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Review

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Metabolomics in Acute Kidney Injury: The Experimental Perspective

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Abstract

Acute kidney injury (AKI) affects increasing numbers of in-hospital patients in Central Europe and the USA, the prognosis remains poor. Although substantial progress has been achieved in the identification of molecular/cellular processes that induce and perpetuate AKI, more integrated pathophysiological perspectives are missing. Metabolomics enables the identification of low-molecular-weight (< 1.5 kD) substances from biological specimens such as certain types of fluid or tissue. The aim of the article was to review the literature on metabolic profiling in experimental AKI and to answer the question if metabolomics allows the integration of distinct pathophysiological events such as tubulopathy and microvasculopathy in ischemic and toxic AKI. The following databases were searched for references: PubMed, Web of Science, Cochrane Library, Scopus. The period lasted from 1940 until 2022. The following terms were utilized: "acute kidney injury" OR "acute renal failure" OR "AKI" AND "metabolomics" OR "metabolic profiling" OR "omics" AND "ischemic" OR "toxic" OR "drug-induced" OR "sepsis" OR "LPS" OR "cisplatin" OR "cardiorenal" OR "CRS" AND "mouse" OR "mice" OR "murine" OR "rats" OR "rat". Additional search terms were "cardiac surgery", "cardiopulmonary bypass", "pig", "dog", and "swine". In total, 13 studies were identified. Five studies were related to ischemic, seven studies to toxic (lipopolysaccharide (LPS), cisplatin), and one study to heat shock-associated AKI. Only one study, related to cisplatin-induced AKI, was performed as a targeted analysis. The majority of the studies identified multiple metabolic deteriorations upon ischemia/the administration of LPS or cisplatin (e.g., amino acid, glucose, lipid metabolism). Particularly, abnormalities in the lipid homeostasis were shown under almost all experimental conditions. LPS-induced AKI most likely depends on the alterations in the tryptophan metabolism. Metabolomics studies provide a deeper understanding of pathophysiological links between distinct processes that are responsible for functional impairment/structural damage in ischemic or toxic or other types of AKI.

Keywords: AKI; Metabolomics; KRT; Recovery of kidney function; Survival

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Introduction

Acute kidney injury (AKI): definition and epidemiology

AKI affects increasing numbers of hospitalized patients worldwide. It must be diagnosed if one of the following criteria are fulfilled: an increase in serum creatinine of at least 0.3 mg/dL, a 1.5-fold increase within 7 days, or a reduction in urine output to under 0.5 mL/kg/h for 6 h or longer [1]. These criteria have been documented in the 2012 revised "KDIGO clinical practice guidelines for acute kidney injury" [2]. In 2018, Hoste et al reported an average in-hospital AKI incidence of 15-30% [3]. In hospitalized subjects, the overall mortality of the syndrome ranges from 15% to 25% [3, 4]. The chance of survival is significantly lower in intensive care units, where up to 60% of all treated subjects acquire AKI. Under these circumstances, AKI has been identified as an independent predictor of death [5]. Certain AKI etiologies are associated with a disproportional increase in mortality risk. For instance, subjects with in-hospital-acquired cardiorenal syndrome type 3 (AKI induces secondary cardiac complications [6]) show an in-hospital chance of survival of only 50% [7]. The coincidence of hematooncological neoplasia, chemotherapy-induced sepsis, and kidney replacement therapy (KRT) requiring AKI has been associated with a mortality probability of 100% [8]. Also, individual AKI episodes have been shown to substantially reduce long-term (over years) survival [9], particularly in more severe cases (AKI "injury" or "failure" according to the RIFLE (risk, injury, failure, loss of kidney function and end-stage kidney disease) classification [10]). In addition, it can no

longer be doubted that AKI is a potent risk factor for chronic kidney disease (CKD) [11]. Forni et al [12] documented a 105-fold hazard ratio increase for CKD, if AKI requires KRT.

AKI: etiology

The AKI etiology is quite heterogeneous [13]. Historically, three major AKI entities have been defined: pre-, intra-, and postrenal AKI. Postrenal AKI, the least frequent AKI entity (up to 10% [14]) potentially results from obstruction of the ureter or bladder or urethra. Many diseases may account for postrenal AKI such as urolithiasis, neoplasia, or neurological diseases that affect the activity of smooth muscle cells in the ureter or bladder. In a broader sense, "prerenal" encompasses all situations in which the effective perfusion of renal tissue is diminished (ischemia) [15]. The most common causes are fluid/blood loss, and acute heart failure. Another cause is cardiac surgery-associated AKI (CSA-AKI) (the second most common type of AKI after septic AKI in intensive care treated patients [16]). It results from various factors including nephrotoxins, ischemia/hypoxia, mechanical trauma, systemic inflammation, and cardiopulmonary bypass [17].

Kidney dysfunction is potentially reversible in the early stages of ischemia, prolonged hypoperfusion however increasingly induces structural damage such as the loss of tubular brush border, vacuolization, and tubular debris secondary to cell apoptosis/necrosis [18]. Prerenal AKI transits to intrarenal AKI. The so-called bilateral cortical necrosis is rarely diagnosed, occasionally in septic and postpartum AKI [19]. Nevertheless, tubular cell necrosis may also occur in patients with drug-induced AKI. The term "nephrotoxic" usually summarizes kidney-related side effects of various types of medications. Environmental contaminants may also act nephrotoxic (cadmium [20], mercury [21]), the overall clinical relevance is nevertheless lower. Regarding drug-induced AKI, the following mechanisms may be involved: tubular cell necrosis (aminoglycosides, vancomycin) [22, 23], interstitial nephritis (proton pump inhibitors) [24], renal vasoconstriction (amphotericin B) [22], tubular obstruction (sulfonamides) [25], and thrombotic microangiopathy (calcineurin inhibitors) [26]. Clinically, many patients acquire AKI for several reasons (e.g., sepsis with subsequent systemic vasodilation and septic cardiomyopathy, additional use of nephrotoxic drugs). Renal ischemia *per se* variably induces three pathophysiological processes or responses: tubulopathy, interstitial and systemic inflammation, and peritubular microvasculopathy [15, 27-29]. Microvascular damage is not restricted to peritubular capillaries but also affects glomerular function and structure [15]. Increased microvascular permeability causes interstitial edema in both the tubular and glomerular compartments. Glomerular/mesangial fluid accumulation potentially reduces the filtration rate even further.

In general, the clinical course of AKI subjects encompasses either complete or incomplete recovery of kidney function (ROKF) [30]. In some individuals, ROKF does not occur at all. If ROKF takes longer than 7 days after an acute event, AKI progresses to acute kidney disease (AKD) [31]. Respective individuals are at significantly higher risk of CKD in the long-term [11]. Also, the long-term survival probability decreases with increasing AKI severity. Thus, patients with so-called "fatal AKI (e.g., bilateral cortical necrosis [32]) show a 7-year survival probability that approximates the life expectancy of patients with end-stage kidney disease (ESKD) [9].

The "-omics": concept

The cellular/molecular processes that induce and perpetuate kidney damage in ischemic and toxic AKI have intensively been studied in the past. However, more integrated approaches were missing over many years. In this regard, "-omics" studies potentially offer new perspectives. The overall aim of the so-called "-omics" concept is to identify cellular/tissue response patterns under both physiological and pathological conditions in a more integrated fashion. "-Omics" are datasets on the detection, quantification, and characterization of biological molecules. Omics studies allow large-scale analysis of numerous proteins, nucleic acids, or metabolites at the same time. Four major types of "-omics" have been established, genomics, transcriptomics, proteomics, and metabolomics [33]. Metabolomics encompasses the analysis of lower molecular weight (< 1.5 kD) substances in cells/certain types of tissue/biological fluids. The current review article discusses experimental data published so far. It particularly aimed to answer the question of whether metabolic profiling enables a more integrated approach to the complex pathophysiology of ischemic or toxic or other types of AKI.

We omit to review the history of metabolomics or the considerable number of methods [33-38] that have been established since the first description of metabolic profiling in 1948 [39]. Metabolic profiling is either being performed as untargeted or targeted analysis [33, 40]. According to Johnson et al [41], untargeted or global metabolomics allows the assessment of metabolites extracted from a biological sample, it can potentially reveal novel perturbations. Targeted metabolomics instead measures the concentrations of a predefined set of metabolites. Both approaches can be used for the generation of new hypotheses.

Methods

The following databases were searched for references: PubMed, Web of Science, Cochrane Library, and Scopus. The period lasted from 1940 until 2022. The following terms were utilized: "acute kidney injury" OR "acute renal failure" OR "AKI" AND "metabolomics" OR "metabolic profiling" OR "omics" AND "ischemic" OR "toxic" OR "drug-induced" OR "sepsis" OR "LPS" OR "cisplatin" OR "cardiorenal" OR "CRS" AND "mouse" OR "mice" OR "murine" OR "rats" OR "rat". Additional search terms were "cardiac surgery", "cardiopulmonary bypass", "pig", "dog", and "swine". The flow chart (Supplemental Material 1, www.jocmr.org) illustrates the searching procedure.

Ischemic AKI

The first study that needs to be discussed was published more

than 10 years ago (Liu et al [42]). Sprague-Dawley rats were subjected to bilateral renal artery clamping for 45 min, either with or without L-carnitine pretreatment. The substance was used due to its known anti-oxidative properties [43]. Serum concentrations of creatinine and blood urea nitrogen (BUN) peaked in post-ischemic animals 24 h after reperfusion, an effect that was markedly abrogated by L-carnitine. So-called "high-performance liquid chromatography coupled with mass spectrometry" was employed for metabolic profiling, and analyses were performed from serum samples. Briefly, the concentrations of the following metabolites increased post-ischemia: lysophospholipids, free fatty acids, and nitrotyrosine. The activity of the enzyme phospholipase A2 and serum levels of malondialdehyde in contrast decreased. Finally, cortical superoxide dismutase activity was reduced. All effects were diminished in L-carnitine-treated mice. The authors proposed alterations of lipid metabolism as key events in ischemia/reperfusion-associated kidney damage.

Two years later (2014), Wei et al [44] published a manuscript on metabolomics in murine ischemic AKI; the aim was a "global analysis of the metabolic changes in renal IRI". Bilateral renal ischemia was applied for 25 min, followed by reperfusion periods for either 2 or 48 h or 7 days. To achieve the goal, plasma and tissue samples from both the renal cortex and the medulla were analyzed with gas chromatography/mass spectrometry (GC/MS) and liquid chromatography/mass spectrometry (LC/MS). Renal ischemia significantly deteriorated kidney excretory function (serum creatinine and BUN peaked at 48 h, respectively), functional impairment was however (partly) reversible until day 7. Metabolomics identified 404 substances from tissue samples and 293 metabolites from plasma. Renal ischemia reduced the plasma availability of several substances in a significant manner: betaine, tyrosine, glutamine, proline, methionine, and others. Overall, the study revealed significant alterations of glucose, lipid, and purine metabolism. There was also evidence for affected osmotic regulation (mannitol, arabitol, threitol, pinitol). Finally, the tissue availability of certain prostaglandins was modulated. The reported findings were highly relevant since they indicated an affected energy supply (induction/perpetuation of tubular damage) and the stimulation of inflammatory processes (prostaglandin dysbalance). Thus, metabolomics truly helped to identify a "link" between hypoperfusion/ischemia and the hallmarks of ischemic AKI: tubulopathy, inflammation, and (micro)vasculopathy.

Huang et al [45] also investigated ischemic AKI but employed a unilateral approach. Only one renal artery was occluded (45 min, Fisher rats (F344)), the other organ remained perfused throughout. Reperfusion either lasted for 4 or 24 h. In addition to metabolomics, the authors also performed proteomics from cortical tissue samples. The proteomic analysis identified 363 out of 2,798 proteins with different expressions in post-ischemic as compared to contralateral kidneys. The differences were most prominent at 24 h. Ischemia particularly stimulated the synthesis of factors involved in stress signaling (heat shock protein 70 (HSP70) and heme-oxygenase 1 (HO-1)), coagulation, complement activity, and fatty acid metabolism [45]). For metabolic profiling, the authors used the following methods: nuclear magnetic resonance spectroscopy (NMR) or gas chromatography-mass spectrometry (GCxGC-MS). Metabolomics showed a substantial tissue increase of lipid metabolites such as palmitate, stearate, linoleate, 1-monopalmitin, cholesterol, and others. The findings already appeared 4 h after the ischemic insult. Intrarenal glucose levels were also diminished at hour 4. Another relevant observation was impaired mitochondrial function and thus adenosine triphosphate (ATP) production at 24 h. Comparable to the previous study, this investigation offers mechanistic "links" between ischemia and further consequences such as inflammation and tubular disfunction.

Fox et al [46] utilized an experimental model of cardiorenal syndrome type 3. The latter has been defined as a disorder in which various cardiac complications may arise in response to AKI [2]. The authors applied bilateral renal ischemia to 8 - 10 weeks old, male C57BL/6 mice for 22 min, respectively. Cardiac metabolic profiling was performed 4 and 24 h and 7 days later. Renal ischemia significantly diminished kidney excretory function, as reflected by elevated serum creatinine (24 h) and BUN (all times points). A total number of 124 metabolites was analyzed, and the concentrations of more than 40% of the substances were altered post-ischemia. Particularly, several amino acids were depleted, and oxidative stress was increased. Higher oxidative stress was also found in renal tissue samples. In addition, cardiac energy production processes were modulated, with stimulation of anaerobic ATP synthesis. In summary, the study confirmed experimental data from others, that showed a dysbalanced cardiac redox system after renal ischemia [47, 48]. It also confirmed the concept of cardiorenal or reno-cardiac cross-talk in AKI, and thus the concept of cardiorenal syndromes in general.

A more recent study from 2022 [49] addressed a very important topic in clinical nephrology: heart surgery-associated AKI. The authors utilized a piglet model of cardiopulmonary bypass including so-called deep hypothermic circulatory arrest (CPB/DHCA). Targeted metabolic profiling was performed from kidney tissue, urine, and serum samples. Ten out of 20 animals that received CPB/DHCA developed AKI during follow-up (4 h). Tissue analysis showed dysregulated tryptophan and purine metabolism. Urine analysis on the other hand revealed stimulation of anaerobic glycolysis. The metabolic patterns in tissue and urine samples did not resemble each other. Although the study additionally identified serum abnormalities (pyroglutamic acid - stress marker), the authors concluded that increased urinary anaerobic glycolysis may qualify as a tool for early AKI recognition in CPB.

Toxic AKI

In this paragraph, we also included lipopolysaccharide (LPS)-induced AKI models, which are commonly used to mimic microenvironmental conditions typically found in sepsis. Septic AKI on the other hand emerges due to various causes such as LPS exposure, renal malperfusion, and systemic hyperinflammation [50, 51].

The first study of interest was published in 2019 [52]. The authors employed a pig model of AKI, initiated by the

administration of living *Escherichia coli* to induce sepsis. The utilization of larger vertebrate organisms (pigs as opposed to mice or rats) facilitated extensive hemodynamic monitoring including the following outcome variables: mean arterial blood pressure (MAP), systemic blood flow (QT), mean pulmonary arterial pressure, renal artery blood flow (QRA), and renal cortical blood flow (QRC). Sepsis was associated with lower QRA and QRC, the urine output decreased as well. Metabolic profiling revealed several abnormalities in kidney tissue, urine, and serum. Kidney tissue lactate and nicotinuric acid were elevated whereas the tissue concentrations of certain amino acids (e.g., valine, aspartate) and of glucose decreased. Serum analysis also revealed higher lactate levels, and glucose concentrations were diminished. Urine analysis showed higher levels of isovaleroglycine, aminoadipic acid, N-acetylglutamine, N-acetylaspartate, and ascorbic acid, myoinositol and phenylacetylglycine were lower in comparison to saline-treated controls. The concentrations of several metabolites in kidney tissue and urine significantly correlated with well-established AKI biomarkers such as neutrophile gelatinase-associated lipocalin (NGAL), leading to the conclusion that metabolomics enables the identification of novel AKI biomarker molecules.

A model of tubulotoxic AKI was studied by Qu et al [53]. Sprague-Dawley rats received intraperitoneal (i.p.) injections of cisplatin (either 7.5 mg/kg or 15 mg/kg), followed by urine and kidney tissue collection 72 h later. The authors used so-called high-performance liquid chromatography-time-of-flight mass spectrometry (HPLC-TOF/MS) and included 37 distinct metabolites in their analyses. Ultimately, seven major metabolic pathways were dysregulated (a detailed description shall be omitted), either involved in energy or amino acid, or lipid metabolism. The conclusion that respective abnormalities are partly responsible for increased oxidative stress and inflammation was legitimate. Additional urine analyses revealed four candidates as potential AKI biomarkers after cisplatin exposure. The study once more highlights one essential role of metabolomics in experimental and clinical AKI: the "screening" of yet unknown pathophysiological and diagnostic pathways/biomarkers.

An untargeted metabolomics approach was also favored by Gao et al [54]. The disease of interest was LPS-induced (multi)-organ failure. The authors used ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry (UPLC/QTOF-MS) in rats that were intraperitoneally injected with LPS at 10 mg/kg once. Significant tissue damage was observed in the liver, lungs, colon, and kidney. Serum analysis showed alterations in a total number of 53 pathways with more than 120 aberrant metabolites (e.g., D-glutamine, D-glutamate, taurine, hypotaurine, and others). It was once more concluded that metabolic abnormalities potentially account for increased systemic inflammation and oxidative stress. The final sentence in the manuscript shall be cited: "The differential metabolites and metabolic pathways identified in this paper should be further studied using targeted metabolomics, lipidomics, and proteomics, in order to elucidate mechanisms and screening therapeutic targets for developing early diagnostic strategies and treatments." The sentence somehow reflects the advantages but also the limitations of untargeted metabolomics in general. It potentially confirms or even modifies pathophysiological concepts of certain disease states such as AKI, but more specific conclusions often remain difficult.

This also applies to the next (untargeted) study, which was published in 2021 [55]. Once more, rats (Sprague-Dawley) underwent LPS treatment (i.p.), and analyses were performed either 2 or 6 h later. Thus, three groups (control (CT), LPS2, and LPS6) were defined, with significant increases in serum creatinine and BUN in the LPS6 group as compared to CT and LPS2 ($P = 0.0009$ and $P = 0.001$). In parallel, the kidney structure of both LPS2 and LPS6 mice was significantly affected (e.g., detachment of the brush border, epithelial cell shedding and, others). The detailed results will not be discussed, but the study ultimately revealed three key findings: LPS-induced stimulation of systemic aerobic and anaerobic metabolism, impaired oxygen supply, and abnormalities in fatty acid metabolism. These events were finally proposed as responsible for the development of sepsis-associated AKI.

A study on targeted metabolic profiling (liquid chromatography-coupled tandem mass spectrometry (LC-MS/MS)) in cisplatin-induced AKI was published in 2021 [56]. The particular aim was to uncover cisplatin-induced alterations in the tryptophan metabolism. Previous studies identified the amino acid and its metabolites as potential biomarkers in CKD and AKI [57, 58]. Therefore, the study particularly focused on the following metabolites: tryptophan, 5-hydroxytryptamin (serotonin), N-acetylserotonin, 3-hydroxyanthranilic acid (HAA), kynurenine (KYN), indole-3-lactic acid (ILA), indole-3-acetamide (IAM), 5-methoxy-3-indoleacetic acid (MIAA), and others. Sprague-Dawley rats were intravenously injected with three different cisplatin doses (group "low" (L): 3.0 mg/kg; group "middle" (M): 6.0 mg/kg; group "high" (H): 9.0 mg/kg), and controls received saline only. Analyses of blood and renal tissue were performed on day 5 after drug exposure. Both analytes, serum creatinine, and BUN gradually increased from "L" to "M" to "H". Tissue analysis was separately performed from cortical and medullary dissections, respectively. Cisplatin injection significantly affected the tryptophan metabolism in cortex and medulla, the medullary area however was more susceptible. Out of 29 studied metabolites, indoxyl sulfate accumulated in a dose-dependent manner. The functional relevance of indoxyl sulfate was proven by additional experiments with chlormethiazole, an inhibitor of CYP2E1 (a member of the cytochrome P450 mixed-function oxidase system). Reduced hepatic indoxyl sulfate synthesis attenuated cisplatin-induced AKI.

Several previously discussed studies identified AKI-associated dysregulation of lipid metabolism, not only in toxic but also in ischemic AKI. Xiong et al [59] performed their study in C57/BL6 mice and in Sprague-Dawley and Wistar rats. AKI was once more induced by i.p. injections of cisplatin (25 mg/kg); animals were euthanized 1, 2, and 4 days later. Metabolomics revealed an accumulation of triglycerides in renal tissue, and the findings were confirmed by oil red O staining. For a more detailed characterization of accumulated triglycerides, the authors used a mass spectrometry-based approach, therefore the investigation was ultimately a lipidomics study. Further analyses focused on the so-called superfam-

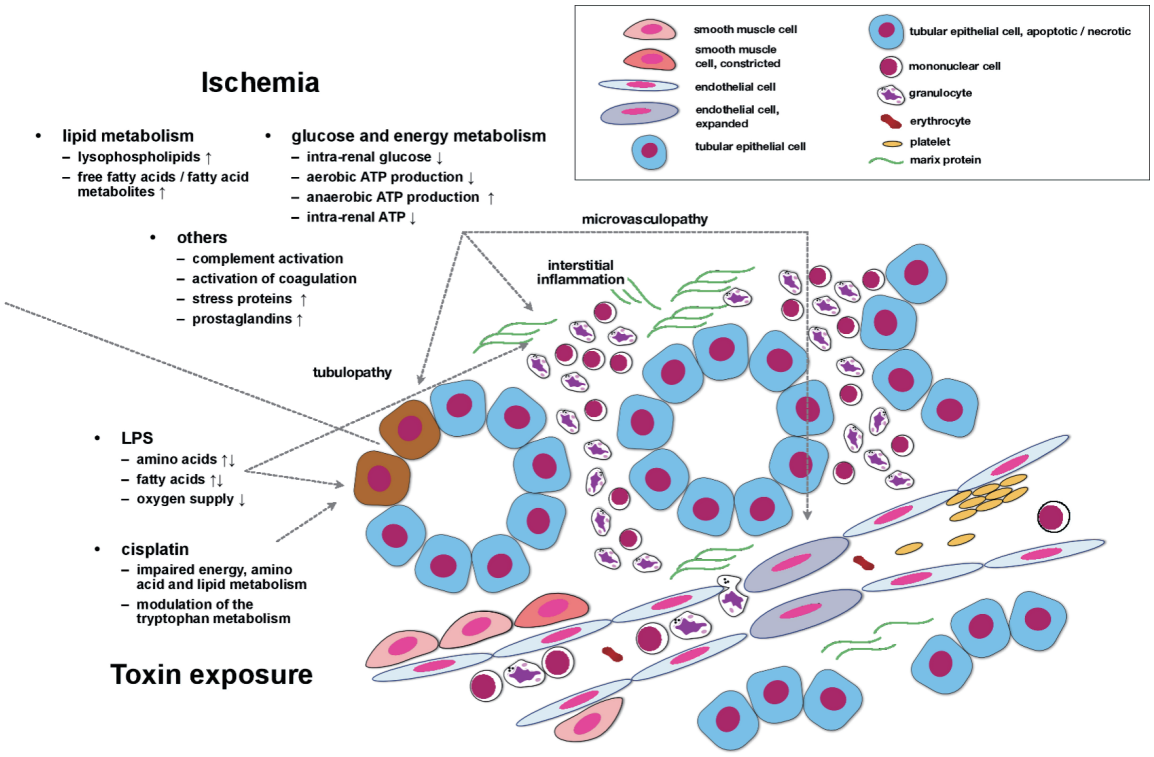

Figure 1. Metabolomics-derived findings in experimental AKI. Ischemia induces multiple deteriorations of lipid, glucose, and energy metabolism. In addition, the complement activity increases, coagulation pathways are activated, and prostaglandin synthesis is stimulated. These events, in conjunction, induce and perpetuate tubular cell dysfunction/damage, interstitial inflammation, and microvasculopathy. Under experimental conditions, both LPS and cisplatin also impair lipid and energy metabolism. Cisplatin particularly modulates the tryptophan pathway, most likely a key mechanism in cisplatin-induced AKI. LPS: lipopolysaccharide; AKI: acute kidney injury; ATP: adenosine triphosphate.

ily of uncoupling proteins (UCPs), which are involved in lipid metabolism. The expression of UCPs 1 - 3 was evaluated in renal tissue, with strong signals for UCPs 1 and 2 under normal conditions (mice and rats). UCP 3 in contrast was hardly detectable at all. AKI induced a decrease in intrarenal UCP 1, and the loss was correlated with AKI severity. Adenovirus-based UCP 1 expression in kidneys of cisplatin-treated mice attenuated three outcome variables: serum creatinine decreased, tissue damage was reduced, and lipid accumulation was diminished. Finally, the authors showed a link between UCP 1 activity and the AMPK/ULK1/autophagy pathway. The study impressively showed impaired intrarenal lipid clearance, most likely resulting from reduced UCP 1 activity and impaired autophagy.

The central role of certain lipid components in the pathogenesis of cisplatin-induced AKI was also documented by Song et al [60]. The study aimed to identify the mechanisms by which the substance astragaloside IV (AS IV), an active compound of the traditional Chinese herb *Astragalus membranaceus*, may attenuate the effects of cisplatin.

Other Types of AKI

Xue et al [61] published an article on heat stroke (HS)-related AKI in 2021. HS potentially induces a systemic inflammatory response syndrome with or without AKI. According to Ren et al [62], two types of HS must be distinguished, exertional HS (EHS) and non-exertional HS (NEHS). HS mainly evolves in younger and physically active subjects, NEHS in contrast affects older individuals with a higher degree of cumulative morbidity. The authors established a murine HS model by increasing the animals' body temperature to 41 °C. The final temperature was maintained only shortly, but serum creatinine significantly increased in HS as compared to control animals. Interestingly, HS mice showed an almost generalized distribution pattern of 18-fluorodeoxyglucose (18FDG) (analyzed by micro-positron emission tomography/computed tomography scanning). Immunoblot analysis revealed higher abundances of high-mobility-group-box protein 1 (HMGB1) and receptor for advanced glycation end products (RAGE) in renal tissue specimens from HS animals. Finally, liquid chromatography-mass spectrometry showed an enrichment of unsaturated fatty acids. The authors concluded a key role for HMGB1/RAGE and unsaturated fatty acids in AKI induction post-HS.

Figure 1 summarizes metabolomics-derived findings in experimental AKI. The figure hardly differentiates between specific areas within the kidney but is intended to illustrate metabolic alterations that occur in ischemic/toxic/other types of AKI in a more general manner.

Table 1. Summary of All Experimental Studies Discussed in the Text

Reference	Design	Outcome/conclusion
Ischemic AKI		
Liu et al, 2012 [42]	Bilateral renal ischemia (45 min) in Sprague-Dawley rats, L-carnitine pretreatment in one group	Increase of serum lysophospholipids and free fatty acids, decreased activity of serum phospholipase A2/ischemia-associated dysregulation of lipid metabolism
Wei et al, 2014 [44]	Bilateral renal ischemia in mice (25 min), analyzes at 2 or 48 h or at 7 days after reperfusion	Alterations in glucose, lipid, and purine metabolism/identification of candidates involved in energy depletion and inflammation
Huang et al, 2018 [45]	Unilateral renal ischemia in rats (45 min)	Increased availability of stress signaling proteins (proteomics analysis), increase of cortical lipid metabolites, accompanied by lower tissue glucose levels
Fox et al, 2019 [46]	Experimental cardiorenal syndrome type 3 (6) in mice (bilateral renal ischemia for 22 min)	Intrarenal amino acid depletion and oxidative stress, intracardiac stimulation of anaerobic ATP synthesis/experimental confirmation of reno-cardiac cross-talk in AKI
Davidson et al, 2022 [49]	Cardiopulmonary bypass including so-called deep hypothermic circulatory arrest (CPB/DHCA) in piglets	Stimulated anaerobic glycolysis in AKI piglets/anaerobic glycolysis as potential biomarker of early AKI in CPB
Toxic AKI		
Izquierdo-Garcia et al, 2019 [52]	Living *Escherichia coli* for sepsis induction in pigs	Multiple metabolic abnormalities in kidney tissue, serum, and urine, correlations between certain urine metabolites and established AKI biomarkers/metabolomics help to identify novel AKI biomarker molecules
Qu et al, 2020 [53]	Intraperitoneal cisplatin injections (Sprague-Dawley rats), urine and renal tissue analyzes	Dysregulation of tissue amino acid and lipid metabolism; additional identification of AKI biomarker candidates in urine samples
Gao et al, 2021 [54]	LPS-induced multiorgan failure in rats	Significant tissue damage in liver, lungs, colon, and kidney, alteration of more than 50 metabolic pathways upon LPS administration/conclusion rather vague
Ping et al, 2021 [55]	LPS treatment of Sprague-Dawley rats	Stimulation of aerobic and anaerobic metabolism, impaired oxygen supply, abnormalities in fatty acid metabolism/alterations proposed as key events in sepsis-associated AKI
Tan et al, 2021 [56]	Cisplatin-induced AKI in Sprague-Dawley rats, targeted analysis of the tryptophan metabolism	Identification of indoxyl sulfate as key regulator of tissue damage in cisplatin-induced AKI
Xiong et al, 2021 [59]	Cisplatin-induced AKI in Sprague-Dawley and Wistar rats	Intrarenal uncoupling protein (UCP) 1 inhibits intrarenal lipid clearance
Other types of AKI		
Xue et al, 2021 [61]	Murine model of heat stroke-related AKI	Intrarenal enrichment of unsaturated fatty acids

CPB/DHCA: cardiopulmonary bypass including so-called deep hypothermic circulatory arrest; AKI: acute kidney injury; ATP: adenosine triphosphate; LPS: lipopolysaccharide.

Table 1 [42, 44-46, 49, 52-56, 59, 61] summarizes all studies discussed in the text, including reference, year, design, and essential findings.

Conclusions

Will metabolomics studies provide a deeper understanding of pathophysiological processes that are responsible for functional impairment/structural damage in ischemic or toxic or other types of AKI? In our opinion, metabolic profiling offers valuable information in this respect. Several studies identified abnormalities in amino acid, glucose, and lipid metabolism. Particularly the role of the latter may not be underestimated, as shown by the study of Xiong et al [59]. One investigation even found impaired energy and prostaglandin metabolism [44] in response to ischemia, both in conjunction, potentially induce tubular dysfunction/damage and stimulated inflammation.

Supplementary Material

Suppl 1. Flow chart: the searching procedure.

Acknowledgments

None to declare.

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Conflict of Interest

The authors declare that they do not have any conflict of interest.

Author Contributions

Daniel Patschan and Susann Patschan wrote the article. Igor Matyukhin searched for references. Meike Hoffmeister and Martin Lauxmann searched for references and assisted in figure preparation. Oliver Ritter provided financial support and assisted in writing. Werner Dammermann designed the manuscript and helped in writing. All authors finally approved the final version of the manuscript.

Data Availability

All data discussed in the article were extracted from the references cited in the text and the bibliography.

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