Gut-Derived and Cardiovascular Dysfunction in Experimental AKI Models

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The formation and metabolism of IS, PCS, and IAA, from their precursors (indole for IS and IAA and p-cresol for PCS), produced by gut microbiota, to their kidney excretion through organic anion transporters (OATs) and the mechanisms that lead to their accumulation in kidney disease, have been well described in recent reviews. A number of experimental studies have explored the relationship between gut microbiota and the kidney in acute and chronic models, highlighting inter-organ crosstalk. Kidney failure is indeed responsible for the disturbance of the gut microbiota, and dysbiosis is linked to the progression of kidney failure. However, factors that may influence PBUT accumulation in the gut–kidney axis appear to be different between CKD and AKI. In CKD, external factors associated with a specific diet (low fiber intake), longterm antibiotic treatment, phosphate binder treatment, and iron supplementation, and the internal factor of high urea levels modify the gut microbiota and intestinal barrier permeability. Although AKI and CKD may share common factors, such as a specific diet or the use of antibiotics, a reduction in short-chain fatty acid levels in AKI may play a specific role in the formation of PBUTs by favoring an inflammatory state associated with intestinal barrier disruption.

Keywords: acute kidney injury ; uremic toxins ; cardiovascular dysfunction ; indoxyl sulfate

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1. Indoxyl Sulfate

Indoxyl sulfate (IS) is a PBUT that strongly contributes to endothelial damage during CKD. IS is known to have many specific deleterious effects on the vascular wall, in particular, by decreasing endothelial relaxation, cell viability, and proliferation and by inducing oxidative stress [1][2][3][4]. In addition, it promotes the expression of adhesion molecules, such as ICAM-1 and MCP-1, which are associated with leukocyte extravasation, and alters endothelial permeability [5][6][7]. Moreover, it is responsible for a pro-thrombotic state by promoting tissue factor production [8][9]. A number of studies have also shown the toxicity of IS for the heart, with cardiac pro-fibrotic, pro-hypertrophic, and pro-inflammatory effects associated with the induction of oxidative stress [10][11][12][13][14][15]. However, in the specific context of AKI, its role in vascular and cardiac dysfunction is poorly understood. A number of studies have examined the vascular effects of IS in vitro using very short-term exposure, which may mimic acute exposure to IS during AKI [3][5][9]. Dou et al. exposed endothelial cells for five hours to four different concentrations of IS and showed an increase in ROS production within one hour of exposure [2]. Moreover, endothelial cells showed reduced viability and NO production after three hours of exposure to IS [4]. An increase in tissue factor and ICAM-1 expression by endothelial cells was also found after two and six hours of IS exposure, respectively [5][8]. Exposure of endothelial progenitor cells (EPCs) to IS was shown to result in a decrease in EPC viability (less proliferation and more senescence and autophagy) and the induction of oxidative stress in a dose-dependent manner. In an animal model of AKI, consisting of a unilateral ischemia-reperfusion model generated by the ligature of the left renal artery for 40 min, IS attenuated eNOs expression in the endothelium of the arteries and ischemic kidney and reduced EPC mobilization from the bone marrow [16]. More recently, two experimental studies highlighted the action of acute IS exposure on the decrease in vasorelaxation in rat aorta linked to a reduction in the release of NO [17][18]. Moreover, Savira et al. explored the role of IS in vascular and cardiac dysfunction [19][20]. They showed that IS induced cardiomyocyte hypertrophy and decreased vasorelaxation by activation of the ASK1 pathway. Furthermore, Shen et al. demonstrated the action of IS on the endothelial expression of E-selectin mediated by IL-1β in an AKI mouse model [21]. E-selectin expression was higher in kidney endothelial cells from AKI mice than in controls. In vitro, E-selectin expression was directly associated with the IS concentration in endothelial cells pre-exposed to IL-1β. These effects were associated with ROS production and higher monocyte adhesion to endothelial cells. As for E-selectin, ICAM-1 expression was induced by IS in endothelial cells pre-exposed to IL-1β in a second study [22]. The acute effect of IS on leukocyte adhesion and extravasation was also confirmed in a rat model exposed to various times of IS infusion [7]. The acute cardiac toxicity of IS was also explored in vitro [23]. The authors demonstrated a dose-dependent increase in cardiomyocyte apoptosis after 24 h of IS exposure. These results were confirmed by animal studies. Shen et al. highlighted cardiac dysfunction with pathological changes in echocardiography parameters associated with higher brain natriuretic peptide (BNP) levels and

greater cardiomyocyte apoptosis in AKI mice. In addition, treatment by AST-120, an oral charcoal adsorbent that decreased IS levels, improved all parameters [22]. Furthermore, they evaluated the cardiac effect of EPC treatment in AKI mice [24]. AKI mice infused with EPC showed improved cardiac echocardiography parameters, with less cardiomyocyte apoptosis initially induced by IS and IL-1β. These results were associated with the inhibition of a pro-apoptotic protein by EPC, probably through the decrease in IS and IL-1β concentrations. These studies confirmed the direct role of IS on vascular and cardiac cell toxicity and induction of the pro-inflammatory and oxidative states during AKI. However, the association between IS, cardiovascular dysfunction, and cardiovascular complications can also be explained by the pathological action of IS on kidney disease progression. Indeed, several experimental studies have highlighted the effect of IS on the development of renal fibrosis through oxidative stress, the activation of endoplasmic reticulum stress, and the epithelial-mesenchymal transition [25][26][27][28][29][30].

2. Para-Cresyl Sulfate

As does IS, para-cresyl sulfate (PCS) shows toxicity towards vascular and cardiac tissues, mainly explored in CKD. It is responsible for endothelial damage, with alterations in endothelial wall permeability, microparticle release, and leukocyte recruitment [7][31][32]. It also acts on the migration and proliferation of vascular smooth muscle cells [33]. Additionally, PCS is directly involved in cardiac diastolic dysfunction by increasing cardiomyocyte apoptosis and ROS production [34]. Similar to IS, it is also responsible for cardiomyocyte hypertrophy and fibroblast collagen synthesis subsequent to the activation of ASK, a regulator of the cellular stress response [19]. P-cresol, the precursor of PCS, also has effects on the endothelium, with a decrease in cell proliferation and the disruption of adherent junctions [3][35]. Only a few experimental studies investigated the role of PCS on vascular and cardiac dysfunction during AKI. Two in vitro studies assessed the stimulatory effect of acute exposure to PCS on leukocytes, showing oxidative burst activity [36][37]. This action was associated with increased leukocyte adhesion to the vascular wall after a short-term infusion of PCS in vivo [7]. Moreover, Gross et al. demonstrated its deleterious effect on vascular reactivity in an ex vivo model of aortic rings exposed to PCS [38]. After short-term exposure to PCS (30 min), the thoracic aorta showed pathological constriction mediated by rho-kinase activation. This effect was associated with ROS production by endothelial and vascular smooth muscle cells in vitro. Moreover, PCS induced higher vascular permeability in rat vessels after 10 to 60 min of exposure at various concentrations, suggesting that PCS can induce endothelial barrier dysfunction [39]. Moreover, Huang et al. explored the effect of various concentrations of PCS on cardiomyoblasts in vitro [40]. After short-term exposure to low-level PCS, the cardiomyoblasts showed less proliferation and mitochondrial hyperfusion. This effect was considered to be a stress-induced response to acute PCS exposure. P-cresol (the gut precursor of PCS before metabolic sulfatation by the liver) was also shown to be responsible for altered cardiomyocyte contractility and the disruption of gap junctions after acute exposure [41]. However, the acute action of PCS in cardiac dysfunction needs to be evaluated in animal studies. As for IS, PCS is also responsible for the progression of renal fibrosis subsequent to the induction of oxidative stress leading to ROS production [30][42][43][44]. Thus, its action on the AKI to CKD transition should also lead to CKD-associated cardiovascular complications.

3. Indole-3-Acetic Acid

Indole-3-acetic acid (IAA), another PBUT, is also known to have adverse effects on vascular function during CKD. Its main role is to activate aryl hydrocarbon receptor (AhR) signaling pathways, similar to IS [8][45]. Thus, it is responsible for ROS production and pro-inflammatory molecule Cox-2 activation, as well as tissue factor production, in endothelial cells [8][46]. Three experimental studies explored the effect of very short-term exposure of endothelial cells to IAA in vitro and highlighted its pro-inflammatory and pro-apoptotic effect on endothelial cells and their progenitors [8][46][47]. However, these results need to be completed by in vivo studies. Moreover, the potential deleterious actions of IAA on the heart are still unknown. Furthermore, its contribution to the possible transition from AKI to CKD and, thus, to CKD-associated CV complications has not been specifically studied.

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