).

4. Conclusions

In conclusion, AhR, by its target genes, seems to play a role in drug metabolism, and could constitute a link between CKD and altered drug clearance. The modulation of its activity could be proposed as a possible and future potential target to modulate drug clearance in patients. Its level of activation in vivo, evaluated by a Callux assay, could help clinicians to adjust the dosage of some drugs. Further works are necessary to prove the usefulness of this approach in the care of patients with CKD.

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References

1. Hallan, S.I.; Coresh, J.; Astor, B.C.; Asberg, A.; Powe, N.R.; Romundstad, S.; Hallan, H.A.; Lydersen, S.; Holmen, J. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J. Am. Soc. Nephrol.* **2006**, *17*, 2275–2284. [[CrossRef](#)]
2. Jha, V.; Garcia-Garcia, G.; Iseki, K.; Li, Z.; Naicker, S.; Plattner, B.; Saran, R.; Wang, A.Y.; Yang, C.W. Chronic kidney disease: global dimension and perspectives. *Lancet.* **2013**, *382*, 260–272. [[CrossRef](#)]
3. Ojo, A. Addressing the global burden of chronic kidney disease through clinical and translational research. *Trans. Am. Clin. Climatol. Assoc.* **2014**, *125*, 229–243. [[PubMed](#)]
4. Steenkamp, R.; Castledine, C.; Feest, T.; Fogarty, D. UK Renal Registry 13th Annual Report [December 2010]: Chapter 2: UK RRT prevalence in 2009: national and centre-specific analyses. *Nephron. Clin. Pract.* **2011**, *2*, c27–c52. [[CrossRef](#)]
5. Modi, G.K.; Jha, V. The incidence of end-stage renal disease in India: a population-based study. *Kidney Int.* **2006**, *70*, 2131–2133. [[CrossRef](#)] [[PubMed](#)]
6. Smith, D.H.; Gullion, C.M.; Nichols, G.; Keith, D.S.; Brown, J.B. Cost of medical care for chronic kidney disease and comorbidity among enrollees in a large HMO population. *J. Am. Soc. Nephrol.* **2004**, *15*, 1300–1306. [[CrossRef](#)]
7. Eckardt, K.U.; Coresh, J.; Devuyst, O.; Johnson, R.J.; Köttgen, A.; Levey, A.S.; Levin, A. Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet.* **2013**, *382*, 158–169. [[CrossRef](#)]
8. Foley, R.N.; Parfrey, P.S.; Sarnak, M.J. Epidemiology of cardiovascular disease in chronic renal disease. *J. Am. Soc. Nephrol.* **1998**, *9*, S16–S23. [[CrossRef](#)]
9. Matsushita, K.; van der Velde, M.; Astor, B.C.; Woodward, M.; Levey, A.S.; de Jong, P.E.; Coresh, J.; Gansevoort, R.T. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative metaanalysis. *Lancet.* **2010**, *375*, 2073–2081.
10. Levin, A.; Singer, J.; Thompson, C.R.; Ross, H.; Lewis, M. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. *Am. J. Kidney Dis.* **1996**, *27*, 347–354. [[CrossRef](#)]
11. Raggi, P.; Bommer, J.; Chertow, G.M. Valvular calcification in hemodialysis patients randomized to calcium-based phosphorus binders or sevelamer. *J. Heart. Valve. Dis.* **2004**, *13*, 134–141.
12. London, G.M.; Guérin, A.P.; Marchais, S.J.; Métivier, F.; Pannier, B.; Adda, H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol. Dial. Transplant.* **2003**, *18*, 1731–1740. [[CrossRef](#)] [[PubMed](#)]
13. Asami, M.; Tanabe, K.; Ito, S.; Yoshida, E.; Aoki, J.; Tanimoto, S.; Horiuchi, Y.; Yoshida, M. Impact of Indoxyl Sulfate on Coronary Plaques in Patients on Hemodialysis. *Int. Heart. J.* **2018**, *59*, 489–4968. [[CrossRef](#)]

14. Karbowska, M.; Kaminski, T.W.; Znorko, B.; Domaniewski, T.; Misztal, T.; Rusak, T.; Pryczynicz, A.; Guzinska-Ustymowicz, K.; Pawlak, K.; Pawlak, D. Indoxyl Sulfate Promotes Arterial Thrombosis in Rat Model via Increased Levels of Complex TF/VII, PAI-1, Platelet Activation as Well as Decreased Contents of SIRT1 and SIRT3. *Front. Physiol.* **2018**, *9*, 1623. [[CrossRef](#)]
15. Kaminski, T.W.; Pawlak, K.; Karbowska, M.; Myśliwiec, M.; Pawlak, D. Indoxyl sulfate - the uremic toxin linking hemostatic system disturbances with the prevalence of cardiovascular disease in patients with chronic kidney disease. *BMC Nephrology* **2017**, *18*(1), 35. [[CrossRef](#)] [[PubMed](#)]
16. Maciel, R.A.P.; Cunha, R.S.; Busato, V.; Franco, C.R.C.; Gregório, P.C.; Dolenga, C.J.R.; Nakao, L.S.; Massy, Z.A.; Boullier, A.; Pecoits-Filho, R.; et al. Uremia Impacts VE-Cadherin and ZO-1 Expression in Human Endothelial Cell-to-Cell Junctions. *Toxins* **2018**, *10*, 404. [[CrossRef](#)]
17. Blacher, J.; Safar, M.E.; Guerin, A.P.; Pannier, B.; Marchais, S.J.; London, G.M. Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int.* **2003**, *63*, 1852–1860. [[CrossRef](#)] [[PubMed](#)]
18. Yu, M.; Kim, Y.J.; Kang, D.H. Indoxyl sulfate-induced endothelial dysfunction in patients with chronic kidney disease via an induction of oxidative stress. *Clin. J. Am. Soc. Nephrol.* **2011**, *6*, 30–39. [[CrossRef](#)]
19. Namikoshi, T.; Tomita, N.; Satoh, M.; Sakuta, T.; Kuwabara, A.; Kobayashi, S.; Higuchi, Y.; Nishijima, F.; Kashiwara, N. Oral adsorbent AST-120 ameliorates endothelial dysfunction independent of renal function in rats with subtotal nephrectomy. *Hypertens. Res.* **2009**, *32*, 194–200. [[CrossRef](#)]
20. Sciarretta, S.; Valenti, V.; Tocci, G.; Pontremoli, R.; Rosei, E.A.; Ambrosioni, E.; Costa, V.; Leonetti, G.; Pessina, A.C.; Trimarco, B.; et al. Association of renal damage with cardiovascular diseases is independent of individual cardiovascular risk profile in hypertension: data from the Italy -Developing Education and awareness on MicroAlbuminuria in patients with hypertensive Disease study. *J. Hypertens.* **2010**, *28*, 251–258. [[CrossRef](#)]
21. Barreto, F.C.; Stinghen, A.E.; de Oliveira, R.B.; Franco, A.T.; Moreno, A.N.; Barreto, D.V.; Pecoits-Filho, R.; Drüeke, T.B.; Massy, Z.A. The quest for a better understanding of chronic kidney disease complications: an update on uremic toxins. *J. Bras. Nefrol.* **2014**, *36*, 221–235. [[CrossRef](#)]
22. Mason, N.A. Polypharmacy and medication-related complications in the chronic kidney disease patient. *Curr. Opin. Nephrol. Hypertens.* **2011**, *20*, 492–497. [[CrossRef](#)] [[PubMed](#)]
23. Verbeeck, R.K.; Musuamba, F.T. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. *Eur. J. Clin. Pharmacol.* **2009**, *65*, 757–773. [[CrossRef](#)]
24. Nolin, T.D. A Synopsis of Clinical Pharmacokinetic Alterations in Advanced CKD. *Semin. Dial.* **2015**, *28*, 325–329. [[CrossRef](#)]
25. Haufroid, V.; Mourad, M.; Van Kerckhove, V.; Wawrzyniak, J.; De Meyer, M.; Eddour, D.C.; Malaise, J.; Lison, D.; Squifflet, J.P.; Wallemacq, P. The effect of CYP3A5 and MDR1 [ABCB1] polymorphisms on cyclosporine and tacrolimus dose requirements and trough blood levels in stable renal transplant patients. *Pharmacogenetics.* **2004**, *14*, 147–154. [[CrossRef](#)] [[PubMed](#)]
26. Ingelman-Sundberg, M.; Gomez, A. The past, present and future of pharmacoepigenomics. *Pharmacogenomics.* **2010**, *11*, 625–627. [[CrossRef](#)]
27. Cotreau, M.M.; von Moltke, L.L.; Greenblatt, D.J. The influence of age and sex on the clearance of cytochrome P450 3A substrates. *Clin. Pharmacokinet.* **2005**, *44*, 33–60. [[CrossRef](#)]
28. Kinirons, M.T.; O'Mahony, M.S. Drug metabolism and ageing. *Br. J. Clin. Pharmacol.* **2004**, *57*, 540–544. [[CrossRef](#)]
29. Zanger, U.M.; Raimundo, S.; Eichelbaum, M. Cytochrome P450 2D6: Overview and update on pharmacology, genetics, biochemistry. *Naunyn. Schmiedeberg's Arch. Pharmacol.* **2004**, *369*, 23–37. [[CrossRef](#)]
30. Dettli, L.; Spring, P.; Habersang, R. Drug dosage in patients with impaired renal function. *Postgrad. Med. J.* **1970**, *10*, 32–35.
31. Dettli, L. Elimination of drugs in patients with renal insufficiency. *Schweiz. Rundsch. Med. Prax.* **1973**, *62*, 476–478.
32. Dreisbach, A.W.; Lertora, J.J. The effect of chronic renal failure on drug metabolism and transport. *Expert. Opin. Drug. Metab. Toxicol.* **2008**, *4*, 1065–1074. [[CrossRef](#)] [[PubMed](#)]
33. Zhang, Y.; Zhang, L.; Abraham, S.; Apparaju, S.; Wu, T.C.; Strong, J.M.; Xiao, S.; Atkinson, A.J., Jr.; Thummel, K.E.; Leeder, J.S.; et al. Assessment of the impact of renal impairment on systemic exposure of new molecular entities: evaluation of recent new drug applications. *Clin. Pharmacol. Ther.* **2009**, *85*, 305–311. [[CrossRef](#)] [[PubMed](#)]

34. Iyanagi, T. Molecular mechanism of phase I and phase II drug-metabolizing enzymes: implications for detoxification. *Int. Rev. Cytol.* **2007**, *260*, 35–112.
35. Köhle, C.; Bock, K.W. Coordinate regulation of human drug-metabolizing enzymes, and conjugate transporters by the Ah receptor, pregnane X receptor and constitutive androstane receptor. *Biochem. Pharmacol.* **2009**, *77*, 689–699. [[CrossRef](#)]
36. Xu, C.; Li, C.Y.; Kong, A.N. Induction of phase I, II and III drug metabolism/transport by xenobiotics. *Arch. Pharm. Res.* **2005**, *28*, 249–268. [[CrossRef](#)] [[PubMed](#)]
37. Kot, M.; Daniel, W.A. Caffeine as a marker substrate for testing cytochrome P450 activity in human and rat. *Pharmacol Rep.* **2008**, *60*, 789–797.
38. Ohnishi, A.; Kato, M.; Kojima, J.; Ushiyama, H.; Yoneko, M.; Kawai, H. Differential pharmacokinetics of theophylline in elderly patients. *Drugs Aging* **2003**, *20*, 71–84. [[CrossRef](#)]
39. Uno, T.; Nakano, R.; Kitagawa, R.; Okada, M.; Kanamaru, K.; Takenaka, S.; Uno, Y.; Imaishi, H. Metabolism of steroids by cytochrome P450 2C9 variants. *Biopharm Drug Dispos.* **2018**, *39*, 371–377. [[CrossRef](#)] [[PubMed](#)]
40. Seden, K.; Dickinson, L.; Khoo, S.; Back, D. Grapefruit-drug interactions. *Drugs* **2010**, *70*, 2373–2407. [[CrossRef](#)] [[PubMed](#)]
41. Gonzalez, F.J.; Tukey, R.H. Chapter 3. Drug Metabolism. In *Goodman & Gilman's. The Pharmacological Basis of Therapeutics*. Brunton, L.; Lazo, J., Parker, K., Eds.; McGraw-Hill: New York, NY, USA, 1996.
42. Bolton, J.L.; Chang, M. Quinoids as reactive intermediates in estrogen carcinogenesis. *Adv. Exp. Med. Biol.* **2001**, *500*, 497–507.
43. Köhle, C.; Bock, K.W. Coordinate regulation of Phase I and II xenobiotic metabolisms by the Ah receptor and Nrf2. *Biochem. Pharmacol.* **2007**, *73*, 1853–1862. [[CrossRef](#)] [[PubMed](#)]
44. Sharom, F.J. ABC multidrug transporters: Structure, function and role in chemoresistance. *Pharmacogenomics.* **2008**, *9*, 105–127. [[CrossRef](#)] [[PubMed](#)]
45. Roth, M.; Obaidat, A.; Hagenbuch, B. OATPs, OATs and OCTs: the organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. *Br. J. Pharmacol.* **2012**, *165*, 1260–1287. [[CrossRef](#)] [[PubMed](#)]
46. Nigam, S.K. What do drug transporters really do? *Nat. Rev. Drug. Discov.* **2015**, *14*, 29–44. [[CrossRef](#)]
47. Nigam, S.K.; Wu, W.; Bush, K.T.; Hoenig, M.P.; Blantz, R.C.; Bhatnagar, V. Handling of Drugs, Metabolites, and Uremic Toxins by Kidney Proximal Tubule Drug Transporters. *Clin. J. Am. Soc. Nephrol.* **2015**, *10*, 2039–2049. [[CrossRef](#)]
48. Owens, D.R. Repaglinide-prandial glucose regulator: a new class of oral antidiabetic drugs. *Diabet. Med.* **1998**, *4*, S28–S36. [[CrossRef](#)]
49. Schumacher, S.; Abbasi, I.; Weise, D.; Hatorp, V.; Sattler, K.; Sieber, J.; Hasslacher, C. Single- and multiple-dose pharmacokinetics of repaglinide in patients with type 2 diabetes and renal impairment. *Eur. J. Clin. Pharmacol.* **2001**, *57*, 147–152. [[CrossRef](#)]
50. Coulomb, F.; Ducret, F.; Laneury, J.P.; Fiorentini, F.; Poggesi, I.; Jannuzzo, M.G.; Fleishaker, J.C.; Houin, G.; Duchêne, P. Pharmacokinetics of single-dose reboxetine in volunteers with renal insufficiency. *J. Clin. Pharmacol.* **2000**, *40*, 482–487. [[CrossRef](#)]
51. Yuan, R.; Venitz, J. Effect of chronic renal failure on the disposition of highly hepatically metabolized drugs. *Int. J. Clin. Pharmacol. Ther.* **2000**, *38*, 245–253. [[CrossRef](#)]
52. Limdi, N.A.; Limdi, M.A.; Cavallari, L.; Anderson, A.M.; Crowley, M.R.; Baird, M.F.; Allon, M.; Beasley, T.M. Warfarin dosing in patients with impaired kidney function. *Am. J. Kidney Dis.* **2010**, *56*, 823–831. [[CrossRef](#)] [[PubMed](#)]
53. Lee, K.H.; Park, H.W.; Cho, J.G.; Yoon, N.S.; Kim, S.S.; Kim, M.R.; Kim, M.C.; Cho, K.H.; Kim, H.K.; Kim, C.H.; et al. Comparison of non-vitamin K antagonist oral anticoagulants and warfarin on clinical outcomes in atrial fibrillation patients with renal dysfunction. *Europace* **2015**, *10*, 69–75. [[CrossRef](#)] [[PubMed](#)]
54. Nolin, T.D.; Frye, R.F.; Le, P.; Sadr, H.; Naud, J.; Leblond, F.A.; Pichette, V.; Himmelfarb, J. ESRD impairs nonrenal clearance of fexofenadine but not midazolam. *J. Am. Soc. Nephrol.* **2009**, *20*, 2269–2276. [[CrossRef](#)] [[PubMed](#)]
55. Dowling, T.C.; Briglia, A.E.; Fink, J.C.; Hanes, D.S.; Light, P.D.; Stackiewicz, L.; Karyekar, C.S.; Eddington, N.D.; Weir, M.R.; Henrich, W.L. Characterization of hepatic cytochrome p4503A activity in patients with end-stage renal disease. *Clin. Pharmacol. Ther.* **2003**, *73*, 427–434. [[CrossRef](#)]
56. Frassetto, L.A.; Poon, S.; Tsourounis, C.; Valera, C.; Benet, L.Z. Effects of uptake and efflux transporter inhibition on erythromycin breath test results. *Clin. Pharmacol. Ther.* **2007**, *81*, 828–832. [[CrossRef](#)] [[PubMed](#)]

57. Leblond, F.A.; Petrucci, M.; Dubé, P.; Bernier, G.; Bonnardeaux, A.; Pichette, V. Downregulation of intestinal cytochrome p450 in chronic renal failure. *J. Am. Soc. Nephrol.* **2002**, *13*, 1579–1585. [[CrossRef](#)] [[PubMed](#)]
58. Leblond, F.A.; Giroux, L.; Villeneuve, J.P.; Pichette, V. Decreased in vivo metabolism of drugs in chronic renal failure. *Drug. Metab. Dispos.* **2000**, *28*, 1317–1320.
59. Leblond, F.A.; Guévin, C.; Demers, C.; Pellerin, I.; Gascon-Barré, M.; Pichette, V. Downregulation of hepatic cytochrome P450 in chronic renal failure. *J. Am. Soc. Nephrol.* **2001**, *12*, 326–332.
60. Uchida, N.; Kurata, N.; Shimada, K.; Nishimura, Y.; Yasuda, K.; Hashimoto, M.; Uchida, E.; Yasuhara, H. Changes of hepatic microsomal oxidative drug metabolizing enzymes in chronic renal failure (CRF) rats by partial nephrectomy. *Jpn. J. Pharmacol.* **1995**, *68*, 431–439. [[CrossRef](#)]
61. Velenosi, T.J.; Fu, A.Y.; Luo, S.; Wang, H.; Urquhart, B.L. Down-regulation of hepatic CYP3A and CYP2C mediated metabolism in rats with moderate chronic kidney disease. *Drug. Metab. Dispos.* **2012**, *40*, 1508–1514. [[CrossRef](#)]
62. Sindhu, R.K.; Vaziri, N.D. Upregulation of cytochrome P450 1A2 in chronic renal failure: does oxidized tryptophan play a role? *Adv. Exp. Med. Biol.* **2003**, *527*, 401–407.
63. Simard, E.; Naud, J.; Michaud, J.; Leblond, F.A.; Bonnardeaux, A.; Guillemette, C.; Sim, E.; Pichette, V. Downregulation of hepatic acetylation of drugs in chronic renal failure. *J. Am. Soc. Nephrol.* **2008**, *19*, 1352–1359. [[CrossRef](#)] [[PubMed](#)]
64. Naud, J.; Michaud, J.; Boisvert, C.; Desbiens, K.; Leblond, F.A.; Mitchell, A.; Jones, C.; Bonnardeaux, A.; Pichette, V. Down-regulation of intestinal drug transporters in chronic renal failure in rats. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 978–985. [[CrossRef](#)] [[PubMed](#)]
65. Naud, J.; Michaud, J.; Leblond, F.A.; Lefrançois, S.; Bonnardeaux, A.; Pichette, V. Effects of chronic renal failure on liver drug transporters. *Drug. Metab. Dispos.* **2008**, *36*, 124–128. [[CrossRef](#)]
66. Laouari, D.; Yang, R.; Veau, C.; Blanke, I.; Friedlander, G. Two apical multidrug transporters, P-gp and MRP2, are differently altered in chronic renal failure. *Am. J. Physiol. Renal. Physiol.* **2001**, *280*, F636–F645. [[CrossRef](#)]
67. Vanholder, R.; De Smet, R.; Glorieux, G.; Argilés, A.; Baurmeister, U.; Brunet, P.; Clark, W.; Cohen, G.; De Deyn, P.P.; Deppisch, R.; et al. European Uremic Toxin Work Group [EUTox]. Review on uremic toxins: classification, concentration, and interindividual variability. *Kidney. Int.* **2003**, *63*, 1934–1943. [[CrossRef](#)]
68. Deltombe, O.; Van Biesen, W.; Glorieux, G.; Massy, Z.; Dhondt, A.; Eloit, S. Exploring Protein Binding of Uremic Toxins in Patients with Different Stages of Chronic Kidney Disease and during Hemodialysis. *Toxins* **2015**, *710*, 3933–3946. [[CrossRef](#)]
69. Rhee, E.P.; Souza, A.; Farrell, L.; Pollak, M.R.; Lewis, G.D.; Steele, D.J.; Thadhani, R.; Clish, C.B.; Greka, A.; Gerszten, R.E. Metabolite profiling identifies markers of uremia. *J. Am. Soc. Nephrol.* **2010**, *6*, 1041–1051. [[CrossRef](#)]
70. Mischak, H.; Delles, C.; Vlahou, A.; Vanholder, R. Proteomic biomarkers in kidney disease: issues in development and implementation. *Nat. Rev. Nephrol.* **2015**, *11*(4), 221–232. [[CrossRef](#)]
71. Vanholder, R.; Pletinck, A.; Schepers, E.; Glorieux, G. Biochemical and Clinical Impact of Organic Uremic Retention Solutes: A Comprehensive Update. *Toxins* **2018**, *1*, 33. [[CrossRef](#)]
72. Ortiz, A.; Covic, A.; Fliser, D.; Fouque, D.; Goldsmith, D.; Kanbay, M.; Mallamaci, F.; Massy, Z.A.; Rossignol, P.; Vanholder, R.; et al. Board of the EURECA-m Working Group of ERA-EDTA. Epidemiology, contributors to, and clinical trials of mortality risk in chronic kidney failure. *Lancet.* **2014**, *383*, 1831–1843. [[CrossRef](#)]
73. Vanholder, R.; Baurmeister, U.; Brunet, P.; Cohen, G.; Glorieux, G.; Jankowski, J.; European Uremic Toxin Work Group. A bench to bedside view of uremic toxins. *J. Am. Soc. Nephrol.* **2008**, *19*, 863–870. [[CrossRef](#)]
74. Bammens, B.; Evenepoel, P.; Keuleers, H.; Verbeke, K.; Vanrenterghem, Y. Free serum concentrations of the protein-bound retention solute p-cresol predict mortality in hemodialysis patients. *Kidney Int.* **2006**, *69*, 1081–1087. [[CrossRef](#)]
75. Liabeuf, S.; Barreto, D.V.; Barreto, F.C.; Meert, N.; Glorieux, G.; Schepers, E.; Temmar, M.; Choukroun, G.; Vanholder, R.; Massy, Z.A. European Uraemic Toxin Work Group [EUTox]. Free p-cresylsulphate is a predictor of mortality in patients at different stages of chronic kidney disease. *Nephrol. Dial. Transplant.* **2010**, *25*, 1183–1191. [[CrossRef](#)]
76. Barreto, F.C.; Barreto, D.V.; Liabeuf, S.; Meert, N.; Glorieux, G.; Temmar, M.; Choukroun, G.; Vanholder, R.; Massy, Z.A.; European Uremic Toxin Work Group [EUTox]. Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. *Clin. J. Am. Soc. Nephrol.* **2009**, *4*, 1551–1558. [[CrossRef](#)] [[PubMed](#)]

77. Dou, L.; Sallée, M.; Cerini, C.; Poitevin, S.; Gondouin, B.; Jourde-Chiche, N.; Fallague, K.; Brunet, P.; Calaf, R.; Dussol, B.; Mallet, B.; Dignat-George, F.; Burtey, S. The cardiovascular effect of the uremic solute indole-3 acetic acid. *J. Am. SocNephrol.* **2015**, *26*, 876–887. [[CrossRef](#)]
78. Sallée, M.; Dou, L.; Cerini, C.; Poitevin, S.; Brunet, P.; Burtey, S. The aryl hydrocarbon receptor-activating effect of uremic toxins from tryptophan metabolism: a new concept to understand cardiovascular complications of chronic kidney disease. *Toxins* **2014**, *6*, 934–949.
79. Jourde-Chiche, N.; Dou, L.; Sabatier, F.; Calaf, R.; Cerini, C.; Robert, S.; Camoin-Jau, L.; Charpiot, P.; Argiles, A.; Dignat-George, F.; et al. Levels of circulating endothelial progenitor cells are related to uremic toxins and vascular injury in hemodialysis patients. *J. Thromb. Haemost.* **2009**, *7*, 1576–1584. [[CrossRef](#)] [[PubMed](#)]
80. Gao, C.; Ji, S.; Dong, W.; Qi, Y.; Song, W.; Cui, D.; Shi, J. Indolic uremic solutes enhance procoagulant activity of red blood cells through phosphatidylserine exposure and microparticle release. *Toxins* **2015**, *7*, 4390–4403. [[CrossRef](#)]
81. Shivanna, S.; Kolandaivelu, K.; Shashar, M.; Belghasim, M.; Al-Rabadi, L.; Balcells, M.; Zhang, A.; Weinberg, J.; Francis, J.; Pollastri, M.P.; et al. The Aryl Hydrocarbon Receptor is a Critical Regulator of Tissue Factor Stability and an Antithrombotic Target in Uremia. *J. Am. Soc. Nephrol.* **2016**, *27*, 189–201. [[CrossRef](#)]
82. Chitalia, V.C.; Shivanna, S.; Martorell, J.; Balcells, M.; Bosch, I.; Kolandaivelu, K.; Edelman, E.R. Uremic serum and solutes increase post-vascular interventional thrombotic risk through altered stability of smooth muscle cell tissue factor. *Circulation.* **2013**, *127*, 365–376. [[CrossRef](#)] [[PubMed](#)]
83. Gondouin, B.; Cerini, C.; Dou, L.; Sallée, M.; Duval-Sabatier, A.; Pletinck, A.; Calaf, R.; Lacroix, R.; Jourde-Chiche, N.; Poitevin, S.; et al. Indolic uremic solutes increase tissue factor production in endothelial cells by the aryl hydrocarbon receptor pathway. *Kidney Int.* **2013**, *84*, 733–744. [[CrossRef](#)] [[PubMed](#)]
84. Pawlak, D.; Pawlak, K.; Malyszko, J.; Mysliwiec, M.; Buczko, W. Accumulation of toxic products degradation of kynurenine in hemodialyzed patients. *Int. Urol. Nephrol.* **2001**, *33*, 399–404. [[CrossRef](#)] [[PubMed](#)]
85. Pawlak, D.; Tankiewicz, A.; Buczko, W. Kynurenine and its metabolites in the rat with experimental renal insufficiency. *J. Physiol. Pharmacol.* **2001**, *52*, 755–766. [[PubMed](#)]
86. Pawlak, K.; Kowalewska, A.; Mysliwiec, M.; Pawlak, D. Kynurenine and its metabolites -kynurenic acid and anthranilic acid- are associated with soluble endothelial adhesion molecules and oxidative status in patients with chronic kidney disease. *Am. J. Med.Sci.* **2009**, *338*, 293–300. [[CrossRef](#)]
87. Opitz, C.A.; Litzemberger, U.M.; Sahn, F.; Ott, M.; Tritschler, I.; Trump, S.; Schumacher, T.; Jestaedt, L.; Schrenk, D.; Weller, M.; et al. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. *Nature* **2011**, *5*, 197–203. [[CrossRef](#)]
88. Reyes, M.; Benet, L.Z. Effects of uremic toxins on transport and metabolism of different biopharmaceutics drug disposition classification system xenobiotics. *J. Pharm. Sci.* **2011**, *100*, 3831–3842. [[CrossRef](#)]
89. Sun, H.; Frassetto, L.; Benet, L.Z. Effects of renal failure on drug transport and metabolism. *Pharmacol. Ther.* **2006**, *109*, 1–11. [[CrossRef](#)]
90. Sato, T.; Yamaguchi, H.; Kogawa, T.; Abe, T.; Mano, N. Organic anion transporting polypeptides 1B1 and 1B3 play an important role in uremic toxin handling and drug-uremic toxin interactions in the liver. *J. Pharm. Pharm Sci.* **2014**, *17*, 475–484. [[CrossRef](#)]
91. Sun, H.; Huang, Y.; Frassetto, L.; Benet, L.Z. Effects of uremic toxins on hepatic uptake and metabolism of erythromycin. *Drug. Metab. Dispos.* **2004**, *32*, 1239–1246. [[CrossRef](#)] [[PubMed](#)]
92. Mutsaers, H.A.; Caetano-Pinto, P.; Seegers, A.E.; Dankers, A.C.; van den Broek, P.H.; Wetzels, J.F.; van den Brand, J.A.; van den Heuvel, L.P.; Hoenderop, J.G.; Wilmer, M.J.; et al. Proximal tubular efflux transporters involved in renal excretion of p-cresyl sulfate and p-cresyl glucuronide: Implications for chronic kidney disease pathophysiology. *Toxicol. In Vitro.* **2015**, *29*, 1868–1877. [[CrossRef](#)]
93. Sinclair, L.V.; Neyens, D.; Ramsay, G.; Taylor, P.M.; Cantrell, D.A. Single cell analysis of kynurenine and System L amino acid transport in T cells. *Nat. Commun.* **2018**, *9*(1), 1981–1992. [[CrossRef](#)]
94. Michaud, J.; Dubé, P.; Naud, J.; Leblond, F.A.; Desbiens, K.; Bonnardeaux, A.; Pichette, V. Effects of serum from patients with chronic renal failure on rat hepatic cytochrome P450. *Br. J. Pharmacol.* **2005**, *144*, 1067–1077. [[CrossRef](#)]
95. Guévin, C.; Michaud, J.; Naud, J.; Leblond, F.A.; Pichette, V. Down-regulation of hepatic cytochrome p450 in chronic renal failure: Role of uremic mediators. *Br. J. Pharmacol.* **2002**, *137*, 1039–1046. [[CrossRef](#)]

96. Liu, H.; Narayanan, R.; Hoffmann, M.; Surapaneni, S. The Uremic Toxin Indoxyl-3-Sulfate Induces CYP1A2 In Primary Human Hepatocytes. *Drug. Metab. Lett.* **2016**, *10*, 195–199. [[CrossRef](#)]
97. Weigand, K.M.; Schirris, T.J.J.; Houweling, M.; van den Heuvel, J.J.M.W.; Koenderink, J.B.; Dankers, A.C.A.; Russel, F.G.M.; Greupink, R. Uremic solutes modulate hepatic bile acid handling and induce mitochondrial toxicity. *Toxicol. In Vitro.* **2019**, *56*, 52–56. [[CrossRef](#)]
98. Mutsaers, H.A.; van den Heuvel, L.P.; Ringens, L.H.; Dankers, A.C.; Russel, F.G.; Wetzels, J.F.; Hoenderop, J.G.; Masereeuw, R. Uremic toxins inhibit transport by breast cancer resistance protein and multidrug resistance protein 4 at clinically relevant concentrations. *PLoS. One* **2011**, *6*, e18438. [[CrossRef](#)]
99. Dankers, A.C.; Mutsaers, H.A.; Dijkman, H.B.; van den Heuvel, L.P.; Hoenderop, J.G.; Sweep, F.C.; Russel, F.G.; Masereeuw, R. Hyperuricemia influences tryptophan metabolism via inhibition of multidrug resistance protein 4 (MRP4) and breast cancer resistanceprotein (BCRP). *Biochim. Biophys. Acta.* **2013**, *1832*, 1715–1722. [[CrossRef](#)]
100. Matsuo, K.; Yamamoto, S.; Wakamatsu, T.; Takahashi, Y.; Kawamura, K.; Kaneko, Y.; Goto, S.; Kazama, J.J.; Narita, I. Increased Proinflammatory Cytokine Production and Decreased Cholesterol Efflux Due to Downregulation of ABCG1 in Macrophages Exposed to Indoxyl Sulfate. *Toxins* **2015**, *7*, 3155–3166. [[CrossRef](#)]
101. Akiyama, Y.; Kikuchi, K.; Saigusa, D.; Suzuki, T.; Takeuchi, Y.; Mishima, E.; Yamamoto, Y.; Ishida, A.; Sugawara, D.; Jinno, D.; et al. Indoxyl sulfate down-regulates SLCO4C1 transporter through up-regulation of GATA3. *PLoS ONE* **2013**, *8*, e66518. [[CrossRef](#)]
102. Enomoto, A.; Takeda, M.; Tak, K.; Takayama, F.; Noshiro, R.; Niwa, T.; Endou, H. Interactions of human organic anion as well as cation transporters with indoxyl sulfate. *Eur. J. Pharmacol.* **2003**, *466*, 13–20. [[CrossRef](#)]
103. Deguchi, T.; Kusuhara, H.; Takadate, A.; Endou, H.; Otagiri, M.; Sugiyama, Y. Characterization of uremic toxin transport by organic anion transporters in the kidney. *Kidney Int.* **2004**, *65*, 162–174. [[CrossRef](#)]
104. Kikuchi, K.; Itoh, Y.; Tateoka, R.; Ezawa, A.; Murakami, K.; Niwa, T. Metabolomic search for uremic toxins as indicators of the effect of an oral sorbent AST-120 by liquid chromatography/tandem mass spectrometry. *J. Chromatogr. B. Analyt. Technol. Biomed. Life. Sci.* **2010**, *878*, 2997–3002. [[CrossRef](#)]
105. Fujii, H.; Nishijima, F.; Goto, S.; Sugano, M.; Yamato, H.; Kitazawa, R.; Kitazawa, S.; Fukagawa, M. Oral charcoal adsorbent [AST-120] prevents progression of cardiac damage in chronic kidney disease through suppression of oxidative stress. *Nephrol. Dial. Transplant.* **2009**, *24*, 2089–2095. [[CrossRef](#)]
106. Yamamoto, S.; Kazama, J.J.; Omori, K.; Matsuo, K.; Takahashi, Y.; Kawamura, K.; Matsuo, T.; Watanabe, H.; Maruyama, T.; Narita, I. Continuous Reduction of Protein-Bound Uraemic Toxins with Improved Oxidative Stress by Using the Oral Charcoal Adsorbent AST-120 in Haemodialysis Patients. *Sci. Rep* **2015**, *5*, 1438. [[CrossRef](#)] [[PubMed](#)]
107. Schulman, G.; Berl, T.; Beck, G.J.; Remuzzi, G.; Ritz, E.; Arita, K.; Kato, A.; Shimizu, M. Randomized Placebo-Controlled EPPIC Trials of AST-120 in CKD. *J. Am. Soc. Nephrol.* **2015**, *26*, 1732–1746. [[CrossRef](#)]
108. Koya, Y.; Uchida, S.; Machi, Y.; Shobu, Y.; Namiki, N.; Kotegawa, T. Prediction of drug interaction between oral adsorbent AST-120 and concomitant drugs based on the invitro dissolution and in vivo absorption behavior of the drugs. *Eur. J. Clin. Pharmacol.* **2016**, *72*, 1353–1361. [[CrossRef](#)]
109. Aoyama, I.; Enomoto, A.; Niwa, T. Effects of oral adsorbent on gene expression profile in uremic rat kidney: cDNA array analysis. *Am. J. Kidney. Dis.* **2003**, *41*, S8–S14. [[CrossRef](#)] [[PubMed](#)]
110. Nolin, T.D.; Appiah, K.; Kendrick, S.A.; Le, P.; McMonagle, E.; Himmelfarb, J. Hemodialysis acutely improves hepatic CYP3A4 metabolic activity. *J. Am. Soc. Nephrol.* **2006**, *17*, 2363–2367. [[CrossRef](#)] [[PubMed](#)]
111. Michaud, J.; Nolin, T.D.; Naud, J.; Dani, M.; Lafrance, J.P.; Leblond, F.A.; Himmelfarb, J.; Pichette, V. Effect of hemodialysis on hepatic cytochrome P450 functional expression. *J. Pharmacol. Sci.* **2008**, *108*, 157–163. [[CrossRef](#)] [[PubMed](#)]
112. Vanholder, R.; Van Landschoot, N.; De Smet, R.; Schoots, A.; Ringoir, S. Drug protein binding in chronic renal failure: evaluation of nine drugs. *Kidney Int.* **1988**, *33*, 996–1004. [[CrossRef](#)]
113. Takamura, N.; Maruyama, T.; Otagiri, M. Effects of uremic toxins and fatty acids on serum protein binding of furosemide: possible mechanism of the binding defect in uremia. *Clin. Chem.* **1997**, *43*, 2274–2280.
114. Watanabe, H.; Noguchi, T.; Miyamoto, Y.; Kadowaki, D.; Kotani, S.; Nakajima, M.; Miyamura, S.; Ishima, Y.; Otagiri, M.; Maruyama, T. Interaction between two sulfate-conjugated uremic toxins, p-cresyl sulfate and indoxyl sulfate, during binding with human serum albumin. *Drug. Metab. Dispos.* **2012**, *40*, 1423–1428. [[CrossRef](#)] [[PubMed](#)]

115. Li, J.; Wang, Y.; Xu, X.; Cao, W.; Shen, Z.; Wang, N.; Leng, J.; Zou, N.; Shang, E.; Zhu, Z.; et al. Improved dialysis removal of protein-bound uremic toxins by salvianolic acids. *Phytomedicine* **2018**, *57*, 166–173. [[CrossRef](#)]
116. Schroeder, J.C.; Dinatale, B.C.; Murray, I.A.; Flaveny, C.A.; Liu, Q.; Laurenzana, E.M.; Lin, J.M.; Strom, S.C.; Omiecinski, C.J.; Amin, S.; et al. The uremic toxin 3-indoxyl sulfate is a potent endogenous agonist for the human aryl hydrocarbon receptor. *Biochemistry* **2010**, *49*, 393–400. [[CrossRef](#)] [[PubMed](#)]
117. Denison, M.S.; Nagy, S.R. Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. *Annu. Rev. Pharmacol. Toxicol.* **2003**, *43*, 309–334. [[CrossRef](#)] [[PubMed](#)]
118. Hubbard, T.D.; Murray, I.A.; Perdew, G.H. Indole and Tryptophan Metabolism: Endogenous and Dietary Routes to Ah Receptor Activation. *Drug. Metab. Dispos.* **2015**, *43*, 1522–1535. [[CrossRef](#)]
119. Dou, L.; Poitevin, S.; Sallée, M.; Addi, T.; Gondouin, B.; McKay, N.; Denison, M.S.; Jourde-Chiche, N.; Duval-Sabatier, A.; Cerini, C.; et al. Aryl hydrocarbon receptor is activated in patients and mice with chronic kidney disease. *Kidney Int.* **2018**, *93*, 986–999. [[CrossRef](#)] [[PubMed](#)]
120. Kolachalama, V.B.; Shashar, M.; Alousi, F.; Shivanna, S.; Rijal, K.; Belghasem, M.E.; Walker, J.; Matsuura, S.; Chang, G.H.; Gibson, C.M. Uremic Solute-Aryl Hydrocarbon Receptor-Tissue Factor Axis Associates with Thrombosis after Vascular Injury in Humans. *J. Am. Soc. Nephrol.* **2018**, *29*, 1063–1072. [[CrossRef](#)]
121. Denison, M.S.; Soshilov, A.A.; He, G.; DeGroot, D.E.; Zhao, B. Exactly the same but different: promiscuity and diversity in the molecular mechanisms of action of the aryl hydrocarbon [dioxin] receptor. *Toxicol. Sci.* **2011**, *124*, 1–22. [[CrossRef](#)]
122. Abel, J.; Haarmann-Stemmann, T. An introduction to the molecular basics of aryl hydrocarbon receptor biology. *Biol. Chem.* **2010**, *391*, 1235–1248. [[CrossRef](#)] [[PubMed](#)]
123. Ikuta, T.; Eguchi, H.; Tachibana, T.; Yoneda, Y.; Kawajiri, K. Nuclear localization and export signals of the human aryl hydrocarbon receptor. *J. Biol. Chem.* **1998**, *273*, 2895–2904. [[CrossRef](#)] [[PubMed](#)]
124. Hankinson, O. Role of coactivators in transcriptional activation by the aryl hydrocarbon receptor. *Arch. Biochem. Biophys.* **2005**, *433*, 379–386. [[CrossRef](#)] [[PubMed](#)]
125. Mimura, J.; Fujii-Kuriyama, Y. Functional role of AhR in the expression of toxic effects by TCDD. *Biochim. Biophys. Acta.* **2003**, *1619*, 263–268. [[CrossRef](#)]
126. Quattrochi, L.C.; Vu, T.; Tukey, R. The human CYP1A2 gene and induction by 3-methylcholanthrene. A region of DNA that supports Ah-receptor binding and promoter-specific induction. *J. Biol. Chem.* **1994**, *269*, 6949–6954.
127. Erichsen, T.J.; Ehmer, U.; Kalthoff, S.; Lankisch, T.O.; Müller, T.M.; Munzel, P.A.; Manns, M.P.; Strassburg, C.P. Genetic variability of aryl hydrocarbon receptor [AhR]-mediated regulation of the human UDP glucuronosyltransferase [UGT] 1A4 gene. *Toxicol. Appl. Pharmacol.* **2008**, *230*, 252–260. [[CrossRef](#)]
128. Emi, Y.; Ikushiro, S.; Iyanagi, T. Xenobiotic responsive element-mediated transcriptional activation in the UDP-glucuronosyltransferase family 1 gene complex. *J. Biol. Chem.* **1996**, *271*, 3952–3958. [[CrossRef](#)]
129. Li, W.; Harper, P.A.; Tang, B.K.; Okey, A.B. Regulation of cytochrome P450 enzymes by aryl hydrocarbon receptor in human cells: CYP1A2 expression in the LS180 colon carcinoma cell line after treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin or 3-methylcholanthrene. *Biochem. Pharmacol.* **1998**, *56*, 599–612. [[CrossRef](#)]
130. Lankisch, T.O.; Gillman, T.C.; Erichsen, T.J.; Ehmer, U.; Kalthoff, S.; Freiberg, N.; Munzel, P.A.; Manns, M.P.; Strassburg, C.P. Aryl hydrocarbon receptor-mediated regulation of the human estrogen and bile acid UDP-glucuronosyltransferase 1A3 gene. *Arch. Toxicol.* **2008**, *82*, 573–582.
131. Kalthoff, S.; Ehmer, U.; Freiberg, N.; Manns, M.P.; Strassburg, C.P. Interaction between oxidative stress sensor Nrf2 and xenobiotic-activated aryl hydrocarbon receptor in the regulation of the human phase II detoxifying UDP-glucuronosyl-transferase 1A10. *J. Biol. Chem.* **2010**, *285*, 5993–6002. [[CrossRef](#)]
132. Zhou, J.; Zhang, J.; Xie, W. Xenobiotic nuclear receptor-mediated regulation of UDP-glucuronosyl-transferases. *Curr. Drug. Metab.* **2005**, *6*, 289–298. [[CrossRef](#)]
133. Urquhart, B.L.; Tirona, R.G.; Kim, R.B. Nuclear receptors and the regulation of drug-metabolizing enzymes and drug transporters: implications for interindividual variability in response to drugs. *J. Clin. Pharmacol.* **2007**, *47*, 566–578. [[CrossRef](#)]
134. Vasiliou, V.; Buetler, T.; Eaton, D.L.; Nebert, D.W. Comparison of oxidative stress response parameters in newborn mouse liver versus simian virus 40 [SV40]-transformed hepatocyte cell lines. *Biochem. Pharmacol.* **2000**, *59*, 703–712. [[CrossRef](#)]

135. Gao, X.; Xie, C.; Wang, Y.; Luo, Y.; Yagai, T.; Sun, D.; Qin, X.; Krausz, K.W.; Gonzalez, F.J. The antiandrogen flutamide is a novel aryl hydrocarbon receptor ligand that disrupts bile acid homeostasis in mice through induction of Abcc4. *Biochem. Pharmacol.* **2016**, *119*, 93–104. [[CrossRef](#)]
136. Le Vee, M.; Jouan, E.; Stieger, B.; Lecureur, V.; Fardel, O. Regulation of human hepatic drug transporter activity and expression by diesel exhaust particle extract. *PLoS One* **2015**, *10*, e0121232. [[CrossRef](#)]
137. Le Vee, M.; Jouan, E.; Lecureur, V.; Fardel, O. Aryl hydrocarbon receptor-dependent up-regulation of the heterodimeric amino acid transporter LAT1 [SLC7A5]/CD98hc [SLC3A2] by diesel exhaust particle extract in human bronchial epithelial cells. *Toxicol. Appl. Pharmacol.* **2016**, *290*, 74–85. [[CrossRef](#)]
138. Santana Machado, T.; Poitevin, S.; Paul, P.; McKay, N.; Jourde-Chiche, N.; Legris, T.; Mouly-Bandini, A.; Dignat-George, F.; Brunet, P.; Masereeuw, R.; et al. Indoxyl Sulfate Upregulates Liver P-Glycoprotein Expression and Activity through Aryl Hydrocarbon Receptor Signaling. *J. Am. Soc. Nephrol.* **2018**, *29*, 906–918.
139. Zhou, S.F.; Chan, E.; Zhou, Z.W.; Xue, C.C.; Lai, X.; Duan, W. Insights into the structure, function, and regulation of human cytochrome P450 1A2. *Curr. Drug. Metab.* **2009**, *10*, 713–729. [[CrossRef](#)]
140. Zhou, S.F.; Wang, B.; Yang, L.P.; Liu, J.P. Structure, function, regulation and polymorphism and the clinical significance of human cytochrome P450 1A2. *Drug. Metab. Rev.* **2010**, *42*, 268–354. [[CrossRef](#)]
141. Al Za'abi, M.; Shalaby, A.; Manoj, P.; Ali, B.H. The in vivo effects of adenine-induced chronic kidney disease on some renal and hepatic function and CYP450 metabolizing enzymes. *Physiol. Res.* **2017**, *66*, 263–271.
142. Smith, G.; Wolf, C.R.; Deeni, Y.Y.; Dawe, R.S.; Evans, A.T.; Comrie, M.M.; Ferguson, J.; Ibbotson, S.H. Cutaneous expression of cytochrome P450 CYP2S1: individuality in regulation by therapeutic agents for psoriasis and other skin diseases. *Lancet.* **2003**, *361*, 1336–1343. [[CrossRef](#)]
143. Rivera, S.P.; Wang, F.; Saarikoski, S.T.; Taylor, R.T.; Chapman, B.; Zhang, R.; Hankinson, O. A novel promoter element containing multiple overlapping xenobiotic and hypoxia response elements mediates induction of cytochrome P4502S1 by both dioxin and hypoxia. *J. Biol. Chem.* **2007**, *282*, 10881–10893. [[CrossRef](#)] [[PubMed](#)]
144. Nebert, D.W.; Russell, D.W. Clinical importance of the cytochromes P450. *Lancet.* **2002**, *360*, 1155–1162. [[CrossRef](#)]
145. Oh, E.T.; Park, H.J. Implications of NQO1 in cancer therapy. *BMB. Rep.* **2015**, *48*, 609–617. [[CrossRef](#)]
146. Ládek, N.E.; Kollander, R.; Sreerama, L.; Kiang, D.T. Cellular levels of aldehyde dehydrogenases [ALDH1A1 and ALDH3A1] as predictors of therapeutic responses to cyclophosphamide-based chemotherapy of breast cancer: a retrospective study. Rational individualization of oxazaphosphorine-based cancer chemotherapeutic regimens. *Cancer. Chemother. Pharmacol.* **2002**, *49*, 309–321.
147. Parajuli, B.; Georgiadis, T.M.; Fishel, M.L.; Hurley, T.D. Development of selective inhibitors for human aldehyde dehydrogenase 3A1 [ALDH3A1] for the enhancement of cyclophosphamide cytotoxicity. *Chembio. Chem.* **2014**, *15*, 701–712. [[CrossRef](#)]
148. Ghosh, C.; Hossain, M.; Puvenna, V.; Martinez-Gonzalez, J.; Alexopolous, A.; Janigro, D.; Marchi, N. Expression and functional relevance of UGT1A4 in a cohort of human drug-resistant epileptic brains. *Epilepsia.* **2013**, *54*, 1562–1570. [[CrossRef](#)] [[PubMed](#)]
149. Mazerska, Z.; Mróz, A.; Pawłowska, M.; Augustin, E. The role of glucuronidation in drug resistance. *Pharmacol. Ther.* **2016**, *159*, 35–55. [[CrossRef](#)] [[PubMed](#)]
150. Erickson-Ridout, K.K.; Sun, D.; Lazarus, P. Glucuronidation of the second generation antipsychotic clozapine and its active metabolite N desmethylclozapine. Potential importance of the UGT1A1 A[TA]₇TAA and UGT1A4 L48V polymorphisms. *Pharmacogenet. Genomics.* **2012**, *22*, 561–576. [[CrossRef](#)] [[PubMed](#)]
151. Kerdpin, O.; Knights, K.M.; Elliot, D.J.; Miners, J.O. In vitro characterisation of human renal and hepatic frusemide glucuronidation and identification of the UDP-glucuronosyltransferase enzymes involved in this pathway. *Biochem. Pharmacol.* **2008**, *76*, 249–257. [[CrossRef](#)]
152. Yamada, A.; Maeda, K.; Ishiguro, N.; Tsuda, Y.; Igarashi, T.; Ebner, T. The impact of pharmacogenetics of metabolic enzymes and transporters on the pharmacokinetics of telmisartan in healthy volunteers. *Pharmacogenet. Genomics.* **2011**, *21*, 523–530. [[CrossRef](#)]
153. Jeong, E.S.; Kim, Y.W.; Kim, H.J.; Shin, H.J.; Shin, J.G.; Kim, K.H. Glucuronidation of fimasartan, a new angiotensin receptor antagonist, is mainly mediated by UGT1A3. *Xenobiotica* **2015**, *45*, 10–18. [[CrossRef](#)]
154. Cho, S.K.; Oh, E.S.; Park, K.; Park, M.S.; Chung, J.Y. The UGT1A3*2 polymorphism affects atorvastatin lactonization and lipid lowering effect in healthy volunteers. *Pharmacogenet. Genomics* **2012**, *22*, 598–605. [[CrossRef](#)] [[PubMed](#)]

155. Fujino, H.; Yamada, I.; Shimada, S.; Yoneda, M.; Kojima, J. Metabolic fate of pitavastatin, a new inhibitor of HMG-CoA reductase: Human UDP-glucuronosyltransferase enzymes involved in lactonization. *Xenobiotica* **2003**, *33*, 27–41. [[CrossRef](#)] [[PubMed](#)]
156. Prueksaritanont, T.; Subramanian, R.; Fang, X.; Ma, B.; Qiu, Y.; Lin, J.H.; Pearson, P.G.; Baillie, T.A. Glucuronidation of statins in animals and humans: a novel mechanism of statin lactonization. *Drug. Metab. Dispos.* **2002**, *30*, 505–512. [[CrossRef](#)]
157. Schirris, T.J.; Ritschel, T.; Bilos, A.; Smeitink, J.A.; Russel, F.G. Statin Lactonization by Uridine 5'-Diphospho-glucuronosyltransferases [UGTs]. *Mol. Pharm.* **2015**, *2*, 4048–4055. [[CrossRef](#)]
158. Vanlersberghe, C.; Camu, F. Propofol. *Handb. Exp. Pharmacol.* **2008**, *182*, 227–252.
159. Sharma, A.; Patrick, B.; Li, J.; Sharma, R.; Jeyabal, P.V.; Reddy, P.M.; Awasthi, S.; Awasthi, Y.C. Glutathione S-transferases as antioxidant enzymes: Small cell lung cancer [H69] cells transfected with hGSTA1 resist doxorubicin-induced apoptosis. *Arch. Biochem. Biophys.* **2006**, *45*, 165–173. [[CrossRef](#)]
160. Locher, K.P. Structure and mechanism of ATP-binding cassette transporters. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **2009**, *364*, 239–245. [[CrossRef](#)]
161. Chang, G. Multidrug resistance ABC transporters. *FEBS. Lett.* **2003**, *555*, 102–105. [[CrossRef](#)]
162. Choi, C.H. ABC transporters as multidrug resistance mechanisms and the development of chemosensitizers for their reversal. *Cancer. Cell. Inter.* **2005**, *5*, 1–13. [[CrossRef](#)]
163. He, S.M.; Li, R.; Kanwar, J.R.; Zhou, S.F. Structural and functional properties of human multidrug resistance protein 1 [MRP1/ABCC1]. *Curr. Med. Chem.* **2011**, *18*, 439–481. [[CrossRef](#)]
164. Gynther, M.; Laine, K.; Ropponen, J.; Leppänen, J.; Mannila, A.; Nevalainen, T.; Savolainen, J.; Järvinen, T.; Rautio, J. Large neutral amino acid transporter enables brain drug delivery via prodrugs. *J. Med. Chem.* **2008**, *51*, 932–936. [[CrossRef](#)]
165. Del Amo, E.M.; Urtti, A.; Yliperttula, M. Pharmacokinetic role of L-type amino acid transporters LAT1 and LAT2. *Eur. J. Pharm. Sci.* **2008**, *35*, 161–174. [[CrossRef](#)] [[PubMed](#)]
166. Gomes, P.; Soares-da-Silva, P. Interaction between L-DOPA and 3-O-methyl-L-DOPA for transport in immortalised rat capillary cerebral endothelial cells. *Neuropharmacology* **1999**, *38*, 1371–1380. [[CrossRef](#)]
167. Kageyama, T.; Nakamura, M.; Matsuo, A.; Yamasaki, Y.; Takakura, Y.; Hashida, M.; Kanai, Y.; Naito, M.; Tsuruo, T.; Minato, N.; et al. The 4F2hc/LAT1 complex transports L-DOPA across the blood-brain barrier. *Brain. Res.* **2000**, *879*, 115–121. [[CrossRef](#)]
168. Kido, Y.; Tamai, I.; Uchino, H.; Suzuki, F.; Sai, Y.; Tsuji, A. Molecular and functional identification of large neutral amino acid transporters LAT1 and LAT2 and their pharmacological relevance at the blood-brain barrier. *J. Pharm. Pharmacol.* **2001**, *53*, 497–503. [[CrossRef](#)]
169. Sampaio-Maia, B.; Serrão, M.P.; Soares-da-Silva, P. Regulatory pathways and uptake of L-DOPA by capillary cerebral endothelial cells, astrocytes, and neuronal cells. *Am. J. Physiol. Cell. Physiol.* **2001**, *280*, C333–C342. [[CrossRef](#)]
170. Soares-da-Silva, P.; Serrão, P.; Fraga, S.; Pinho, M.J. Expression and function of LAT1, a neutral amino acid exchanger, in renal porcine epithelial cell line LLC-PK. *Acta. Physiol. Scand.* **2005**, *185*, 71–78. [[CrossRef](#)] [[PubMed](#)]
171. Fraga, S.; Sampaio-Maia, B.; Serrão, M.P.; Soares-da-Silva, P. Regulation of apical transporter of L-DOPA in human intestinal Caco-2 cells. *Acta. Physiol. Scand.* **2002**, *175*, 103–111. [[CrossRef](#)] [[PubMed](#)]

