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Research Report

Hippocampal transcriptional dysregulation after renal ischemia and reperfusion

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ABSTRACT

Neurological complications contribute largely to the morbidity and mortality in patients with acute renal failure. In order to study pathophysiological complications of renal failure, a murine model of renal ischemia/reperfusion-induced acute kidney injury (AKI) was generated by 60 min bilateral ischemia, and followed by 2 h or 24 h reperfusion (B-60'IRI). Compared to the sham-operated mice, B-60'IRI mice exhibited a significant inflammatory injury to remote brain. We found that serum and brain levels of KC, G-CSF and MCP-1 were significantly increased in B-60'IRI mice after 2 h and 24 h reperfusion when compared with sham-operated mice. Moreover, B-60'IRI mice exhibited increased numbers of activated microglial cells in the brain, and severe blood–brain barrier (BBB) permeability when compared with the control sham mice. The technology of cDNA microarray and quantitated RT-PCR are used to identify hippocampal genes whose expression is altered in response to AKI in B-60' IRI mice. The initiation of transcriptional abnormality was indicated by the finding that B-60' IRI mice exhibited upregulated mRNA levels of genes involved in inflammation, cell signaling, extracellular matrix and cell-cycle regulation and downregulated mRNA levels of genes involved in transporters, G protein-coupled receptor signaling, cell survival and chaperone. Our data suggest that renal IR contributes to a complicated hippocampal gene irregulation in inflammation and physiological homeostasis.

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1. Introduction

Acute kidney injury (AKI) occurs frequently in critically ill patients and it contributes significantly to mortality and morbidity in both adults and children (Mehta et al., 2007). AKI often arises from insults such as severe infection/sepsis, trauma, medication and contrast agents, or following major surgery. Depending on the definition of AKI used, 7–18% of all hospitalized patients suffer from AKI, approximately 35% of patients requiring intensive care have AKI (Akcan-Arikan et al., 2007; Metnitz et al., 2002). Among these, 5% of intensive care patients have AKI severity enough to require dialysis (Vanderlaan et al., 2005). Since the availability of dialysis, AKI-associated distant organ dysfunction constitutes the major cause of death in these patients, with the mortality rate still in the 50% range (Hoste and Schurgers, 2008). Isolated AKI has a much better prognosis than AKI-associated multi-organ failure. Most studies of AKI-associated mechanisms have focused on intrarenal changes. However, mortality during AKI is largely due to extrarenal manifestation. Recent clinical and animal studies revealed a strong association between AKI and dysfunction of extrarenal organs.

Patients with AKI are more susceptible to encephalopathy than to chronic kidney disease, as there is less time to adapt to uremia in AKI. In general, encephalopathy presents with complex symptoms progressing from mild sensorial clouding to delirium and coma. It is often associated with headache, visual abnormalities, tremor, asterixis, multifocal myoclonic jerks, chorea and generalized seizures. Dialysis improves but does not fully correct central nervous system manifestations or other distant organ effects from renal failure, either acutely or chronically (Arieff et al., 1973). Recent studies showed that inflammation is a major component of the initiation and exacerbation of kidney injury during AKI. In addition, the inflammatory effects of AKI are not only limited to the kidney, but can also lead to inflammatory effects in other organs, including the lung (Hoke et al., 2007; Kramer et al., 1999), heart (Kelly, 2003) and brain (Liu et al., 2008). In a murine model of ischemic AKI, concomitant inflammation-associated transcriptional changes in the kidney and lung tissues were identified (Grigoryev et al., 2008). Previous studies have shown that ischemic AKI induces functional and transcriptional changes in the lung which are distinct from those induced by uremia alone (Hassoun et al., 2007). Thus, it is possible that ischemic AKI may attribute to the transcriptional dysregulation in the brain.

In the present study, we prepared a renal ischemia and reperfusion (IRI) animal model and we found a significant inflammatory effect of AKI on the brain. To evaluate blood–brain barrier (BBB) permeability, extravasation of Evans Blue dye was assayed. To test the involvement of transcriptional abnormality in the hippocampus after renal ischemia and reperfusion, microarray analysis was performed to detect altered hippocampal mRNA expressions in renal IRI mice. Our study provides the evidence that AKI is attributed to a wide array of gene irregulation in the hippocampus. This includes the functional role of upregulated genes most involved in inflammation, cell signaling, extracellular matrix and cell-cycle regulation, but downregulated genes were indicated in transporters, signal transduction, cell survival and chaperone.

2. Results

2.1. *Bilateral 60 min renal ischemia and reperfusion resulted in systemic and brain inflammation*

Renal ischemia-reperfusion produced significantly elevated serum creatinine concentration after 24 h of reperfusion in B-60'IRI (2.3±0.28) mice compared to sham mice (0.45±0.02) (Fig. 1A) or serum BUN level after 24 h of reperfusion in B-60'IRI (178.9±4.8) mice compared to sham mice (23.17±1.3) (Fig. 1B). To identify systemic and brain inflammation after renal ischemia and reperfusion, we measured serum and brain cytokines at 2 h and 24 h after reperfusion. We found that serum levels of G-CSF, MCP-1, KC, IL-6 and IL-10 were significantly increased in B-60'IRI mice at 2 h and 24 h after reperfusion, as compared to sham-operated mice (Fig. 2A). We also found that brain from B-60'IRI mice had significantly increased in KC and G-CSF at 2 h (Fig. 2B) and increased in KC, G-CSF and MCP-1 at 24 h (Fig. 2C) after reperfusion. Subsequently, to determine

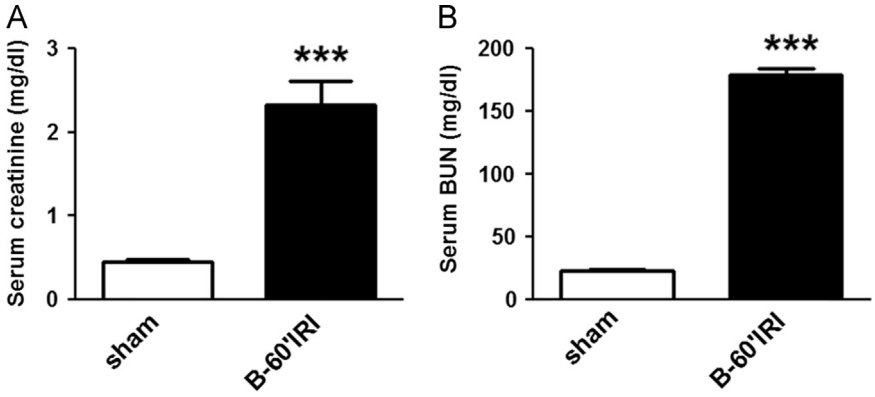

Fig. 1 – Effect of ischemia-reperfusion injury in mouse kidney. Serum creatinine (mg/dL; (A)) and blood urea nitrogen (BUN; mg/dL; (B)) and were determined after 60 min (B-60'IRI) of bilateral renal ischemia followed by 24 h of reperfusion. There were significant level increases of serum creatinine (A) and BUN (B) in B-60'IRI mice, as compared to control sham-operated mice. (* $P<0.0001$ versus sham; $n=6$ in each group).**