European Review for Medical and Pharmacological Sciences 2014; 18: 34-38

Protective effect of 3-aminobenzamide, an inhibitor of poly (ADP-ribose) polymerase in distant liver injury induced by renal ischemia-reperfusion in rats

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Abstract. – BACKGROUND AND AIMS: Renal ischemia followed by reperfusion causes remote liver injury. This research was planned to investigate whether 3-aminobenzamide (3-AB), has any preventive effect against distant liver injury triggered by renal IR.

MATERIALS AND METHODS: Twenty four rats were randomly divided into three different groups Each group has 8 rats. The groups were as follows: (1) Sham operated group; (2) Renal ischemia-reperfusion (IR) group; (3) Renal IR+ 3-AB group. 3-AB (10 mg/kg) was given intraperitoneally 10 minute before reperfusion. At the end of study, the rats were sacrificed. Their liver tissues and serum samples were collected for measurement of malondialdehyde (MDA) levels, total oxidant status (TOS), total antioxidant status (TAS), paraoxonase (PON-1) activity and nitric oxide (NO).

RESULTS: Renal IR injury significantly increased Oxidative stress index (OSI) and MDA, TOS levels and significantly decreased PON-1 actvity and TAS, NO levels in serum and liver tissue ($p < 0.05$). Despite that, changes in these biochemical parameters related with IR injury were diminished by 3-AB administration ($p < 0.05$).

CONCLUSIONS: The inhibition of PARP [Poly(ADP-Ribose)Polymerase] by 3-AB showed protective effects against distant liver injury triggered by renal ischemia-reperfusion by the ameliorating effects of 3-AB on oxidative stress.

Key Words:
3-aminobenzamide, Poly (ADP-Ribose) polymerase (PARP), Ischemia- reperfusion, Remote liver injury, Oxidative stress.

Introduction

Acute kidney injury is an ordinary and significant therapeutic contest for clinicians. Researchers emphasized that the frequency of acute kidney injury varies between clinical statements and populations. According to reports, more than 5000 acute kidney injury patients per million people per year classified as for non-dialysis-requiring, while about 300 sufferers per million people per year require dialysis treatment[1,2]. Ischaemia-reperfusion (IR) injury induced acute renal injury arises in many clinical circumstances, such as urinary tract surgery, septic shock conditions, organ transplantation. The danger of renal failure remains – a devastating problem[3]. Latest researches have established that acute kidney injury triggered by IR induces dysfunction in liver[4,5]. Renal IR injury decreases antioxidant enzyme activities[3,5,6] and increase oxidative stress and hepatic lipid peroxidation products[5-7] in liver tissue.

The poly(adenosine diphosphate-ribose) polymerase (PARP) is an enzyme which modifies proteins and polymerises nucleotides. It is considerably demonstrated in the nucleus[8]. PARP tract is implicated in the pathogenesis of distinct forms of IR injury[9-11]. In several organ systems, the PARP inhibitor 3-aminobenzamide (3-AB) has been used successfully to decrease IR injury[9,12-15].

This study was planned to research the potential protective effect of 3-AB in distant liver injury induced by renal IR in rats.

Materials and Methods

Animals

Twenty four Wistar albino male rats weighing between 200 and 240 g were used in the present study. In the course of experiment, the rats were kept and maintained in constant laboratory conditions recommended by NIH. The study was initiated after obtaining approval from Dicle University Local Committee on Animal Research

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Ethics. We meticulously complied with the principles for the "Protection of Animal Rights" specified by the National Institutes of Health (NIH) during the entire course of the research.

Experimental Method and Procedure

Rats were put under anaesthesia with ketamine (75 mg/kg i.p.) and xylazine (8 mg/kg i.p.). Body temperature was maintained in every part of surgery at 37 ± 1°C. All rats were submitted to surgical exposure of the left and right renal pedicles via midline incision. To create renal ischemia, both renal pedicles were blocked for 45 min with vascular clamps. After 45 min of blockage, the clamps were taken away and kidneys examined to endure reperfusion for 24 hrs. Rats were randomly divided into three different groups (n= 8). The groups were as follows: (1) Sham operated group; (2) Renal IR group; (3) Renal IR+ 3-AB group. 3-AB (10 mg/kg) (Sigma, St. Louis, MO, USA) was administered intraperitoneally 10 minute before reperfusion. At the end of experimental procedure, the rats were sacrificed. Their liver tissues and serum samples were collected for biochemical analysis. The excised liver tissue samples were weighed and all samples instantly stored at –70°C.

Biochemical Assay

The liver tissues washed with 1.15% ice-cold KCl, minced, then homogenized in five volumes (w/v) of the same solution. Assays were performed on the supernatant of the homogenate. The protein concentrations of the tissue and serum sample were assessed by the method of Lowry et al[16]. Lipid peroxidation level was phrased as malondialdehyde (MDA). It was assessed by the method of Ohkawa et al[17]. Nitric oxide (NO) levels were assessed with Griess' method[18]. Paraoxonase (PON-1) activity was assessed spectrophotometrically by modified Eckerson et al method[19]. The total antioxidant status (TAS) of supernatant fractions was appraised by using a Erel method[20]. TAS results are expressed as nmol Trolox equivalent/mg protein. The total oxidant status (TOS) of supernatant fractions was appraised by using a new method Erel[21]. The results are expressed in terms of nmol H_2O_2 equivalent/mg protein[22]. The TOS/TAS ratio was considered as the oxidative stress index (OSI). The tissue OSI value was calculated as follows: OSI = TOS/TAS[23].

Statistical Analysis

Statistical analysis was performed using SPSS (version 11.0; SPSS Inc., Chicago, IL, USA). Data were shown as means ± standard deviation, and Kruskal-Wallis test was used for analysis. In the event of significant results, the Mann-Whitney U test was used for comparisons of differences between two independent groups. A p value < 0.05 was estimated statistically significant.

Results

Consequences of Renal Ischemia on Blood Biochemical Variables

Serum MDA, TOS, TAS, OSI, NO levels and PON-1 enzyme activities are demonstrated in Table I. There were notable changes in the PON-1 enzyme activities and MDA, TOS, TAS, OSI, NO levels in the serum of the IR group compared to sham operated group ($p < 0.01$). In the 3-AB treated IR group, TAS, NO and PON-1 levels were notably elevated when compared to the IR group ($p < 0.001$). On the other hand, MDA ($p < 0.05$), TOS ($p < 0.01$) and OSI ($p < 0.01$) levels were notably reduced in IR+3-AB group when compared to the IR group ($p < 0.05$).

Table I. Levels of MDA, TOS and TAS, OSI, PON-1 activity and NO in serum samples.

Groups	Sham (n: 8)	IR (n: 8)	IR+3-AB (n: 8)
MDA (nmol/g protein)*	259.9 ± 22.1	367.4 ± 54.4[a]	256.4 ± 42.9[c]
TOS (mmol H_2O_2 Equiv./g protein)*	57.4 ± 12.4	162.4 ± 11.1[a]	78.0 ± 21.4[b]
TAS (mmol Trolox Equiv./g protein)*	1.16 ± 0.12	0.84 ± 0.08[a]	1.28 ± 0.22[b]
OSI (H_2O_2/Trolox)*	49.5 ± 11.3	196.0 ± 34.3[a]	60.9 ± 13.3[b]
PON-1 activity (U/mg protein)*	165.7 ± 29.1	124.5 ± 11.0[a]	146.1 ± 28.3[b]
NO (μmol/g protein)*	365.7 ± 55.7	139.7 ± 45.3[a]	362.3 ± 77.1[b]

Results are presented as means ± standard deviation. *$p < 0.01$ for Kruskal Wallis test. [a]$p < 0.01$ as compared to the sham operated group, [b]$p < 0.001$ as compared to the IR group. [c]$p < 0.05$ as compared to the IR group. IR: Ischemia-reperfusion, 3-AB: 3-aminobenzamide. MDA: malondialdehyde, TOS: Total oxidant status, TAS: Total antioxidant status, OSI: Oxidative stress index, PON-1: paraoxonase activity, NO: Nitric oxide.

Consequence of Renal Ischemia on Liver Biochemical Parameters

The MDA, TOS, TAS, OSI, NO levels and PON-1 enzyme activities in the liver tissues are demonstrated in Table II. MDA, TOS and OSI levels were notably raised and TAS, NO and PON-1 levels were notably reduced in the IR as compared to the sham operated group ($p < 0.01$). However, TAS ($p < 0.05$), NO ($p < 0.01$) and PON-1 ($p < 0.01$) levels were notably elevated in 3-AB treated IR group compared to the IR group. MDA ($p < 0.01$), TOS ($p < 0.05$) and OSI ($p < 0.05$) levels were notably reduced in IR+3-AB group compared to the IR group ($p < 0.05$).

Discussion

This research was planned to explore whether 3-AB, a PARP inhibitor, has a protective effect on distant liver damage triggered by renal IR by diminishing oxidative stress. PARP is an enzyme that modifies proteins and polymerises nucleotides. It is considerably found in the nucleus. The essential stimulus of PARP activation is DNA single strand break, which can be generated by a variety of environmental factors and free radical and oxidants[8]. The PARP pathway is implicated in the pathogenesis of various forms of IR injury[9-11]. Reactive oxygen species (ROS) generated during IR are powerful activators of DNA single-strand cleavage and the consequent activation of the nuclear enzyme PARP[24]. Inhibition of PARP activation exerts beneficial effects that ameliorate the metabolic alterations but not the occurrence of DNA damage in inflammatory response during IR processes[25]. Over activation of PARP may cause to cell death due to energy depletion[26-28]. Because of an immediate depletion of intracellular nicotinamide adenine dinucleotide (NAD^+) and adenosine triphosphate (ATP) energy pools, glycolysis and the mitochondrial respiration rate decelerate, leading to cellular dysfunction and death[29]. Totally, this activity is called as the poly (ADP-ribose) polymerase suicide hypotheses[30]. This cell suicide phenomenon is driven by PARP activation and has been shown in several cell types[25]. PARP inhibition exerts favourable effects against free radical-mediated cell injury[31]. In several organ systems, the PARP inhibitor 3-AB has been used successfully to decrease IR injury[12-15].

It was demonstrated that IR of the tissue to be associated with lipid peroxidation, which is an autocatalytic process causing to oxidative demolition of the cellular membranes, and their catabolites can cause to form harmful metabolites and cell death[7,32-34]. Lipid peroxidation, as a free radical-producing system, has been proposed to be tightly linked to IR -induced tissue damage, and MDA is an important parameter of oxidative stress is a good pointer of lipid peroxidation[7]. In this study, in IR group the level of MDA notably elevated in the serum and liver tissue, while exogenously administered 3-AB repressed MDA elevation notably. This finding indicates that renal IR induced lipid peroxidation is likely to be improved with 3-AB administration in liver tissue.

Besides MDA level, assessment of TOS, TAS, and OSI contributes unusual and predictable index of oxidative stress. We assayed oxidative status as TOS and TAS along with the assessment of OSI, a pointer of oxidative stress, which exhibits the redox balance between oxidation and antioxidation[35]. Since separate measurement of different oxidant molecules such as superoxide radical anion, hydrogen peroxide is not functional and their oxidant effects are linear, we measured TOS in serum as previously described by Erel[21]. Likewise, we measured TAS, instead of assaying antioxidant mole-

Table II. Levels of MDA, TOS and TAS, OSI, PON-1 activity and NO in liver tissue samples.

Groups	Sham (n: 8)	IR (n: 8)	IR+3-AB (n: 8)
MDA (nmol/g protein)*	237.6 ± 20.2	335.8 ± 49.8[a]	234.4 ± 39.2[b]
TOS (mmol H_2O_2 Equiv./g protein)*	44.7 ± 22.1	97.1 ± 27.9[a]	76.5 ± 31.8[c]
TAS (mmol Trolox Equiv./g protein)*	1.14 ± 0.24	0.70 ± 0.21[a]	0.93 ± 0.24[c]
OSI (H_2O_2/Trolox)*	39.2 ± 18.3	149.5 ± 68.7[a]	90.2 ± 49.1[c]
PON-1 activity (U/mg protein)*	6.08 ± 1.78	2.40 ± 0.65[a]	5.57 ± 1.90[b]
NO (μmol/g protein)*	490.1 ± 74.6	187.2 ± 60.7[a]	485.5 ± 103.3[b]

Results are presented as means ± standard deviation. *$p < 0.01$ for Kruskal Wallis test. [a]$p < 0.01$ as compared to the sham operated group, [b]$p < 0.001$ as compared to the IR group. [c]$p < 0.05$ as compared to the IR group. IR: Ischemia-reperfusion, 3-AB: 3-aminobenzamide. MDA: malondialdehyde, TOS: Total oxidant status, TAS: Total antioxidant status, OSI: Oxidative stress index, PON-1: paraoxonase activity, NO: Nitric oxide.

cules separately following the methods of Erel[36] and Cikrikcioglu et al[37]. Lately, it has been published that OSI may exhibit the oxidative status more accurately than TOS or TAS level alone[38]. In this research, serum and liver tissue TOS levels and OSI values were notably increased and the level of TAS was notably reduced in IR group compared with sham operated group. On the other hand, in 3-AB treated IR rats TAS level was significantly increased compared with IR group. These results showed that renal IR leads to increase of oxidative stress in liver tissue, and this increase was prevented by administration of 3- AB.

PON-1, an enzyme associated with high-density lipoprotein that is mainly secreted by the liver. Although its physiological activity has not been completely clarified, it seems PON-1 is responsible for hydrolyzing lipid peroxides and also to play a major role in the antioxidant system[39]. PON-1 protects liver against inflammation, liver disease and fibrosis[40,41]. In this study, we found decreased PON-1 activity in the serum and liver tissues of IR rats compared to sham operated rats. 3-AB treatment was reversed the reduced activity of PON-1 in IR+3-AB group. 3-AB treatment prevented the reduced activity of PON-1 in liver tissue. Our data show that a reduction in PON-1 activity is linked to oxidative damage in the liver tissues caused by renal IR and 3-AB administration reverses the decrease of PON-1 activity in these tissues.

NO in the liver also exerts vasodilatory and cytoprotective effects. Inhibition of NO production in the liver has conventionally been demonstrated to be harmful in reperfusion injury models[8,42]. Studies show that nitric oxide synthase inhibitors reduce microvascular perfusion and aggravate liver injury during IR[8,43]. These data were also supported in eNOS gene knockout mice[8,44,45]. A reduction of NO during IR, generally caused by endothelial dysfunction and reduction of endothelial nitric oxide synthase activity[46,47]. In this work, renal IR reduced the NO level and 3- AB treatment increased NO content in serum and hepatic tissue. These findings showed that 3-AB can increase renal IR associated endothelial dysfunction and reduction of endothelial nitric oxide synthase activity.

Conclusions

This report is the first to investigate the effects of 3-AB against distant liver injury triggered by renal ischemia-reperfusion in rats. Data revealed that the inhibition of PARP by 3-AB showed protective effects against distant liver injury triggered by renal ischemia-reperfusion by the ameliorating effects of 3-AB on oxidative stress.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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