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An insight into the role of cyclooxygenase and lipooxygenase pathway in renal ischemia

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Abstract. – OBJECTIVE: Renal ischemia (RI) is a clinical condition that occurs due to marked decrease in renal blood flow. The pathophysiology of RI is interlinked with atherosclerotic renal artery stenosis, infarction, organ transplantation and sepsis. The mechanism of RI injury depends on various factors such as inflammatory response, oxidative stress and apoptosis. In this review, we evaluate the role of cyclooxygenase and lipoxygenase in modulating the process of ischemic renal injury.

MATERIALS AND METHODS: This is a literature review of articles published on PubMed and Web of Science in English.

RESULTS: RI is characterized by an inflammatory response and oxidative stress, which are further worsened by the metabolites of the arachidonic acid pathway.

CONCLUSIONS: RI results from a vigorous process involving inflammation and some mediators in a multifaceted interaction. Indulgence of oxidative stress and lipid peroxidation seems to be major factors which promote the inflammation process during RI.

Key Words:
Renal ischemia, Cyclooxygenase, Lipooxygenase, Inflammation, Oxidative stress.

Introduction

Renal ischemia (RI) is a clinical condition characterized by occlusion of renal blood flow to kidney. This may occur after atherosclerotic renal artery stenosis, infarction, organ transplantation and sepsis. Kidney is a highly perfused organ which receives 20-25% of cardiac output through renal arteries. However, extent of oxygenation differs, where cortex being highly perfused and medulla being less oxygenated in normal conditions. Kidney has significant adaptive ability to tolerate changes in renal blood flow to prevent the occurrence of tissue hypoxia. Yet, continued insult to the renal system may lead to pathological conditions causing acute renal failure which accounts for high mortality rates in hospitals. The mechanism of renal ischemic injury is multifactorial which includes inflammatory response, oxidative stress and apoptosis. In this review, we evaluate the role of cyclooxygenase (COX) and lipooxygenase (LOX) pathways and their interplay with the pathophysiology of RI.

Materials and Methods

Articles on ischemia/reperfusion induced acute renal failure, acute kidney injury and, COX and LOX pathways published on PubMed and Web of Science.

Results

Localization of COX and LOX in Kidney

The differential expression and distribution of the two COX isoforms indicate that they are involved in the regulation of various physiological functions in the kidney. In animals, between the two isoforms, COX- 1 is dominant and expressed in glomerular mesangial cells, arteriolar endothelial cells, and medullary and cortical collecting ducts of kidney. In human renal system, COX-1 is seen in collecting duct cells, interstitial cells and vasa recta. COX-2 is largely localized in macula densa cells of the cortical thick ascending limb of Henle and interstitial cells in rodents, rabbit, and dogs. In humans, COX-2 is associated with parts of the renal vasculature, loop of Henle, and podocytes[1]. The cells of myeloid origin express 5-LOX mainly neutrophils, eosinophils, macrophages/monocytes, and mast cells. In the pathophysi-

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ology of renal dysfunction by RI, LTB4 plays a major role associated with infiltration of the kidney with polymorphonuclear cells (PMN). The activation of PMNs by LTB4 changes their shape, prompts the expression of cell-adhesion molecules and, thereby, promotes binding of PMN to endothelium[2,3].

Renal Ischemia – Morphological and Hemodynamic Changes

Morphological structure is a factor defining an organ function. In ischemic injury, the prominent changes are damage/change in shape of tubule cells, injury of proximal tubule brush border, proximal tubular dilation, damage of distal tubules and areas of cellular regeneration. Peritubular capillaries show severe vascular congestion, damaged endothelium and leukocyte accumulation. Necrosis is observed in the outer medullary regions. Recently, studies have suggested the occurrence of apoptotic cell death in proximal and distal tubules associated with ischemic insult[4,5]. Renal microvasculature plays a vital role in the progression of ischemic injury. In early phases of ischemia, the adaptive abilities of micro vessels, which transport blood to renal parenchyma, maintain renal function. Markedly, there are a clear congestion and hypo-perfusion in the outer medullary region, which persist even after increase in cortical blood flow during reperfusion[6]. These morphological alterations coupled with hemodynamic changes turn on the COX-LOX system in the kidney[4,7,8].

COX-LOX and Vasoconstriction

In renal physiology, the enzymes 5-LOX and COX plays crucial role in maintaining the homeostasis by catalyzing the production of prostaglandins (PGs) and leukotrienes (LTs) through arachidonic acid (AA) pathway. The metabolites of AA formed through 5-LOX and COX pathway, exert potent vasoactive and pro-inflammatory effects. Since they are invariably important to the homeostasis, any alterations in their levels will have its effects on the normal physiology. Other characteristics of ischemic injury are higher leukocyte-endothelial adhesion and leukocyte activation. All of the mentioned processes contribute directly to the pathophysiology of RI. In case of RI, there is a marked localized impairment in the supply of oxygen and nutrients to the kidney microenvironment. Also, impaired waste removal from the kidneys worsens the situation. As a result of these, renal injury is caused, which if untreated, leads to apoptosis and necrosis[2]. Macrophages are present in the glomerulus, interstitium of renal cortex and also in medulla. They represent the innate immune system in kidney, which is the response against tissue insult. During RI, macrophages stimulate the inflammatory response by COX-2 mediated production of vasoconstrictor prostaglandins PGF2 and TXA2[9]. In RI, leukocyte aggregation is seen in peritubular capillaries, interstitial space and renal tubules. Moreover, the involvement of ischemic injury activates LOX system resulting in leukocyte endothelial adhesion and activation leading to the production of vasoconstrictor prostaglandins by COX pathway. Through NF-kB intracellular signaling pathway and MAP kinase pathway, macrophages release pro-inflammatory cytokines- IL-6, TNF, IL1, IL12 and also pro-inflammatory chemokines as MCP-1, IL-8, RANTES, etc.[4,10]. Chemokines are the major mediators of inflammation that modulate the actions of pro-inflammatory cytokine, expression of adhesion molecule and leukocyte infiltration/activation. Activation of Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway mediates also release pro-inflammatory cytokines. Inflammatory mediators, ROS and cell adhesion molecules – intracellular adhesion molecule-1 (ICAM-1) and P-selectin – recruit leukocytes and neutrophil infiltration into post ischemic tissue, then leads to increased leukocyte – endothelial interactions, which promote cell injury, endothelial cell swelling and hinder blood flow[11]. In a post-ischemic kidney, increased levels of ET1, AT2, TXA_2, PGH_2, LTC_4 and D_4, and adenosine are seen commonly. It worsens the situation because most of them are vasoactive leading to further vasoconstriction which is partly increased due to post-ischemic decline in nitric oxide production [12-14].

Oxidative Stress and Ischemia/Reperfusion Damage

During RI, the damaged tissue produces excessive amount of ROS, which causes oxidative stress leading to mitochondrial oxidative phosphorylation, ATP depletion, increase intracellular calcium and activation of membrane phospholipids proteases. The blood flow during reperfusion phase of RI produces oxygen free radicals in high amounts, which lead to lipid peroxidation. In RI, formation of free radicals causes peroxidation of lipids in membrane, conformational changes

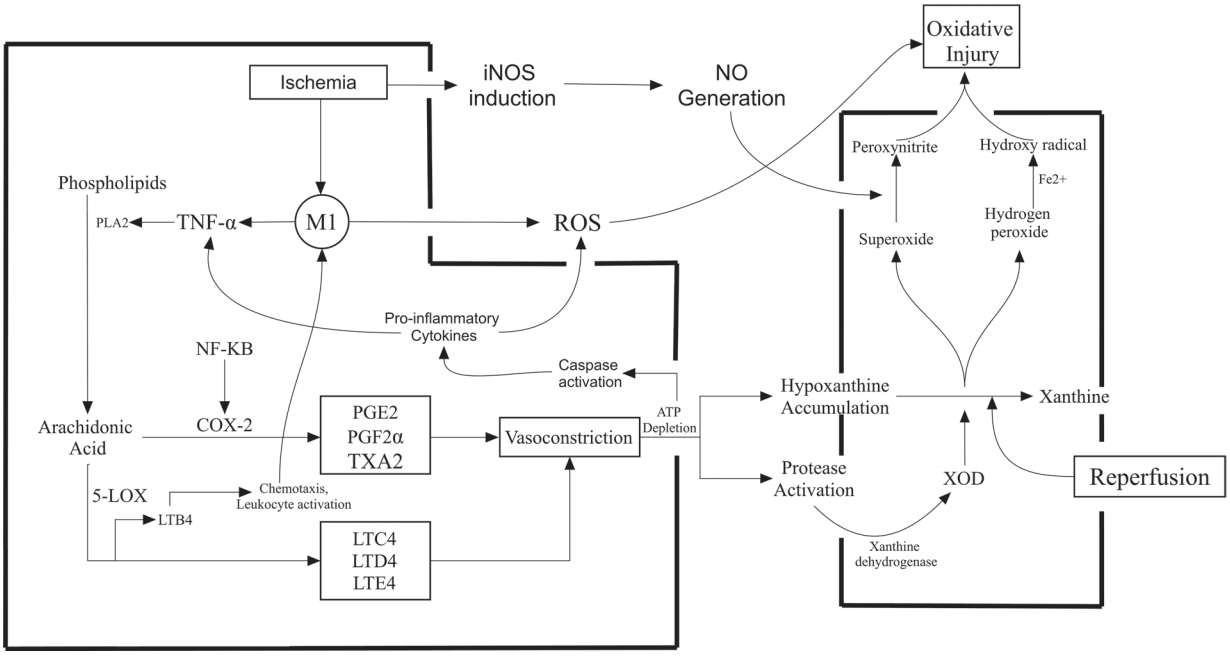

Figure 1. Mechanisms of ischemia/reperfusion in acute renal failure.

in proteins, and DNA leading to apoptotic cell death[15]. Further, decreased antioxidant enzyme defense system such as catalase, superoxide dismutase, and glutathione peroxidase, contribute to the pathophysiology of ischemia-reperfusion injury. Therefore, inhibiting this pathway or prevention of free radical production is a strategy to protect the tissue during RI[16-18]. Nitric oxide (NO) indirectly plays an eminent role in aggravating the oxidative injury to the kidney. On occurrence of ischemic condition, there is iNOS induction in the epithelium of blood vessels, which ultimately leads to formation of NO. Once the reperfusion starts, conversion of hypoxanthine to xanthine begins rapidly, generating superoxide and hydrogen peroxide in the process. The NO generated earlier acts as a catalyst to convert the superoxide to peroxynitrates which contribute directly to the oxidative injury[19,20].

Renin-Angiotensin-Aldosterone (RAAS) System

The decreased blood flow due to ischemia leads to a rapid fall in renal blood flow which is the activating signal for RAAS system. Moreover, the sodium depletion due to ischemia in renal microvasculature upregulates the COX-2, which in turn increases formation of PGs. These PGs bind to the PG receptor increasing the production of cAMP as a result of which, renin is released from juxtaglomerular cells[21,22]. The Angiotensin II formed on the activation of cascade binds to ATII receptor subtype I, the action of which is seen as marked vasoconstriction in the renal vasculature thus further worsening the ischemic injury.

Conclusions

RI results from a intense process involving inflammation and some mediators in a multifaceted interaction. Indulgence of oxidative stress and lipid peroxidation seem to be the major factors which promote the inflammation process during RI.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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