



The role of NRF-2 in renal damage in cardiopulmonary bypass

NRF-2 level in renal damage

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Abstract

Cardiopulmonary bypass, which allows cardiac interventions, is a standard perfusion technique used in cardiac surgery, which provides cardiac arrest by using cardioplegic solutions and oxygenates the blood outside the body through extracorporeal circulation and redirects blood back to the patient. With the use of cardiopulmonary bypass technique, serious complications may develop in the perioperative and postoperative periods. One of the most important of these developing complications is kidney damage. New biomarkers that will enable the early detection of this developing kidney damage are being investigated, one of which is NRF-2. Our aim in this review article is to investigate current information about NRF-2 and to identify the role factors associated with kidney damage.

Keywords

NRF-2, kidney injury, cardiopulmonary bypass, cardiac surgery

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Introduction

Cardiac diseases can cause high costs for the health system, limited quality of life in humans, and serious organ damage.¹²

The development of the cardiopulmonary bypass (CPB) technique is necessary to achieve the desired procedures, and high mortality of early cardiac operations such as embolectomy has accelerated this process.³ Factors encountered with CPB application include systemic inflammatory response, anemia, impaired oxygenation, coagulopathy following foreign surface exposure, hemodilution associated with the use of prime solution causing renal vasoconstriction, and non-pulsatile flow agents typically used in CPB.⁴

The CPB circuit includes a pump, oxygenator, aspiration catheters, filters that damage erythrocytes and increase plasma-free hemoglobin.⁵ Free hemoglobin depletes circulating haptoglobin and damages the kidneys by catalyzing free radical production, precipitating with Tamm-Horsfall proteins in the renal collecting system, and inducing renal arteriole vasoconstriction by eliminating nitric oxide.⁶

Ultrafiltration (UF) is a technique commonly used during CPB to reduce the harmful components in the blood to remove it.⁷ In the CPB circuit and in the plasma fluid, their soluble components are removed as the blood passes through the ultrafilter fibers. Common UF techniques include modified ultrafiltration, conventional ultrafiltration, and zero-balance ultrafiltration. All these techniques have a common goal: to compensate for changes in blood concentration, filtration, and electrolyte plasma concentration such as potassium overload, thus protecting the kidney and avoiding homologous blood transfusions.⁸ Kidney damage associated with CPB is seen in approximately 18.2% of adult patients undergoing CPB and may cause a two-fold increase in the mortality rate.⁹ Kidney damage mechanisms associated with cardiac surgery can be defined as perioperative renal ischemia, reperfusion injury, CPB-induced hemolysis and pigment nephropathy,¹⁰ oxidative stress and inflammation.¹¹

Renal perfusion has a complex structure. Although 20% of cardiac output perfuses the kidneys, most of the blood filtered by the cortical glomeruli is shunted from the vasa recta. This shunt may help maintain electrolyte and water concentration gradients in the renal medulla required for tubule and collecting system reabsorption, but this renders the renal medulla and corticomedullary space more hypoxic than other tissues (PO₂ 10–20 mmHg). CPB can disrupt the balance between cortical and medullary perfusion by providing non-pulsatile blood flow. In this case, increased cortical perfusion may accelerate corticomedullary ischemia due to increased medullary oxygen consumption resulting from increased solute transport.¹²

Aortic cannulation and cross-clamping increase atheroembolism to the kidneys and induce inflammation by exacerbating ischemia.¹³

NRF-2

Nuclear factor (erythroid-derived 2)-like 2 (NRF-2) is a transcription factor encoded by the NFE2L2 gene in humans, first identified by Moir et al. in 1994.¹⁴

NRF-2 is an essential leucine zipper (bZIP) protein that regulates the expression of antioxidant proteins that protect against oxidative damage triggered by injury and inflammation.¹⁵

Under normal conditions, NRF-2 is retained in the cytoplasm by a rapidly degrading protein cluster. Under oxidative stress, NRF-2 is not degraded but instead travels to the nucleus where it binds to a DNA promoter and initiates transcription of antioxidative genes and proteins. NRF-2 is retained in the cytoplasm by Kelch-like-ECH-associated protein 1 (KEAP1) and Cullin 3, which degrades NRF-2 by ubiquitination.¹⁶

Cullin 3 ubiquitinates NRF-2, while Keap1 is a substrate adapter protein that facilitates the reaction. When NRF-2 is ubiquitinated, it is transported to the proteasome, where it is degraded and its

components are recycled. Under normal conditions, the half-life of NRF-2 is only 20 minutes.¹⁷

The Cytosolic Mechanism of NRF-2

Nuclear factor (erythroid-derived 2)-like 2 plays an important role in the antioxidant and anti-inflammatory mechanism and activates elements of the antioxidant response (ARE).¹⁸

NRF-2 has six Neh (NRF2-ECH homology) domains, where Neh1 is a bZIP construct that enables NRF-2 to dimerize and bind to DNA.¹⁹ Neh2 and Neh6 is known as a degron, therefore, via B-TrCP (proteins containing B-transducin repeats) and mainly through KEAP1 is a point that can be recognized by proteasomal degradation systems.^{20–22}

Immunological Mechanism of NRF-2

The immune system, infectious, neoplastic, toxic agents are all involved in multiple protective mechanisms in proinflammatory processes that must be adequately counter-regulated to avoid a persistent or excessive inflammatory process. NRF-2 responds to inflammatory cell and tissue stimuli with pleiotropic effects that are not yet well defined.²² In the regulation of innate immunity, the lack of NRF-2 expression brings about a disruption in the protective process of the host, as well as increased damage by hyperoxia, inefficiency in the increase and elimination of ROS and increased production of proinflammatory cytokines.^{23,24}

Kidney Damage and NRF-2

Numerous stressors, including ischemia, diabetes, chemotherapies, hypertension, inflammation, environmental exposures and radiation, raise ROS levels in cells. Random free radical formation causes oxidative damage in cell components in the form of DNA damage, mitochondrial dysfunction, and cell death.²⁵

The first pathological manifestation of acute kidney injury (AKI) is tubular cell death followed by tubular proliferation, regeneration and differentiation. In this context, non-apoptotic cell death has an important role. NRF-2 (nuclear factor E2 related factor), a vital regulator of the antioxidant system, neutralizes cellular oxidative stress activation and has been found to balance oxidative stress and inhibit AKI. It is an important transcription factor that protects cells from various oxidative attacks by inducing genes encoding proteins related to inflammation, injury, antioxidant detoxification, metabolic enzymes, and response to environmental stress.²⁶

The results of many studies show that NRF-2 signaling plays a protective role in kidney damage caused by numerous pathological conditions. Also, in chronic kidney disease (CKD), defects in the activity of NRF-2 and suppression of its target genes were determined. The involvement of NRF-2 in different signaling pathways has made it an accurate and valuable target in AKI. Induction and activation of Nrf-2 signaling by pharmacological interventions may be effective in protecting against inflammation and oxidative stress involved in renal dysfunction in both AKI and CKD.^{27,28}

NRF-2 in the Pathophysiology of Kidney Damage

Renal tubular epithelial cells (RTECs) are more exposed to ROS products due to their high metabolic activity in the kidney. Therefore, ischemia is common in these cells due to higher O₂ consumption.²⁹

It has been shown that NRF-2 maintains renal homeostasis by regulating the content of NADPH and GSH levels in the kidney.³⁰

NRF-2 and Ferroptosis in Kidney Damage

Cellular energy collapse as a result of ROS production during ischemia-hypoxia and reperfusion processes are two important pathological manifestations of IRI. It has been shown that in the reperfusion phase, in which autophagy can occur in both phases in renal tubular epithelial cells, hypoxia and AKI induce apoptosis and ferroptosis as a type of cell death induced by erastin, a type of cell death.³¹

NRF-2 Treatment Target in Kidney Injury

Since oxidative stress is a crucial factor for tissue damage in all organs in diseases in which inflammatory and oxidative stress participate in the pathogenesis, potentiation of the antioxidant Keap1-NRF-2 system by activators of NRF-2 or Keap-1 inhibitors is the most promising therapeutic for the prevention and amelioration of a variety of looks like a target. In recent years, various agents have been investigated to prevent oxidative stress and inflammation in kidney tissue. By targeting NRF-2/Keap-1 signaling, these interventions can be used as therapeutic or preventive agents in kidney damage.³²

Ethics Approval

Not applicable.

Statistical Analysis

Not applicable.

Reporting Guidelines

Not applicable.

Results

The CPB technique, which allows cardiac surgical interventions to be performed, has many complications together with the advantages it provides, and many organs such as the heart and kidneys are affected. Despite these complications that may develop, it is a standard technique used today. Many substances that can show biomarker properties are secreted in organs exposed to these damages. Especially in CPB, oxidative damage and infection conditions necessitated the investigation of new biomarkers in the diagnosis and treatment of acute damage to kidney tissues. Many studies have shown that NRF-2 has an active role in the regulation of cellular processes that prevent the progression of kidney damage. Studies on NRF-2 continue, which shows promise in the diagnosis of kidney diseases. With the activation of NRF-2 and the activation of different signaling mechanisms, it can be considered as a new therapeutic target in kidney diseases. Large-scale advanced studies are needed to more clearly define the biological and therapeutic effects of NRF-2 in the development of kidney damage and in different pathological conditions.

Discussion

Dysfunction of any of the physiological activities between the kidney, heart and blood vessels causes a condition that increases the disturbances in the entire cardiorenal process.³³

NRF-2 is a transcription factor sensitive to the body's redox reaction, which can regulate the redox state in cells. NRF-2 fundamentally monitors the oxidation state in cells, prevents cellular oxidation and maintains a basic antioxidant status. If the level of NRF-2 is lowered, various diseases occur by causing excessive oxidative stress and inflammation.^{34,35}

Liver, heart, kidney, brain, intestine, testis, eyes, extremities, etc. ischemia, which plays an important role in the pathogenesis of many diseases, re-induces transcriptional programming, leading to hypoxia and post-translational activation of inflammatory signaling cascades, causing severe damage by inducing reperfusion and inflammatory responses. Oxidative stress (OS) created by the overproduction of free oxygen radicals plays an important role in ischemia/reperfusion mediated tissue damage. NRF-2 is a key molecule responsible for the proper regulation of the antioxidant system and cytoprotective genes. Studies show that NRF-2 induces the expression of antioxidant enzymes and plays a very important role in protection against oxidative stress. NRF-2 migrates from the cytoplasm to the nucleus under the stress condition, thereby activating the expression of multiple target genes encoding antioxidant and drug metabolizing enzymes and transporters

heme and iron metabolic enzymes. Many experimental studies show that NRF-2 is a promising molecule to prevent and treat organ damage caused by ischemia/reperfusion.³⁶

Fangyong Wu. et al. in a study on Sprague-Dawley rats kept the coronary artery occluded for 6 hours for the development of myocardial ischemia in the 1st group and then performed reperfusion for 30 minutes (I/R group). In the second group, parecoxib sodium (10 mg/kg) was injected consecutively twice a day for 3 days before ischemia, followed by reperfusion for 6 hours. For each group, they recorded and evaluated changes in heart function and infarct area with echocardiography. Changes in apoptosis-associated proteins were determined by immunohistochemistry and western blotting, then the degree of oxidative stress was assessed. Then, NRF-2 level was evaluated by PCR. According to the study, after parecoxib sodium treatment, infarct area and apoptosis level, ROS level and OS decreased. They also concluded that the redox imbalance was regulated by NRF-2. There was an upregulation of NRF-2 after parecoxib sodium treatment, which decreased proinflammatory cytokines ($p < 0.01$).³⁷

Declarations

Animal and Human Rights Statement

No human or animal subjects were directly involved in this study.

Informed Consent

Not applicable.

Data Availability

No datasets were generated or analyzed during the current study.

Conflict of Interest

The author declares no conflict of interest.

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Scientific Responsibility Statement

The author declares responsibility for the scientific content of the manuscript, including study design, literature evaluation, manuscript preparation, and approval of the final version.

Abbreviations

AKI: Acute kidney injury

ARE: Antioxidant response element

bZIP: Basic leucine zipper

CKD: Chronic kidney disease

CPB: Cardiopulmonary bypass

DNA: Deoxyribonucleic acid

GSH: Glutathione

IRI: Ischemia-reperfusion injury

KEAP1: Kelch-like ech-associated protein 1

NADPH: Nicotinamide adenine dinucleotide phosphate

NRF-2: Nuclear factor erythroid 2-related factor 2

OS: Oxidative stress

PCR: Polymerase chain reaction

ROS: Reactive oxygen species

RTECs: Renal tubular epithelial cells

UF: Ultrafiltration

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