Progrès en urologie (2014) 24, S4-S12

Disponible en ligne sur
SciVerse ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Ischemia-reperfusion: From cell biology to acute kidney injury

Ischémie-reperfusion : de la biologie cellulaire à la lésion rénale

N. Chatauret[a,b], L. Badet[a], B. Barrou[a], T. Hauet[a,b,c,*]

[a]INSERM, U1087, Ischémie-reperfusion en transplantation d'organe : mécanismes et innovations thérapeutiques, Poitiers ; université de Poitiers, faculté de Médecine et de Pharmacie, 86021 Poitiers, France
[b]CHU de Poitiers, Laboratoire de biochimie, 86021 Poitiers, France
[c]IBISA, Domaine expérimental du Magneraud, 17700 Surgères, France

KEYWORDS
Acute Kidney Injury;
Chronic allograft nephropathy;
Innate Immune Response;
Ischemia-reperfusion injury;
Reactive oxygen species

Summary
Ischemia reperfusion injury occurs in the kidney when blood supply is interrupted in clinical settings such as kidney transplantation or nephron sparing surgery for renal tumors. These lesions lead to acute kidney injury (AKI) a detrimental situation associated with impaired short-term allograft function (delayed graft function or primary non function) but also long-term transplant survival through the onset of chronic allograft nephropathy.
The present review details the cellular and molecular consequences of ischemia reperfusion in a native kidney as well as in a kidney graft after cold ischemia time, giving a comprehensive description of biological pathways involved during the phase of ischemia and during the reperfusion period where the rapid return to normoxia leads to a large burst of reactive oxygen species along with a dramatic reduction in antioxidant defenses. This work also focuses on the distinct susceptibilities of kidney cells to ischemia (endothelial vs epithelial) and the outcome of acute kidney injury.

*Corresponding author.
E-mail adress: t.hauet@chu-poitiers.fr (T. Hauet).

MOTS CLÉS
Immunité innée ;
Ischémie-reperfusion ;
Nécrose tubulaire aigue ;
Néphropathie chronique ;
Radicaux libres ;
Stress oxydatif

Résumé
Les lesions d'ischémie-reperfusion rénales surviennent lorsque le flux sanguin rénal est interrompu, dans des situations cliniques comme la transplantation rénale ou la chirurgie conservatrice pour le traitement des tumeurs rénales. Ces lésions conduisent à une atteinte rénale aigue compromettant la fonction rénale à court terme (reprise retardée de fonction ou non-fonction primaire en transplantation rénale) mais aussi à long terme par le développement de lésions de néphropathie chronique d'allogreffe ou de fibrose rénale.
Cette revue détaille les mécanismes moléculaires et cellulaires impliqués lors de la phase d'ischémie rénale mais aussi lors de la période de reperfusion, lorsque le retour rapide à des conditions normoxiques entraine un relargage massif des dérivés de radicaux libres contemporain d'une diminution drastique des mécanismes de défense contre le stress oxydant. Ce travail décrit aussi les différences de sensibilité entre les cellules endothéliales et épithéliales et les conséquences globales des lésions rénales aigues post-ischémiques.

Introduction

Ischemia reperfusion (IR) injury occurs when blood supply to part or the whole of an organ is interrupted or drastically reduced. For the kidney, IR is either due to cardiac arrest (systemic hypoperfusion), shock, surgical interventions leading to local renal hypoperfusion such as aortic cross-clamping, partial nephrectomy as well as transplantation. The duration of ischemia at either body temperature for the organs *in situ* or at 4 °C for grafts will determine the extent of tissue injury ranging from no visible symptoms to acute kidney injury (AKI). AKI has been traditionally defined as a rapid (ranging from hours to weeks) decrease in kidney function measured by increases in serum creatinine levels [1]. AKI is independently associated with increased morbidity and mortality as well as increased length of hospital stays [2]. It is commonly accepted that AKI may have chronic consequences. Indeed, AKI is associated with a high risk of developing a chronic kidney disease (CKD) or exacerbates a CKD, leading more rapidly to end-stage renal disease [3]. In kidney transplantation, ischemia-reperfusion injury can be associated with a form of AKI recognized as delayed graft function (DGF) (requirement for at least one dialysis session during the first week post-transplantation) [4], slow graft function (SGF) (defined as a reduction in serum creatinine from immediately after transplant to day 7 by less than 70%) [5] or PNF (primary non function) define as no reduction in serum creatinine level due to irreversible cellular lesion. DGF and SGF are associated with higher risks of chronic allograft nephropathy and fibrosis [6]. Ischemia-reperfusion-induced AKI for native kidneys or DGF for transplanted kidneys share similar cellular and molecular pathophysiological changes linked to both blood flow cessation and restoration. In addition, the IR lesions in kidney transplantation are associated with hypothermic injuries sustained during cold storage of the graft. This review will detail the cellular and molecular consequences of ischemia reperfusion in a native kidney as well as in a kidney graft.

Consequences of ischemia reperfusion at the cellular level

In any organs, a drastic blood flow reduction will lead to decreases, at the cell level, in oxygen and nutrients deliveries as well as waste product removal.

During ischemia

Depending on the importance and duration of ischemia, the organ will either completely recover or will sustain cellular injuries once a critical ischemia duration is exceeded. In humans, the critical ischemia duration, at body temperature, depends on the organ, ranging a few minutes for brain to 30 minutes for the kidney [7]. Longer exposure to hypoxia will invariably lead to changes in cellular metabolism with deleterious consequences after reperfusion (Fig. 1).

The first change induced by ischemia is associated to the decreased oxygen delivery. Decreased O_2 levels will induce a switch from aerobic (generation of 36 molecules of ATP from 1 molecule of glucose *via* the tricarboxylic acid cycle) to anaerobic glucose metabolism (generation of 2 molecules of ATP from 1 molecule of glucose by lactate synthesis) [8]. This anaerobic metabolism is insufficient to meet the demands of aerobic tissues [8] and the lack of oxygen will further enhance ATP consumption in the mitochondria by reversal of the F1F0 ATP synthase (hydrolyzing ATP instead of synthesizing it) in order to maintain the mitochondrial membrane potential compromised by the inhibition of the electron transfer chain [9]. Therefore, intracellular ATP levels will rapidly fall and this fall will be directly linked to the duration of ischemia. In addition, the lactate-dependent ATP production causes intracellular acidosis by accumulation of lactic acid in the cells as well as in the interstitium as it is no longer removed by blood flow. Lowering of both the intracellular pH and ATP levels will: i) destabilize the lysosome membrane which will leak various hydrolases leading to disruption of