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Supplementary Information for

Review on Kidney-Liver Crosstalk: Pathophysiology of Their Disorders

Niloofar Khoshdel Rad, Ph.D.[1, 2#], Zahra Heydari, Ph.D.[3#], Amir Hossein Tamimi, Ph.D.[1], Ensieh Zahmatkesh, Ph.D.[1], Anastasia Shpichka, Pharm.D., Ph.D.[3, 4, 5], Maryam Barekat, M.D.[1], Peter Timashev, Ph.D.[3, 4, 5*], Nikoo Hossein-khannazer, Ph.D.[6], Moustapha Hassan, Ph.D.[7], Massoud Vosough, M.D., Ph.D.[1, 7*]

1. Department of Regenerative Medicine, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran
2. Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. World-Class Research Center "Digital Biodesign and Personalized Healthcare", Sechenov University, Moscow, Russia
4. Institute for Regenerative Medicine, Sechenov University, Moscow, Russia
5. Chemistry Department, Lomonosov Moscow State University, Moscow, Russia
6. Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
7. Experimental Cancer Medicine, Institution for Laboratory Medicine, Karolinska Institute, Stockholm, Sweden

Ischemia and ischemia–reperfusion-induced injury

This process is orchestrated by the activation of the nuclear factor κ-light-chain-enhancer of activated B-cell (NF-kB) receptors. Elevated levels of TNF-α can result in a dramatic increase in myeloperoxidase (MPO) activity. Studies have shown that this results in a decrease in superoxide dismutase (SOD) and catalase (CAT) enzymes, accompanied by an elevation in glutathione levels, ultimately causing cell damage through oxidative stress. It has also been shown that an increase in the level of spermidine/spermine N1-acetyltransferase (SSAT), a limiting factor in polyamine metabolism, is responsible for the production of reactive oxygen species during ischemia (ROS). ROS produced in this pathway adds up to those caused by the reperfusion itself. In addition, ARF specifically increases the levels of IL-6 and IL-10 in the liver. These cytokines are related to liver cirrhosis and hepatocellular carcinoma development (1). Park and colleagues used a murine model of ARF using renal ischemia-reperfusion or bilateral nephrectomy to examine the intestinal sources of pro-inflammatory mediators in ARF patients. They showed that ARF stimulates the synthesis and secretion IL-17A by Paneth cells and triggers hepatic damage through hepatic and systemic production of IL-17A by macrophages. These events increase bilirubin and alanine transaminase (ALT), as well as, hepatic cell apoptosis and vascular permeability (2). Another study showed that ischemia-reperfusion kidney injury leads to vascular crowding and liver necrosis, resulting in liver inflammation and injury. It is accompanied by elevated serum levels of ALT, aspartate transaminase, lactate dehydrogenase, and bilirubin (3). Current treatments for renal ischemia-reperfusion injury involve antioxidants and anti-inflammatory agents. The recent study investigates the connection between Xanthine oxidase (XO) and PPAR-γ pathways in ischemia-reperfusion injury. The results showed that the XO inhibitor allopurinol (ALP) protects the kidney and liver by activating PPAR-γ. Rats with ischemia-reperfusion injury treated with ALP exhibited improved kidney and liver function, reduced inflammation, and nitrosative stress. However, when PPAR-γ was inhibited alongside ALP, the beneficial effects were diminished. This suggests that enhancing PPAR-γ through ALP could be a valuable therapeutic approach to prevent ischemia-reperfusion injury (4).

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*Corresponding Addresses: Institute for Regenerative Medicine, Sechenov University, Moscow, Russia
P.O.Box: 16635-148, Department Regenerative Medicine, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran
Emails: timashev_p_s@staff.sechenov.ru, masvos@Royaninstitute.org

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Table S1: Exploring the impact of acute kidney injury on hepatic function and inflammatory response: experimental studies

Related hepatic disease	Related kidney disease	Important findings	Animal model	Ref.
Systemic inflammation	AKI (IRI)	IRI and bilateral nephrectomy increased ALT and bilirubin, hepatic cytokines, peri-portal hepatocyte vacuolization, vascular permeability, apoptosis, necrosis and neutrophil infiltration.	Mouse	(5)
Hepatic oxidative stress and inflammation	AKI (IRI)	IRI provoked elevated activities of transaminases, hepatic stress and inflammation including MDH, MPO, catalase, XO, NO high; treatment with melatonin reduced these factors.	Rat	(6)
Hepatic oxidative stress and inflammation	AKI (IRI)	IRI and bilateral nephrectomy caused early liver inflammation, increased cell death, and oxidative stress. Antioxidant levels dropped, and TNF-α levels rose in the liver and serum. Infusing glutathione before IRI/ bilateral nephrectomy helped reduce liver damage	Rat	(7)
Hepatic oxidative stress and inflammation	AKI (IRI)	ALP, an XO inhibitor, protects the kidney and liver during IRI by activating the PPAR-γ pathway. Rats treated with ALP exhibited improved organ function, reduced inflammation, and nitrosative stress.	Rat	(4)

IRI; Ischaemia–reperfusion injury, AKI; Acute kidney injury, ALT; Alanine aminotransferase, MDH; Malondialdehyde, MPO; Myeloperoxidase, XO; Xanthine oxidase, NO; Nitric oxide, and ALP; Allopurinol.

Table S2: The randomized controlled clinical trials of vasoactive drugs for treatment of hepatorenal syndrome

Drug	Mechanism	Outcome	References
Terlipressin	Splanchnic vasoconstrictor	Increasing renal function and urinary output, improving survival ACLF	(8)
Terlipressin *vs.* placebo/control	Splanchnic vasoconstrictor	improving renal functions, HRS reversal, improved survival rate	(9-15)
Terlipressin *vs*. norepinephrine	Splanchnic vasoconstrictor+systemic vasoconstrictor	HRS reversal, decreasing serum creatinine and increase in urinary output	(16-19)
Dopamine plus furosemide *vs.* terlipressin	Positive inotropic drugs	Improving renal function, increase in urinary output	(20)
Midodrine plus octreotide *vs.* terlipressin	A systemic vasoconstrictors +a splanchnic vasodilator	HRS reversal, improving renal function; improved survival	(21)
Midodrine plus octreotide *vs.* noradrenaline	Vasoconstrictors	HRS reversal	(22)
Norepinephrine plus albumin vs. midodrine and octreotide plus albumin	Peripheral vasoconstrictor+albumin	improving renal function; improved survival	(23)

Midodrine; Activation of α1 adrenergic receptors on vascular smooth muscle cells, Norepinephrine; Activation of α-1 adrenergic receptors on vascular smooth muscle cells, Octreotide; inhibiting secretion of glucagon, Terlipressin; Effect on 1A and 1B receptor, ACLF; Acute-on-chronic liver failure, HRS; Hepatorenal syndrome.

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